European Review for Medical and Pharmacological Sciences 2024; 28: 2501-2508

Dexmedetomidine protects the uterus against ischemia-reperfusion injury in rats

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Abstract. – OBJECTIVE: This study aimed to analyze the histopathological and biochemical effects of dexmedetomidine on the rat uteri exposed to experimental ischemia-reperfusion injury.

MATERIALS AND METHODS: Twenty-four female rats were randomly divided into three groups. Group 1 was defined as the control group. An experimental uterine ischemia-reperfusion model was created in Group 2. Group 3 was assigned as the treatment group. Similar uterine ischemia-reperfusion models were created for the rats in Group 3, and then, unlike the other groups, 100 μg/kg of dexmedetomidine was administered intraperitoneally immediately after the onset of reperfusion. In blood biochemical analysis, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) activities and malondialdehyde (MDA), interleukin 1beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels were measured. In the histopathological analyses, endometrial epithelial glandular changes (leukocytosis, cell degeneration) and endometrial stromal changes (congestion, edema) were analyzed using the tissue damage scoring system.

RESULTS: It was observed that IL-1β, IL-6, and TNF-α levels were significantly suppressed in Group 3 compared to Group 2 (p=0.001, p<0.001 and p=0.001, respectively). MDA level was noted as the highest in Group 2. The MDA value in Group 3 was measured at 5.37±0.82, which was significantly decreased compared to Group 2 (p<0.001). An increase in antioxidant enzyme activities (SOD and GSH-PX) was observed in Group 3 compared to Group 2 (p=0.001 and p=0.006, respectively). In our histopathological analysis, a significant improvement in endometrial epithelial glandular and endometrial stromal changes was revealed in Group 3 compared to Group 2 (p<0.001).

CONCLUSIONS: In our study, it has been documented that dexmedetomidine protects the uterine tissue against ischemia-reperfusion injury.

Key Words:
Dexmedetomidine, Uterus, Oxidative damage.

Introduction

In recent years, clinicians have started to show increasing interest in non-life-saving organ transplants aimed at improving the quality of life. In this context, uterus transplantation is a highly popular topic today[1]. 5-7% of the general population suffer from absolute uterus factor infertility. For these patients, uterus transplantation is the only chance for fertility[2]. The first uterus transplant was performed in 2000 but ended in failure during the third postoperative month due to uterine necrosis[3]. Although cases of having children through uterus transplantation have been reported in this century, the success rate of these procedures is quite low[4]. Transplantation success is limited by ischemia-reperfusion injury, and researchers are conducting intensive studies to regulate uterine tolerance to ischemia-reperfusion injury. Ischemia-reperfusion injury is closely related to the high amount of reactive oxygen radicals that suddenly occur with reperfusion in the ischemic tissue, the inflammatory response that begins with neutrophil clusters accumulating in the transplanted tissue, endothelial dysfunction, microcirculatory disorders, apoptosis, and necrosis. This situation plays a critical role in both acute and chronic rejection in organ transplantation[5,6]. Today, various pharmacological agents such as remifentanil, mycophenolate mofetil, relaxin, erythropoietin, melatonin, glycine, crocetin, and resveratrol have been studied[1,5,7-10] to minimize oxidative stress by creating a uterine ischemia-reperfusion model.

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Dexmedetomidine is a potent and highly selective α2-adrenoreceptor agonist. It provides sedation and analgesia without respiratory depression and high-level loss of cooperation. Due to its shorter mechanical ventilation and intensive care unit stay durations compared to other sedative drugs, it is a frequently used pharmacological agent in anesthesia clinics[11]. In addition, dexmedetomidine has antioxidant, anti-inflammatory, and anti-apoptotic properties. Experimental studies[6,12-15] conducted in various tissues such as the penis, liver, intestinal system, kidney, and heart documented the protective effects of dexmedetomidine against oxidative damage due to these functions.

This study aimed to determine the possible protective effects of dexmedetomidine against uterine ischemia-reperfusion injury. As far as we know, this is the first experimental study in the English literature where dexmedetomidine was administered in rats with a uterine ischemia-reperfusion model.

Materials and Methods

Study Design

Approval was obtained from the Tokat Gaziosmanpasa University local Ethics Committee (2022 HADYEK-22) for all surgical and experimental procedures. In this study, 24 Albino-Wistar female rats (235-415 g) were used. The experiment was conducted under a 12-hour light/dark cycle at a constant temperature. (22±2°C). Experimental animals were observed in the laboratory in accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals, as well as institutional guidelines. All experimental animals were fed with standard food and water. Only the rats in Group 3 were administered the specified dexmedetomidine.

Group 1 was defined as the control group. In this group, only uterine tissues were removed, and blood samples from the inferior vena cava were collected.

Group 2 was determined as the uterus ischemia-reperfusion group. Uterus-ischemia reperfusion injury was created in this group as previously described in the literature.

Group 3 was assigned as the treatment group. A uterine ischemia-reperfusion model similar to that in Group 2 was created. In addition, 100 µg/kg of dexmedetomidine was administered intraperitoneally to this group immediately after the onset of reperfusion.

The rats were administered 50 mg/kg of ketamine hydrochloride and 10 mg/kg of xylazine hydrochloride intramuscularly for anesthesia. After anesthesia was achieved, all rats were placed in the supine position; then, the surgical area was shaved and disinfected with a povidone-iodine solution. Then, all the rats underwent laparotomy with a 2-3 cm long vertical incision in the midline and lower abdominal sac. The intestines were gently pushed to the left side with the help of moist gauze, and the abdominal aorta was exposed. In Group 1, the experiment was terminated at this stage; uterine tissues were removed, and blood samples were collected from the inferior vena cava. The uterus ischemia-reperfusion model was created for the rats in Groups 2 and 3. In this context, the distal abdominal aorta was clamped with an atraumatic microvascular clamp approximately 0.5 cm above the aortic bifurcation. Then, both ovaries were temporarily ligated with Vicryl 3-0 sutures, including the artery and its surroundings, to prevent collateral circulation. The abdomen was closed, creating warm ischemia for 1 hour. Then, the microvascular clamp and sutures from the ovarian arteries were removed, and uterine blood flow was restored. Reperfusion continued for 1 hour. At the end of the reperfusion period, blood samples were collected from the inferior vena cava, and uterine tissues were removed[8].

Biochemical Analysis

Blood samples were taken into tubes for biochemical analysis. After centrifugation at 4,000 rpm for 10 min at 4°C, serum samples were frozen and stored at -20°C until the day of study. The commercial and analytical grade chemical materials (Sigma-Aldrich, Merck, Alfa Aesar, Acros Organics B.V.B.A., Tekkim, Isolab) were used for the determination of the following parameters. Superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities and malondialdehyde (MDA) levels in serum samples were determined by spectrophotometric method, similar to the methods in our previous study. GSH-Px activity was determined according to the method of Paglia and Valentine[16], and SOD enzyme activity was determined by the method modified by Sun et al[17]. Lipid peroxidation was determined according to the Esterbauer measurement method[18]. Interleukin 1beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were determined by the Elisa method and were studied as described in the package inserts of the kits.

Tissue Processing and Hematoxylin-Eosin Staining

At the end of the experiment, the uteri of the rats were removed and placed in a 4% buffered neutral formalin solution for histological analysis and fixed for 72 hours. Blocked uteri were sectioned into consecutive thin slices with a rotary microtome (Leica RM2135, Wetzlar, Germany) at a thickness of 5 μm. The obtained uterine tissue sections were placed on frozen slides with ground edges for hematoxylin and eosin staining and were made into preparations for histopathological analyses to detect tissue damage. Hematoxylin-eosin-stained uterine tissue sections from the study groups were analyzed with a light microscope (Nikon Eclipse 200, Tokyo, Japan) using a 40x objective.

Histopathological analyses were performed using the scoring system utilized by Atalay et al[1]. In this scoring system, endometrial epithelial glandular (leukocytosis, cell degeneration) and endometrial stromal changes (congestion, edema) were graded from 0 to 3. Scored from 0 to 3 according to the severity (0=no pathological finding; 1=pathological findings in <33% of the uterine section; 2=pathological findings in 33-66% of the uterine section; 3=pathological findings in >66% of the uterine section).

Statistical Analysis

Descriptive statistics were used to provide information about the general characteristics of the study groups. Data for the variables were described using mean ± standard deviation and range (min-max). Group differences in variables were assessed using One-Way Analysis of Variance (ANOVA). Post-hoc Tukey HSD or Tamhane's T2 tests were used for further comparisons. Ready-to-use statistical software was used for the calculations. (SPSS 22, IBM Corp., Armonk, NY, USA). Statistical significance was accepted for $p<0.05$.

Table I. Comparison of SOD and GSH-Px activity, TNF-α, IL-1β, IL-6, and MDA levels obtained from blood between rat groups.

	Groups	n	Mean±SD	Min-max	*p*-value	Post-hoc *p*-value
SOD (U/ml)	1	8	7.67±1.27	6.22-9.80	**<0.001***	1-2: <0.001*
	2	8	4.63±1.05	3.21-6.30		1-3: 0.528
	3	8	6.84±1.19	5.43-9.10		2-3: 0.001*
GSH-PX (U/ml)	1	8	705.60±85.75	587.20-864.20	**<0.001***	1-2: <0.001*
	2	8	428.75±119.19	288.50-603.00		1-3: 0.008*
	3	8	589.50±57.09	499.10-698.40		2-3: 0.006*
MDA (μmol/mL)	1	8	4.28±0.84	2.80-5.34	**<0.001***	1-2: <0.001*
	2	8	7.32±1.03	5.89-9.21		1-3: 0.030*
	3	8	5.37±0.82	3.98-6.21		2-3: <0.001*
TNF-α (ng/L)	1	8	548.97±59.98	495.10-681.20	**<0.001***	1-2: <0.001*
	2	8	782.52±88.45	634.40-935.30		1-3: 0.509
	3	8	628.99±94.09	505.59-777.80		2-3: 0.001*
IL-1β (ng/ml)	1	8	10.85±1.01	9.80-13.20	**<0.001***	1-2: <0.001*
	2	8	17.43±1.88	15.08-19.98		1-3: 0.001*
	3	8	13.68±1.73	11.10-16.21		2-3: 0.001*
IL-6 (ng/L)	1	8	17.91±3.44	10.81-22.31	**<0.001***	1-2: <0.001*
	2	8	31.40±4.14	26.10-38.90		1-3: 0.028*
	3	8	22.37±3.28	18.77-30.01		2-3: <0.001*

SOD, Superoxide dismutase; GSH-Px, Glutathione peroxidase; MDA, malondialdehyde; TNF-α, Tumor necrosis factor-alpha; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; SD, standard deviation. Test: One-Way Analysis of Variance (ANOVA). Differences between groups were examined with Post-hoc Tukey HSD or Tamhane's T2. *Statistically significant ($p<0.05$).

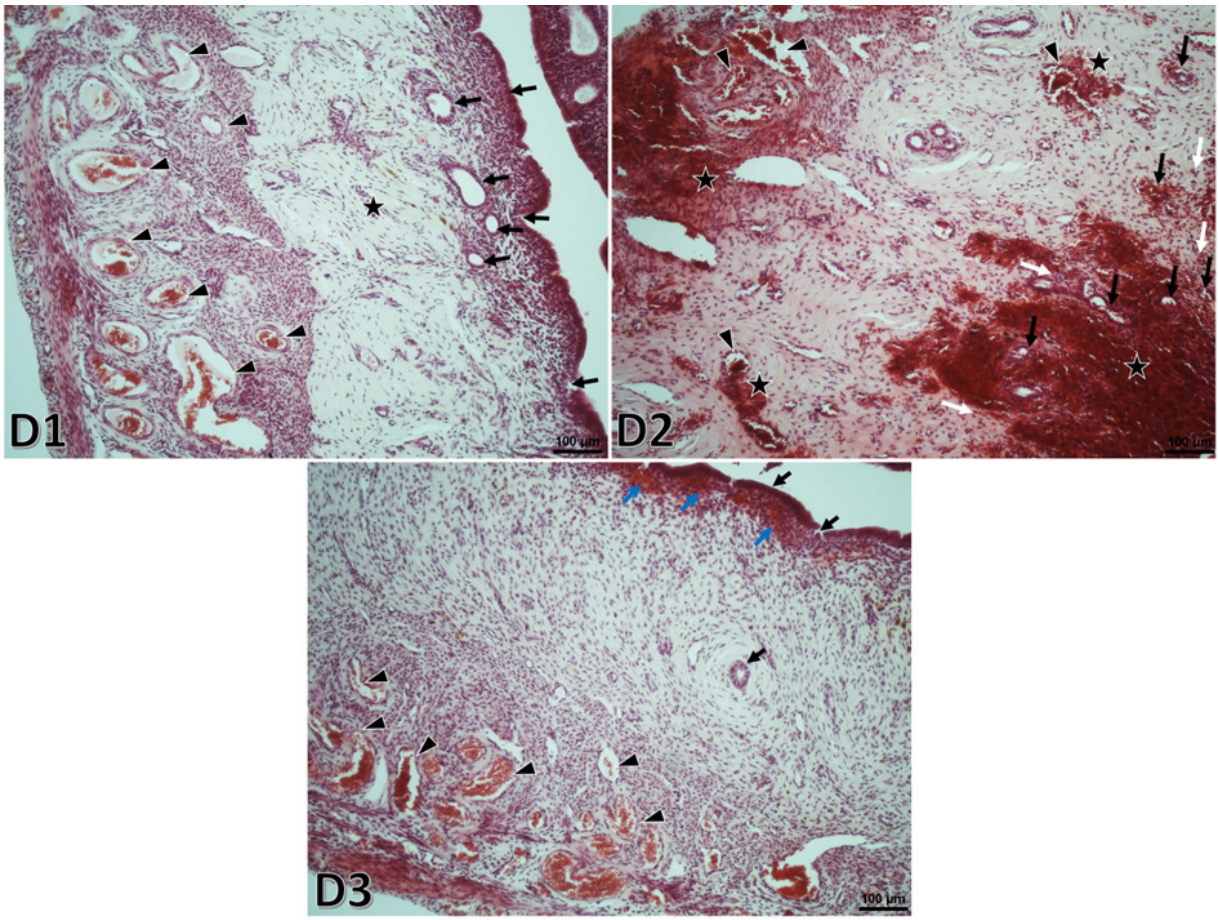

Figure 1. Representative microscopic images of uteruses from each study group. In the control group (**D1**), a uterus with a normal histological structure with normal uterine lumen epithelial invaginations, uterine glands (black arrow), endometrial stroma (asterisk), and blood vessels (arrowhead) is seen. In the ischemia group (**D2**), uterine tissue is characterized by disrupted overall histological architecture with deformed epithelial glandular structures (black arrow), hemorrhagic and ischemic endometrial stroma (asterisk), vascular congestion (arrowhead), and infiltration of inflammatory cells (white arrow). In the treatment group (**D3**), the uterus exhibits a histological appearance similar to the control group, with regenerating epithelial and glandular structures (black arrow), moderate congestion (arrowhead), and minimal hemorrhage (blue arrow) (Hematoxylin and Eosin, Scale bar: 100 µm).

Results

Biochemical Results

Our blood biochemical analysis results are documented in Table I. Antioxidant enzyme activity (SOD and GSH-Px) was recorded as 6.84±1.19 and 589.50±57.09 in Group 3, respectively. These values were statistically significantly higher compared to Group 2 (p=0.001 and p=0.006, respectively). The level of MDA, the end product of lipid peroxidation, was highest in Group 2 and was measured as 7.32±1.03 (p<0.001). A significant decrease was observed in Group 3 (p<0.001). Considering the pro-inflammatory cytokine (IL-1β, IL-6, and TNF-α) levels it was measured as 13.68±1.73, 22.37±3.28 and 628.99±94.09 in Group 3, respectively. All proinflammatory values were found to be suppressed compared to Group 2 (p=0.001, p<0.001 and p=0.001, respectively).

Histopathological Results

In our histopathological analysis, it was observed that there was a significant improvement in the tissue damage level in Group 3 compared to Group 2. The highest endometrial epithelial glandular tissue damage score was in Group 2 and was measured as 2.3±0.31 (p<0.001). A significant decrease in epithelial cell degeneration and leukocyte concentration was observed in Group 3 compared to Group 2. Endometrial epithelial glandular tissue damage score was recorded as 1.07±0.26 in Group 3 (p<0.001). Similarly,

the highest endometrial stromal damage score was in Group 2 and was measured as 2.22±0.32 (p<0.001). It was observed that there was a decrease in the level of stromal edema and vascular congestion in Group 3 compared to Group 2. Endometrial stromal damage score was recorded as 1.2±0.24 in Group 3 (p<0.001, Figure 1). When the total scores were examined, it was reported as 1.14±0.25 in Group 3, which was significantly decreased compared to Group 2 (p<0.001, Table II).

Discussion

Approximately one million women worldwide are waiting to be treated for infertility due to the absence of a uterus (Mayer-Rokitansky-Küster-Hauser syndrome, hysterectomy due to postpartum bleeding, large myomas or malignancies), or the presence of a dysfunctional uterus (sepsis, myomic uterus or Asherman syndrome). This patient group has no genetic or gestational chance of becoming a mother, and the only treatment option reported today is uterine transplantation[3,7,8]. It is estimated that at least 80 uterus transplantations have been performed worldwide to date. However, current published scientific data reports[19] that there were 24 live births after uterus transplantation. Unsuccessful uterus transplantation may be encountered due to complications related to surgical procedures such as bleeding, vaginal cuff dehiscence, urinary system, or adjacent organ injuries. However, ischemia-reperfusion injury occurring in solid organ transplantations is closely related to graft dysfunction and rejection[7].

Ischemia-reperfusion injury, which arises with the reperfusion of tissues and paradoxically leads to highly harmful effects, is a highly complex condition[20,21]. In ischemic tissue, where anaerobic metabolism is dominant, a decrease in intracellular pH and adenosine triphosphate is observed. Consequently, ATPase-dependent ion channels cannot perform their functions adequately. Secondary to this situation, an increase in intracellular and mitochondrial calcium levels is observed. These changes in calcium levels activate calcium-dependent cytosolic proteases and convert the enzyme hypoxanthine dehydrogenase into xanthine oxidase[20,21]. Upon the reperfusion of ischemic tissue, oxygen that infiltrates the tissue becomes oxidant through chemical reactions mediated by xanthine oxidase, resulting in a significant production of reactive oxygen radicals in the environment. In this case, the rapidly increasing levels of reactive oxygen radicals significantly surpass the antioxidant mechanisms such as GSH-Px, SOD, and catalase[1,21]. On the other hand, ischemia-reperfusion injury also leads to acute inflammatory response through neutrophil activation. This inflammation increases microvascular permeability, elevates cytotoxic protein levels, and accelerates the production of reactive oxygen radicals[6,21]. Reactive oxygen radicals, which are present in high amounts in the environment, play a key role in transplant tissue damage through lipid peroxidation, protein oxidation, and DNA strand breaks that lead to apoptosis[5].

Dexmedetomidine is a lipophilic imidazole compound and can reach an effective dose curve in a short time with its rapid distribution phase[6].

Table II. Comparison of endometrial epithelial glandular and endometrial stromal changes in rat groups.

	Groups	n	Mean±SD	Min-max	*p*-value	Post-hoc *p*-value
Endometrial epithelial glandular damage	1	8	0.09±0.03	0.04-0.13	**<0.001***	1-2: <0.001*
	2	8	2.3±0.31	1.88-2.68		1-3: <0.001*
	3	8	1.07±0.26	0.57-1.31		2-3: <0.001*
Endometrial stromal damage	1	8	0.11±0.03	0.07-0.17	**<0.001***	1-2: <0.001*
	2	8	2.22±0.32	1.75-2.62		1-3: <0.001*
	3	8	1.2±0.24	0.68-1.41		2-3: <0.001*
Total scores	1	8	0.1±0.03	0.04-0.17	**<0.001***	1-2: <0.001*
	2	8	2.26±0.31	1.75-2.68		1-3: <0.001*
	3	8	1.14±0.25	0.57-1.41		2-3: <0.001*

Test: One-Way Analysis of Variance (ANOVA). Differences between groups were examined with Post-hoc Tukey HSD or Tamhane's T2. *Statistically significant (p<0.05).

It has been reported[14] that the half-life of this molecule, when administered intravenously, is approximately 6 minutes long, and the elimination half-life does not exceed 3 hours. In addition to its use for sedation in anesthesia clinics, operating rooms, and intensive care units, recent studies in the literature have shown that dexmedetomidine has important protective properties against ischemia-reperfusion injury. The molecular basis of this protective effect against oxidative damage cannot be clearly explained[6]. Dexmedetomidine seriously suppresses the immune system by reducing proinflammatory cytokines and inhibiting neutrophil infiltration in ischemia-reperfusion injury. On the other hand, it has effects on regulating NO levels[22]. However, dexmedetomidine causes a significant increase in antioxidant enzyme levels[23]. In addition, dexmedetomidine inhibits apoptosis secondary to ischemia-reperfusion injury by upregulating Bcl-2 expression and suppressing Bax expression[24]. On the other hand, experimental studies[22] have shown that dexmedetomidine reduces free oxygen radical formation by activating presynaptic α2 receptors, preventing the increase in plasma catecholamine levels in ischemia-reperfusion injury.

Hall et al[25] observed that intracisternal dexmedetomidine prevented the increase in plasma norepinephrine in an intracranial hypertension rat model. They attributed this to reducing MDA levels, maintaining cardiac function, and improving ECG abnormalities. Taniguchi et al[26] demonstrated in their study evaluating endotoxin-exposed rats that dexmedetomidine modulated cytokine production from macrophages and monocytes and significantly reduced mortality rates. In the same study, it was concluded that dexmedetomidine administration could be a beneficial agent in sepsis. Sezer et al[27] observed that dexmedetomidine could prevent liver damage related to local and systemic inflammatory response in experimentally developed sepsis models. In the study conducted by Kim et al[14], they reported that dexmedetomidine showed protective activity against renal ischemia-reperfusion damage by inhibition of NOD-like receptor protein 3 inflammatory activation in diabetic rats. In Lim et al[28] rat models of hepatic ischemia-reperfusion, it was observed that dexmedetomidine alleviated oxidative damage by suppressing the inflammation response and apoptosis by decreasing IL-6 and upregulating Bcl-2 expression. Similarly, Sun et al[29] reported that dexmedetomidine showed anti-apoptotic activity on human epithelial cells by inhibition of caspase activation; moreover, they reported that it showed anti-inflammatory activity by significantly reducing the expression of COX-2 as well as the production of prostaglandin E2 and TNF-α. Although apoptotic indexes were not evaluated in our study, it was observed that dexmedetomidine significantly suppressed the inflammatory response resulting from uterine ischemia-reperfusion injury. Another positive role of dexmedetomidine in oxidative damage is strengthening the antioxidant systems. It is also an effective scavenger for reactive oxygen radicals[23]. In the study conducted by Dong et al[15] by creating a cardiac ischemia-reperfusion model, they reported that dexmedetomidine showed antioxidant activity by causing an increase in SOD activity, resulting in a decrease in MDA level and having a protective effect on heart tissue against oxidative stress. In another study[23], they also demonstrated that the administration of dexmedetomidine in rats with skeletal ischemia-reperfusion injury increased SOD, GSH, and catalase activity, creating a stronger antioxidant activity than vitamin E. In the study of Kuyrukluyıldız et al[30], they similarly reported that dexmedetomidine showed a protective function against oxidative damage in the stomach by increasing antioxidant activity. Similarly, in our study, it was observed that the administration of dexmedetomidine caused a significant increase in SOD and GSH-Px, which are very powerful antioxidant enzymes.

Limitations

The most important missing feature of our study is that the possible side effect profile of dexmedetomidine in rats was not evaluated. On the other hand, the lack of detailed immunohistochemical staining and the inability to measure apoptotic indices due to technical limitations are the other aspects that were missing in our study.

Conclusions

As a result, our study was the first study in English literature to evaluate the effectiveness of dexmedetomidine in rats created as a uterine ischemia-reperfusion model. According to the data obtained in our study, dexmedetomidine was found to be a highly effective pharmacological agent in suppressing inflammation secondary to uterine ischemia-reperfusion injury, improving oxidative stress, and protecting uterine tissue. For our study to provide guidance for routine obstetrics and gynecology practices, there is a need for large-scale randomized studies.

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Conflict of Interest
The authors declare that they have no conflict of interest to declare.

Ethics Approval
This experimental study was performed after receiving approval from the Local Experimental Animal Ethics Committee of Tokat Gaziosmanpasa University (2022 HADYEK-22) (23-1-2023).

Informed Consent
Not applicable.

Funding
This study did not receive any financial support from elsewhere.

Acknowledgments
The authors would like to thank the staff of the Experimental Animals Research Unit of Tokat Gaziosmanpasa University for providing valuable support.

Authors' Contributions
Conception and design of the study: V.K., T.K., S.K., M.K. Experimental protocols: V.K., T.K., S.K., Laboratory examinations: V.K., V.U., F.G., M.K., Acquisition of data: V.K., T.K., S.K., M.K, M.G.B. Analysis, and interpretation of data: V.K., T.K., S.K., H.T., M.G.B. Drafting the article: V.K., V.U., F.G., M.K., H.T, S.K., T.K. Critical review: V.K., H.T., T.K., S.K. All authors read and approved the final version of the manuscript.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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