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Effects of boric acid on reproductive hormones and utero-ovarian tissues in female rats: A dose-response study

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ABSTRACT

Boric acid is a widely used form of boron, and its potential as a therapeutic agent is being increasingly investigated. This study aimed to evaluate the dose-dependent effects of oral boric acid administration on reproductive hormone levels and the histopathological architecture of ovarian and uterine tissues in female rats. Twenty-four young adult female rats were randomly divided into four groups: control, low-dose boric acid (10 mg/kg), medium-dose boric acid (100 mg/kg), and high-dose boric acid (1000 mg/kg). Boric acid or saline was administered orally once daily for 21 days. Serum estradiol and progesterone levels were measured and ovarian and uterine tissues were examined histopathologically. Low and medium doses of boric acid did not significantly alter estradiol or progesterone levels compared to controls ($p>0.05$). However, high-dose boric acid administration significantly decreased estradiol levels while increasing progesterone levels ($p<0.05$). Histological evaluation revealed dose-dependent pathological changes, including edema, vascular congestion, follicular degeneration in the ovaries, and hyperplasia of endometrial glands in the uterus, particularly prominent at high doses. Boric acid exposure at high doses could disrupt the hormonal balance and induce significant structural damage in reproductive tissues, suggesting a potential risk to female reproductive health. These findings emphasize the necessity for cautious evaluation of boric acid exposure levels, particularly given its widespread industrial and medical applications.

1. Introduction

Boric acid, commonly used in industrial and medical products, is a naturally occurring mineral [1]. Boron, which has been widely used in many different areas until today, has a wide variety of functions in our body, and its effects in the field of health are also of great importance [2]. Boric acid's regulatory influence on steroid hormone metabolism, particularly estrogen and progesterone, has gained increasing attention in recent years. Insufficient boric acid intake is associated with compromised bone health, an elevated risk of osteoporosis, impaired cognitive function, and a weakened immune response [3]. It also has antioxidant, anticancer, and antimicrobial properties, in addition to its role in sex hormone modulation [4]. In this context, its potential role in modulating estrogen and progesterone levels is of particular relevance to female reproductive physiology. In addition to their function in reproduction, sex steroid hormones such as progesterone and estrogen have been linked to the onset and course of several illnesses. These hormones offer protection against conditions like osteoporosis, neurodegenerative diseases, and atherosclerosis [5]. These protective effects may be influenced by micronutrients such as boron, depending on the level of exposure.

Although beneficial outcomes have been reported at low or physiological doses, boric acid exhibits dose-dependent behavior. At moderate levels, it may support hormonal balance and antioxidant defense, whereas high-dose exposure has been associated with toxicological risks [6]. Progesterone is involved in reproductive processes in females and acts in synergy with estrogen, often requiring an initial estrogen effect [7]. Increased sex hormone levels, potentially triggered by boric acid administration at appropriate doses, may support fertility, enhance muscle strength, and reduce the risk of cardiovascular, neurodegenerative, and metabolic diseases [8]. It was reported that boron can potentiate the physiological actions of 17β-estradiol, supporting the idea that its hormonal effects may occur through synergistic interactions rather than direct action [9].

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Boric acid and sodium borates are classified as Category 1B for reproductive toxicity under the CLP Regulation, labeled with "H360FD," because high-dose animal studies have shown adverse reproductive outcomes [10]. In a previous study, high-dose boric acid exposure produced testicular lesions in adult male rats characterized by inhibited spermiation, which may progress to atrophy [11]. However, current literature provides limited information on the reproductive toxicity of high-dose boric acid in the ovaries and uterus of female rats. This distinction highlights the importance of dose when evaluating boric acid's contrasting biological effects. Inorganic boron compounds (boric acid and borates) can exert toxic effects on reproduction and may have significant regulatory effects on the female hormonal system [12, 13]. These adverse outcomes have predominantly been observed under high-dose conditions, reinforcing the need to investigate dose-response relationships. Therefore, this study was designed to evaluate the dose-dependent effects of orally administered boric acid on serum estradiol and progesterone levels in female rats, along with associated histopathological changes in the ovaries and uterus.

2. Materials and Methods

2.1. Chemical

Boric acid (H_3BO_3), with a purity of ≥99.5%, was obtained from Chemistry Lab (Türkiye). Boric acid solution was prepared in 0.9% saline. The chemicals used were of analytical grade and were received without any purification processing.

2.2. Animals

Experimental procedures were approved by the Pamukkale University Animal Experiments Ethics Committee (Ethical approval no: PAUHDEK-2025/21). In this study, twenty-four young female Wistar Albino rats aging between 8-10 weeks and weighing between 180-210 g were purchased from Pamukkale University Experimental Surgery Application and Research Center. The experimental animals were housed in cages within the animal unit at a maintained temperature of 22 ± 1°C, 50% humidity, and 12-hour light/dark cycle, with consistent ventilation. They received standard rat chow and fresh drinking water ad libitum daily.

2.3. Experimental protocol

Rats were randomly divided into four groups as follows: Control, L-BA, M-BA, and H-BA (Table 1). Physiological saline (1 ml) was given orally by gastric gavage to the rats in the control group every day for 21 days. Boric acid (10 mg/kg, 100 mg/kg, and 1000 mg/kg) was given by oral gastric gavage for 21 days. The acute median lethal dose (LD50) of boric acid is approximately 3450 mg/kg in mice and 2660 mg/kg in rats [14]. Following a 24-hour after the final application, the animals were anaesthetized with intraperitoneal injection of 10 mg/kg xylazine HCl and 80 mg/kg ketamine HCl to end the 21-day experimental period. Blood samples were collected from the aorta of each rat into serum separator tubes. After centrifugation at 3000 rpm for 10 minutes at 4°C, serum was separated and collected. Estradiol and progesterone levels were measured from serum samples using the Cobas c 702 module (Clinical Chemistry, Roche Diagnostics, Switzerland).

Table 1. Groups and procedures used in experiments (n=6).

Groups	During the 21-day period	Termination of the experiment
Control group	Saline (1 ml) was given orally	On the 22nd day of the experiment, rats in all groups were sacrificed
Low dose-boric acid (L-BA)	10 mg/kg of boric acid was given orally	
Medium dose-boric acid (M-BA)	100 mg/kg of boric acid was given orally	
High dose-boric acid (H-BA)	1000 mg/kg of boric acid was given orally	

2.4. Histopathological procedures

Ovarian and uterus tissue samples intended for histopathological examination were fixed in a 10% neutral buffered formalin solution. Following formalin fixation, tissue samples were trimmed to 2-3 mm thickness and appropriate dimensions before being placed in tissue processing cassettes. These cassettes were then washed overnight in tap water and subsequently dehydrated through a graded series of ethanol (50%, 70%, 80%, 96%, and absolute), cleared in xylene, infiltrated with a xylene-paraffin mixture and then with paraffin wax (melting point 56-58°C) for 2 hours at each step, and finally embedded in paraffin blocks. Serial sections of 5 µm thickness were cut from each paraffin block using a microtome (RM 2245, Leica, Germany) and mounted onto glass slides via a water bath (HI 1210, Leica, Germany). The slides were then dried in an oven (Heratherm, Thermo Fisher Scientific, USA) for 10 minutes to prepare them for histological staining. All sections were deparaffinized and rehydrated through a series of xylene and graded alcohols (absolute, 96%, 80%, 70%, and 50%) and subsequently stained with hematoxylin and eosin (H&E) according to Luna's method [15]. The stained slides were examined using a binocular light microscope (Eclipse Ci, Nikon, Japan). Photomicrographs of selected slides were captured using a microscopic digital camera system (DS Fi3, Nikon, Japan). The histopathological lesion distributions of the uterus and ovary were evaluated semi-quantitatively at x20 magnification. Histopathological changes were scored as none (0), mild (1), moderate (2), severe (3), and extremely severe (4).

2.5. Statistical Analysis

Statistical analysis was performed using GraphPad Prism software (version 9.0, GraphPad Software Inc., USA). The Shapiro-Wilk test was used to verify the normal distribution of the data. Differences between groups were analyzed using one-way ANOVA, with Tukey's multiple comparisons test applied for post-hoc comparisons. All data were expressed as mean ±SEM. For histopathological lesion scores, the difference between the groups was determined by one of the nonparametric tests, Kruskal-Wallis, and the Mann-Whitney U test. Statistical significance was defined as a p-value of less than 0.05. The sample size for each group was n=6.

3. Results

As shown in Figure 1, oral boric acid supplementation did not exert a significant effect on estradiol levels in the low-dose boric acid (L-BA) and medium-dose boric acid (M-BA) groups compared to the control group ($p>0.05$). However, a statistically significant reduction in estradiol levels was observed in the high-dose boric acid (H-BA) group compared to control ($p=0.006$) and L-BA groups ($p=0.028$), exhibiting a dose-dependent relationship. Additionally, there is no significant difference between the M-BA and H-BA groups.

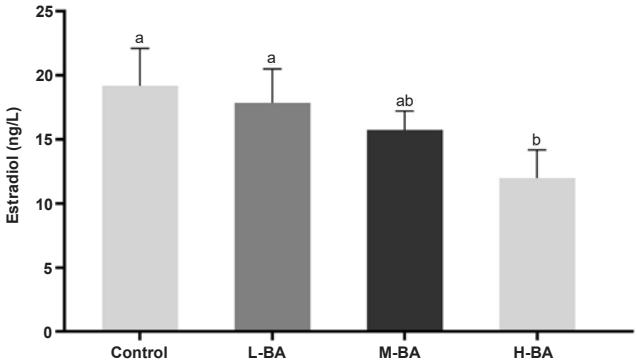

Figure 1. Serum estradiol levels in orally boric acid-administered rats.

As shown in Figure 2, oral boric acid supplementation did not exert a significant effect on progesterone levels in the L-BA group compared to the control group ($p>0.05$). However, there is a significant difference in progesterone levels between the L-BA and M-BA groups ($p=0.001$). There is a statistically significant dose-dependent increase in progesterone levels in the H-BA group compared to the L-BA and control groups ($p<0.001$). Additionally, there is no significant difference between the M-BA and H-BA groups.

As demonstrated in Figure 3, histopathological evaluation of the ovarian and uterine tissues revealed notable differences between the control and boric acid groups. In ovarian sections (A panels), the control group (A1) exhibited normal architecture with distinct

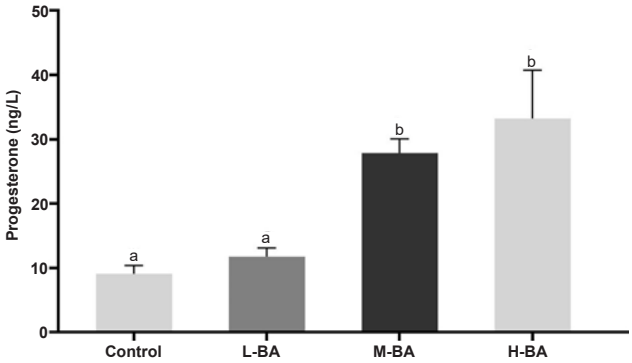

Figure 2. Serum progesterone levels in orally boric acid-administered rats. Data are presented as the mean ± standard error of the mean (SEM) for each group (n=6). Different letters (a, b) on the columns indicate a statistical difference between the groups ($p<0.05$). The treatment groups were as follows: L-BA (low-dose boric acid, 10 mg/kg), M-BA (medium-dose boric acid, 100 mg/kg), and H-BA (high-dose boric acid, 1000 mg/kg).

corpus luteum (cl) and secondary follicles (sf). In the L-BA group (A2), the overall structure remained largely preserved, although slight primordial follicle (star) prominence was observed. However, the M-BA (A3) and H-BA (A4) groups demonstrated marked pathological changes, including edema (thick arrows), vascular congestion (arrowheads), and degeneration (drop) in the ovarian tissue.

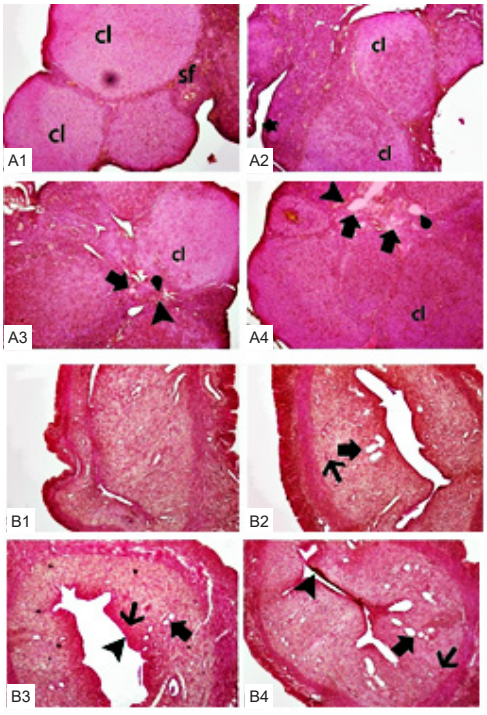

Figure 3. H&E staining of ovarian (A panel) and uterine (B panel) tissues of all groups, x20. In A panel; cl: corpus luteum, sf: secondary follicles, star: primordial follicle, drop: degeneration, edema (thick arrows), vascular congestion (arrowheads), In B panel; endometrial gland hyperplasia (thick arrows), vascular hyperemia (thin arrows), degenerative changes in the simple columnar epithelial cells (arrowheads).

In uterine sections (B panels), the control group (B1) showed normal histological features. The L-BA group (B2) exhibited mild endometrial gland hyperplasia (thick arrows) and vascular hyperemia (thin arrows). More pronounced alterations were observed in the M-BA (B3) and H-BA (B4) groups, characterized by significant hyperplasia of endometrial glands (thick arrows), severe vascular hyperemia (thin arrows), and degenerative changes in the simple columnar epithelial cells (arrowheads). These findings suggest a dose-dependent effect of boric acid on ovarian and uterine histopathology. Histopathological scores and statistical results between independent groups are given in Table 2.

4. Discussion

The present study aimed to investigate the effects of oral boric acid administration on reproductive hormone levels and the histopathological structure of ovarian and uterine tissues in female rats. The results indicated a dose-dependent effect of boric acid on serum hormone levels and reproductive tissue integrity. Boric acid caused a significant reduction in estradiol levels, while progesterone levels increased in a similar manner. Histopathological examination revealed significant degenerative changes in the ovarian and uterine tissues following boric acid exposure, and these alterations were particularly evident at high doses.

Boric acid and its associated compounds have been widely studied for their broad biological effects, including antioxidant, anti-inflammatory, and endocrine-modulating properties [16]. it is reported that boric acid (4, 25, 75 mg/kg) exhibited the estrogen-like effect in ovariectomized rats [17]. Estrogen plays an important role in the female reproductive system, bone health, the central nervous system, and cardiovascular system [18]. The findings from the present study are largely in line with previous research suggesting that boron compounds may alter steroid hormone metabolism, particularly estrogen and progesterone [19]. In our study, estradiol levels decreased in a dose-dependent manner following boric acid administration, and this reduction was especially prominent at higher doses (1000 mg/kg). This reduction could be explained by the potential suppressive effects of high concentrations of boric acid on steroidogenic cells in the ovaries, which may impair estradiol synthesis [20]. Moreover, boric acid's effect on estradiol could be due to its ability to influence enzymes involved in steroidogenesis, such as aromatase, which is responsible for the conversion of androgens to estrogens [21].

Progesterone is a sex hormone found primarily in females and is one of the most important hormones during pregnancy [22]. Additionally, progesterone plays an important role in influencing cycle length in rodents, and progesterone and estrogen act synergistically [23]. In the present study, we showed that medium (100 mg/kg) and high doses (1000 mg/kg) of boric acid significantly increased progesterone levels in a dose-dependent manner. Boric acid may have a regulatory effect on steroid hormone metabolism, particularly progesterone. This may indicate a compensatory mechanism in response to decreased estradiol production [24]. Alternatively, medium and high concentrations of boric acid may have directly stimulated the luteal cells or altered enzymatic activity in favor of progesterone production [25]. In contrast, studies on human exposure have reported no significant alterations in reproductive hormones such as FSH, LH, or testosterone at daily boron intakes of approximately 47 mg, indicating that the endocrine effects of boric acid may vary depending on dose and biological context [26].

Low-dose boric acid may contribute to tissue recovery in the reproductive system, whereas high doses have the potential to induce toxicity. It was reported that boric acid supplementation at 20 mg/kg.day reduced cyclophosphamide-induced damage in the uterus and fallopian tubes, supporting its potential protective effects at low exposure levels [27]. Similarly, It was concluded that boric acid at 20 mg/kg.day had a protective effect on the ovarian damage caused by endotoxemia induced by LPS in female rats [28]. In our study, histopathological examination revealed no significant tissue damage in the low-dose boric acid group, while medium and high doses induced marked pathological alterations. The most prominent

Table 2. Histopathological scores of utero-ovarian tissues between groups (n=6)

Çalışma	Control	L-BA	M-BA	H-BA	p value
Edema	0.42 ± 0.16^{b}	1.17 ± 0.28^{b}	1.17 ± 0.25^{b}	3.83 ± 0.17^{a}	p<0.001
Vascular congestion	0.33 ± 0.15^{c}	0.67 ± 0.2^{c}	1.50 ± 0.28^{b}	2.17 ± 0.31^{a}	p<0.01
Endometrial gland hyperplasia	0.50 ± 0.17^{b}	0.83 ± 0.22^{b}	2.50 ± 0.34^{a}	3.50 ± 0.29^{a}	p<0.001
Vascular hyperemia	0.67 ± 0.18^{c}	0.75 ± 0.43^{c}	1.83 ± 0.22^{b}	3.17 ± 0.20^{a}	p<0.01
Degenerative changes	0.33 ± 0.15^{c}	0.67 ± 0.21^{c}	1.50 ± 0.28^{b}	2.67 ± 0.30^{a}	p<0.01

Histopathological changes were scored on a scale from 0 to 4.
The values were expressed as means ± SEM (n:6)
^{a,b,c} Different letters in the same row represent statistically significant differences (p<0.05).

ovarian findings included edema, vascular congestion, and follicular degeneration, whereas uterine tissue exhibited endometrial gland hyperplasia and severe vascular hyperemia. These results indicate that boric acid may exert biphasic effects on reproductive tissues, with low doses being relatively safe or protective and higher doses causing structural disruption. Consistent with this, postnatal growth in rats has been reported to be sensitive to boron exposure at 20 mg/kg/day, highlighting the importance of evaluating dose and developmental stage when assessing toxicity [29]. In contrast, epidemiological data from Duydu et al. demonstrated no adverse reproductive outcomes in individuals exposed to approximately 24.67 mg/day of boron, suggesting that moderate exposure may not pose significant risk under human environmental conditions [30]. The degenerative tissue changes observed in our study may be due to oxidative stress induced by high concentrations of boric acid at 1000 mg/kg.day. High concentrations can disrupt the antioxidant-prooxidant balance, leading to oxidative damage in some tissues and potentially leading to toxic effects. These effects may be due to prooxidant activity (observable as protein/lipid peroxidation) or changes in antioxidant enzyme activity [31]. Therefore, the histopathological damage identified in this study may reflect the pro-oxidant properties of boric acid at elevated doses. Further studies are needed to explore this dose-dependent effect more comprehensively.

Study limitation: the study was conducted on a relatively small sample size of young adult female rats, and the findings may not be directly translatable to other species, including humans. Future research should include a larger cohort and consider different age groups to evaluate potential age-related vulnerabilities. Second, the study focused on acute, short-term exposure (21 days). The long-term effects of chronic boric acid administration on reproductive hormones and tissue morphology remain unknown and warrant further investigation. Additionally, while the study measured estradiol and progesterone, it did not assess other key hormones involved in the hypothalamic-pituitary-gonadal axis. Future studies could provide a more comprehensive hormonal profile. Finally, the study was limited to histopathological examination, and molecular and biochemical mechanisms underlying the observed changes were not explored. Further research is needed to elucidate the precise cellular pathways by which high-dose boric acid exerts its reproductive toxicity.

5. Conclusions

The current investigation revealed that low to moderate concentrations of boric acid did not induce statistically significant alterations in reproductive hormone levels or elicit notable histopathological changes. Conversely, exposure to a high dose of boric acid was correlated with substantial hormonal dysregulation and significant tissue damage. The findings of this study underscore the critical necessity of establishing safe exposure thresholds for boric acid, particularly given its prevalent utilization across diverse industrial and medical sectors. Future research should prioritize elucidating the mechanistic basis of the dose-dependent effects of boric acid, with particular emphasis on oxidative stress and the prooxidant/antioxidant balance, while also exploring its impact on inflammation, steroid hormone biosynthesis, and tissue integrity. Furthermore, long-term studies designed to evaluate the impact of boric acid on fertility and overall reproductive outcomes are necessary for a comprehensive assessment of its safety profile.

6. Conflict of interest

No conflict of interest was declared by the authors.

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