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Strain-dependent effects of *Toxoplasma gondii* on ovarian health and inflammation in a rat model

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Abstract

Toxoplasma gondii, an obligatory intracellular parasite, is the causative agent of toxoplasmosis, a widespread disease affecting approximately one-third of the global population. This study investigates the strain-specific effects of *T. gondii* infection on immune responses, reproductive physiology, and oxidative stress in Wistar rats, comparing the highly virulent RH strain to the less virulent VEG strain. The results show that the RH strain significantly reduced levels of the anti-inflammatory cytokine IL-10 ($p < 0.01$) while increasing pro-inflammatory IFN-γ ($p < 0.05$), suggesting a strong inflammatory response. In contrast, the VEG strain produced a more balanced immune profile, with no significant change in IL-10 and a moderate rise in IFN-γ. Although no visible damage to ovarian tissue was observed in any group, the RH strain resulted in a higher number of growing follicles ($p < 0.05$), while the VEG strain led to significantly larger follicles ($p < 0.05$). Both strains elevated CRP levels, with the RH strain inducing a more significant inflammatory response. However, oxidative stress markers showed no significant differences among the experimental groups. In conclusion, the findings indicate that the highly virulent RH strain elicits a strong inflammatory response, whereas the less virulent VEG strain induces a more moderate immune reaction, without causing significant damage to ovarian tissue.

Keywords Toxoplasmosis, *Toxoplasma* strains, Immune modulation, Ovarian physiology

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Introduction

Toxoplasma gondii, an intracellular parasite, causes toxoplasmosis, a widespread disease affecting nearly one-third of the global population. While felines are the definitive hosts of *T. gondii*, all warm-blooded animals, including humans, can serve as intermediate hosts [1, 2]. *T. gondii* transmission occurs through the ingestion of raw or undercooked meat from infected animals, consumption of food or water contaminated with sporulated oocysts, transplacental transmission in seronegative pregnant women, and via organ transplantation [3]. During acute toxoplasmosis, tachyzoites are detectable

in various body fluids, including milk, saliva, semen, urine, and feces. In this acute phase, tachyzoites are typically found in multiple organs and can negatively impact reproduction by disrupting the reproductive cycles of intermediate hosts, which is of considerable importance in public health and medicine [4, 5]. *T. gondii*, considered one of the most prevalent parasites globally, is a significant opportunistic pathogen in immunocompromised individuals [6, 7]. *T. gondii* strains show considerable genetic diversity, with three predominant clonal types (I, II, and III) [8]. Type I is highly virulent, causing fatal infections in mice, while Types II and III typically lead to nonlethal, chronic infections affecting the CNS and muscles. Although usually mild in healthy adults, toxoplasmosis during pregnancy can severely harm the developing fetus [9, 10]. The precise mechanism by which *T. gondii* alters reproductive parameters remains unclear. One proposed pathway involves hormonal regulation via gonadotropin levels (LH and FSH). *T. gondii* may modulate the release of corticotropin-releasing factor (CRF) through peripherally circulating cytokines, thereby inhibiting gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, ultimately leading to pituitary gonadotropin insufficiency [11, 12]. However, this proposed mechanism requires further investigation as the connection between toxoplasmosis and altered gonadotropin levels has not been definitively established.

Studies suggest that chronic toxoplasmosis in female rats results in endometriosis, impaired ovarian function, disrupted folliculogenesis, uterine atrophy, and decreased gonadal weight [13, 14]. During *T. gondii* infection, neutrophils rapidly migrate to the infection site, where they activate dendritic cells, triggering a T-helper 1 (Th1) inflammatory response. The host mounts a strong cytokine-mediated defense specific to the parasite, with interferon-gamma (IFN-γ) playing a central role. As a key Th1 cytokine, elevated levels of IFN-γ inhibit *T. gondii* replication and drive its transition from the tachyzoite to the bradyzoite stage [12, 15].

Pregnancy is regarded as an anti-inflammatory state with a Th2 bias. Any imbalance in the cytokines produced during pregnancy can lead to complications [16]. The immune response varies during pregnancy based on gestational stage and external factors, such as infectious agents. In the first trimester, certain T-lymphocyte populations induce a pro-inflammatory state, and *T. gondii* infection during this period may result in miscarriage. In contrast, a strong Th2 polarization induced by pregnancy in the third trimester can counteract the Th1 response caused by *T. gondii*, thereby preventing stillbirth and preterm birth [15, 17]. Previous studies have shown that cytokine expression profiles differ in *Toxoplasma*-seropositive women, making them useful indicators for evaluating the patho-immunological effects of latent or active infection [15]. The immunological response to *T. gondii* infection involves the production of IFN-**γ** and interleukin-2 (IL-2) by T-helper lymphocytes. During pregnancy, the maternal immune system exhibits complex adaptations to *T. gondii* infection, including the inhibition of Th1 cytokines and suppression of local inflammatory responses, which are associated with successful pregnancy outcomes by promoting maternal tolerance toward the fetus. Suppressed maternal Th1 cytokine production may facilitate the transplacental spread of *T. gondii* tachyzoites, posing risks to fetal health [5, 15]. Based on this background, the present study aims to investigate the strain-specific effects of *T. gondii* infection on immune modulation, reproductive physiology, and oxidative stress in Wistar rats.

Materials and methods

Animal

Twenty-five female Wistar rats (7–8 weeks old, 150–180 g) were obtained from Tabriz University of Medical Sciences. The animals were housed under controlled conditions (22 ± 2 °C, 12-hour light/dark cycle) with ad libitum access to standard pellet feed and water. Before the experiments, the rats were allowed a one-week period of environmental adaptation without treatment. All experimental procedures were approved by the Iran National Science Foundation (Grant No. 4020748).

Grouping and *T. gondii* infection

In this study, the rats were randomly divided into five groups ($n = 5$); a sham group that received no injection, a control group administered 1 mL of phosphate-buffered saline (PBS) intraperitoneally, a group infected with the type I strain (RH) of parasite. *gondii*, and a group infected with the type III strain (VEG).

T. gondii strains were obtained from the Toxoplasmosis Research Center at Mazandaran University of Medical Sciences, Iran, and were routinely passaged in mice for maintenance [18].

To induce infection with the RH strain of *T. gondii* in the second group, 10^4 tachyzoites/mL were injected intraperitoneally on days 0, 14, and 28. The VEG strain (Type III) group was infected following the same schedule, using 100 cysts/mL. Infection was confirmed by measuring anti-*Toxoplasma* antibody levels in rat sera, following the manufacturer's instructions.

Tissue and blood sampling

Blood samples were collected via cardiac puncture for serum hormone analysis. Following euthanasia by intraperitoneal overdose of ketamine and xylazine (two months post-infection), tissue samples were harvested. Ovarian tissues for real-time PCR analysis were placed individually in cryovials and stored at -80 °C, while other

sections were fixed in 10% formalin for histopathological evaluation.

Real-time PCR assay

To evaluate the expression of IFN-**γ** and IL-10, total RNA was extracted from ovarian tissues using Traysol reagent (Traysol: 0000124, MaxZol) following the manufacturer's protocol. Then, RNA was reverse-transcribed to cDNA (cDNA synthesis kit; YT4500, Yekta Tajhiz Azma). Specific primer pairs were designed using online software by considering different variables for each gene. Subsequently, a quantitative real-time polymerase chain reaction (qRT-PCR) was performed using cDNA and SYBR Green (RealQ Plus 2x Master Mix Green, Ampliqon) with the "Rotor-Gene Q" system. The PCR reaction program was performed in 45 cycles including denaturation, annealing, and extension at 95, 60, and 72 °C, respectively, each lasting 15 s. Reaction specificity was confirmed by analysis of melting curves. Gene expression was quantified using the 2^−ΔΔCt method, with β-actin serving as the internal reference gene [19].

Measurements of serum levels of FSH, LH, and E2

To measure serum levels of FSH, LH, and E2, blood samples were collected in glass tubes, allowed to clot, and centrifuged at 400xg for 20 min. The serum was then stored at -80 °C. Measurements were performed using enzyme-linked immunosorbent assay (ELISA) kits for FSH (0334 – 96, Monobind), LH (0234 – 96, Monobind) and E2 (4925–300 A, Monobind) [20].

Assessment of enzyme activity involved in oxidative stress

Glutathione Peroxidase (GPX) activity was assessed by mixing ovarian tissue homogenate with a working reagent and cumene hydroperoxide, measuring absorbance at 340 nm using an alcyon 300 analyzer. Superoxide Dismutase (SOD) activity was evaluated by combining a diluted sample with a Mixed Substrate and Xanthine oxidase, with readings taken at 505 nm. Malondialdehyde (MDA) levels were determined by mixing sample with phosphoric acid and thiobarbituric acid, boiling the mixture, and measuring absorbance at 532 nm against a standard curve. Finally, Total Antioxidant Capacity (TAC) was measured by mixing the sample with a chromogen and substrate, taking initial and final absorbance readings at 600 nm to calculate the difference [21].

CRP measurement

CRP levels were measured using an immunoturbidimetric method on a BT3500 autoanalyzer (Biotecnica) with a diagnostic kit according to the manufacturer's instructions. CRP values below 6 mg/L were considered within the normal reference range.

Histopathological examination

For the histopathological assessment, tissue samples were fixed in 10% buffered formalin. These samples were subsequently embedded in paraffin, sectioned to a thickness of approximately 5 µm, and stained with hematoxylin and eosin (H&E). Microscopic examination was performed using a light microscope (Olympus-CH30, Japan) to evaluate pathological changes, including inflammation, necrosis, hemorrhage, and vascular congestion, as well as the number and size of developing follicles. The histological procedures were conducted in accordance with the methods previously described [22].

Data analysis

Data were analyzed using GraphPad Prism 8 software. One-way ANOVA and Fisher's LSD post-hoc tests were used for multiple-group comparisons, and while the Student's *t*-test applied for two-group comparisons. *P*-values less than 0.05 were considered statistically significant.

Results

Real time PCR results for cytokine expression

The study demonstrates the differential immunomodulatory effects of *T. gondii* strains with distinct virulence profiles on cytokine expression in Wistar rats. The highly virulent RH strain significantly downregulated IL-10 mRNA expression ($p < 0.01$) while markedly upregulating IFN-γ mRNA expression ($p < 0.05$), indicating a strong pro-inflammatory response accompanied by reduced anti-inflammatory signaling. In contrast, the less virulent VEG strain does not significantly alter IL-10 mRNA levels compared to the control group but induced a moderate increase in IFN-γ expression, suggesting a more balanced immune response (Fig. 1).

Serum hormone levels

The serum levels of the hormones LH, FSH, and estradiol were evaluated across the experimental groups. In rats infected with the highly virulent RH strain of *T. gondii*, a significant increase in FSH levels was observed ($p < 0.05$), while LH and estradiol levels decreased; however, these reductions were not statistically significant ($p > 0.05$). In contrast, infection with the less virulent VEG strain led to a significant decrease in FSH levels compared to the control group ($p < 0.05$), whereas LH and estradiol levels showed an upward trend, though the increases were not statistically significant (Fig. 2).

Oxidative stress analysis

Assessments of GPX, SOD, MDA, and TAC revealed no significant differences in enzyme activities or oxidative stress markers among the experimental groups ($p > 0.05$). These results suggest that *T. gondii* infection did not

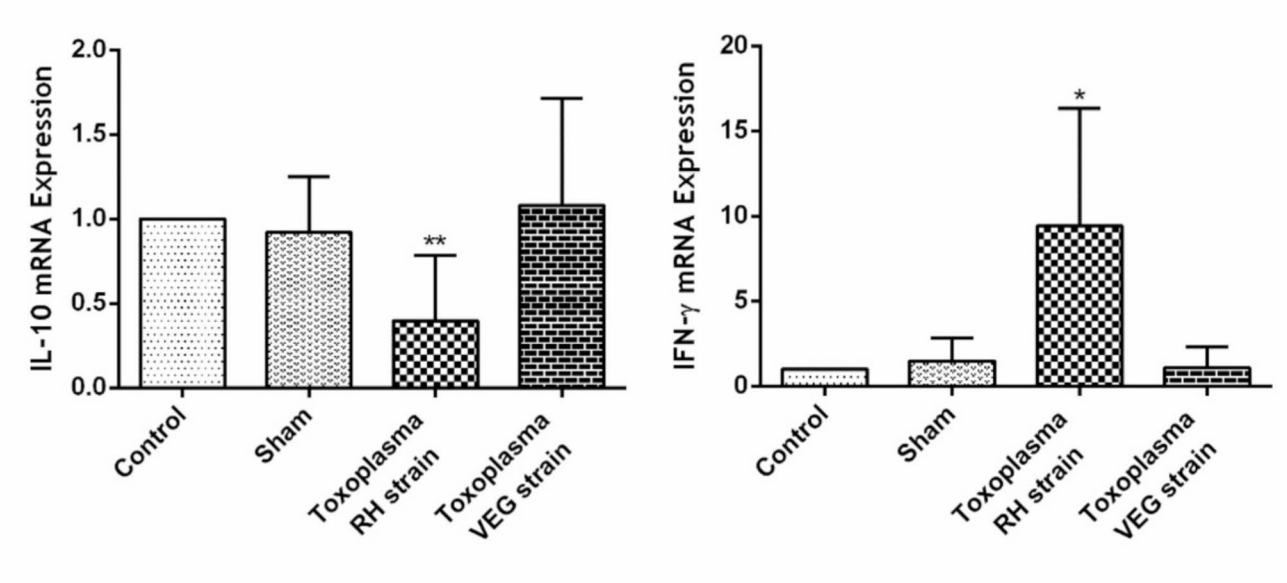

Fig. 1 IFN-**γ** and IL-10 levels in different experimental groups

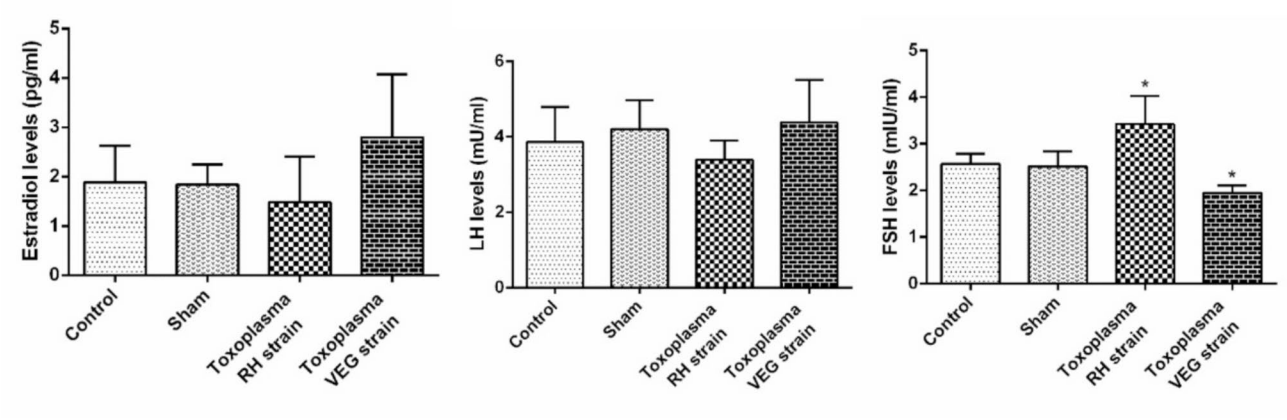

Fig. 2 LH, FSH, and estradiol levels in different experimental groups

notably affect oxidative stress parameters under the conditions tested (Fig. 3).

Serum CRP levels in response to *T. gondii* infection

The findings indicate that both strains of *T. gondii* elicit an inflammatory response, as demonstrated by increased CRP levels; however, the type I strain (RH) triggers a significantly stronger response than the type III strain (VEG) (Fig. 4).

Histopathological analysis

The histopathological findings are summarized in Table 1; Fig. 5. Ovaries from the control and sham groups exhibited a normal parenchymal structure, with no evidence of pathological lesions, including inflammation, necrosis, hemorrhage, or vascular congestion. Similarly, the RH and VEG groups exhibited normal ovarian structures devoid of such pathological alterations. All groups exhibited primary follicles, consisting of single-layered cuboidal granulosa cells, and secondary follicles, distinguished by multi-layered cuboidal granulosa cells. Notably, the RH group presented a significantly higher number of growing follicles compared to the other groups ($p < 0.05$). In contrast, the VEG group demonstrated significantly larger growing follicles ($p < 0.05$) relative to the other groups.

Discussion

This study aimed to investigate the strain-specific impacts of various *T. gondii* strains on immune responses and reproductive health in Wistar rats, specifically focusing on cytokine expression, oxidative stress, and hormonal alterations. The findings highlight significant strain-dependent differences in how different *T. gondii*

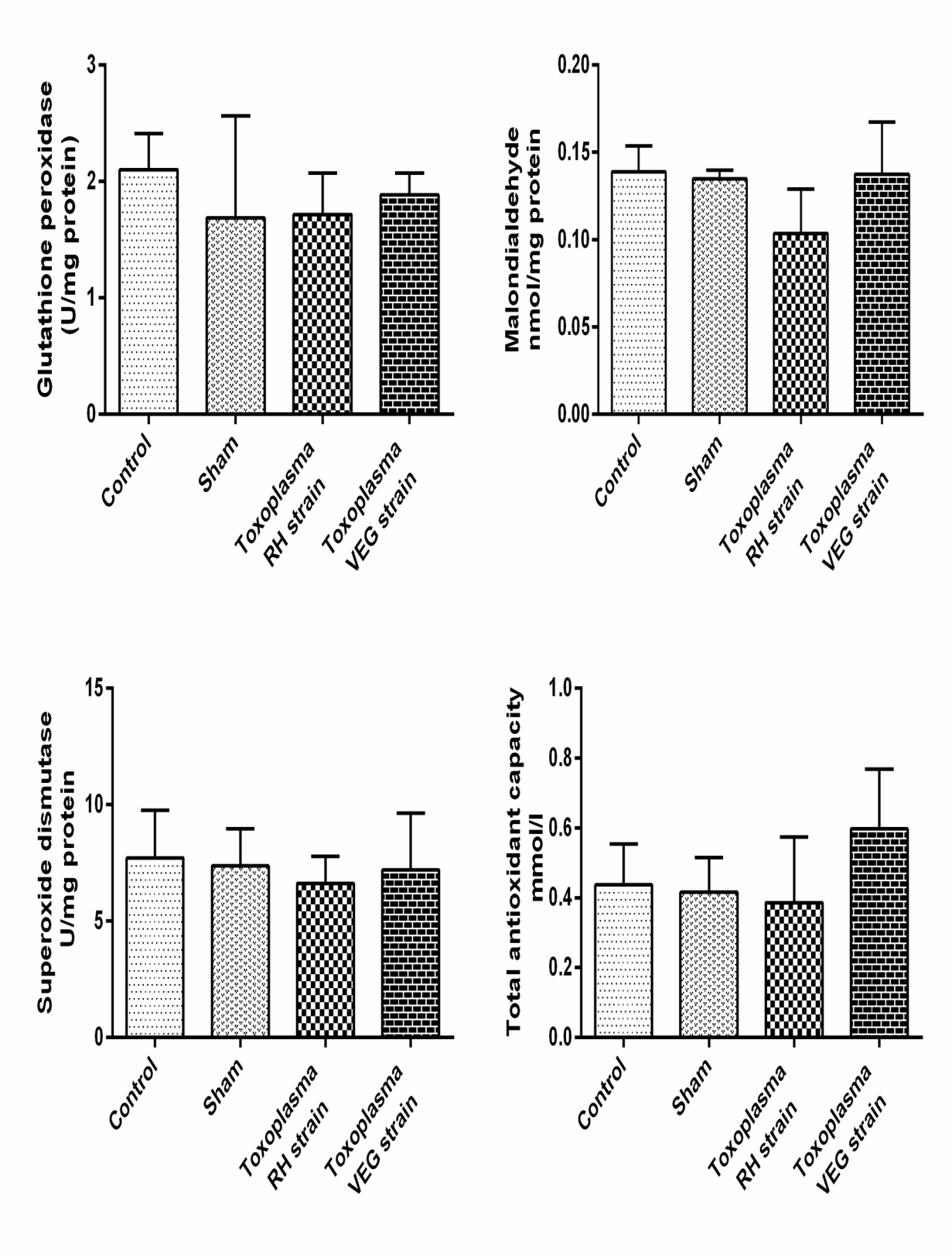

Fig. 3 GPX, SOD, MDA, and TAC levels in different experimental groups

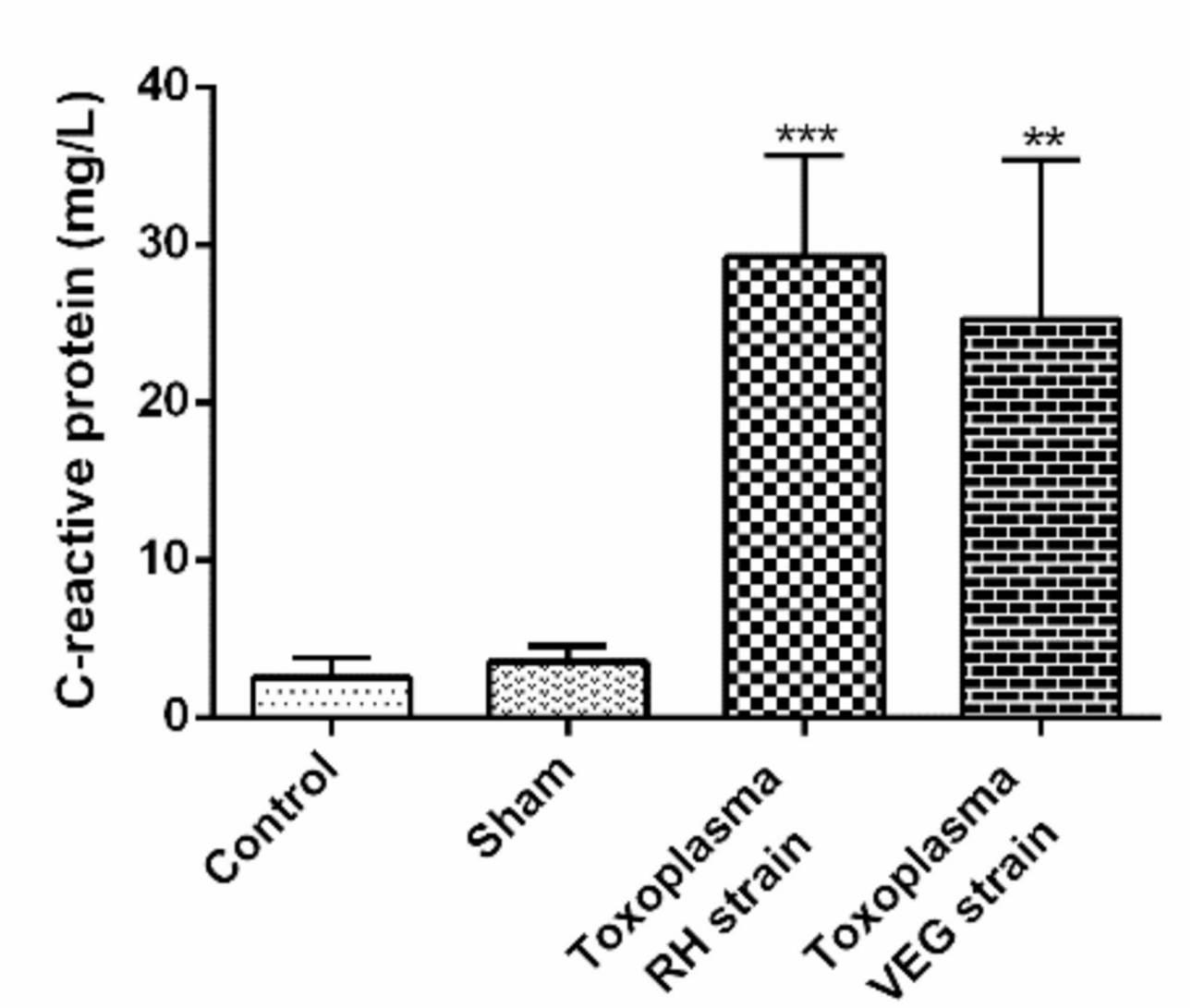

Fig. 4 Serum CRP levels in different experimental groups

Table 1 The numbers and sizes of the growing follicle (Mean ± SD) in various experimental groups

Groups	Numbers of the follicles	Size of the follicles
Sham	$4.41 \pm 0.38^{a*}$	3.91 ± 0.72^{a}
Control	4.5 ± 0.66^{b}	3.25 ± 0.25^{b}
RH	7.58 ± 62^{abc}	4.08 ± 0.62^{c}
VEG	4.75 ± 0.25^{c}	10.41 ± 0.38^{abc}
***p*-value**	0.00	0.00

*the same letters show the significant differences

strains modulate immune responses and impact reproductive. Hackmon et al. reported that IFN-γ plays a role in preeclampsia in pregnant women [23]. Additionally, inflammation and parasite proliferation can impair white matter and block the aqueduct of Sylvius in fetal brain tissue, resulting in neurological abnormalities such as hydrocephalus, microcephaly, and psychomotor retardation [24]. Fetal infection during the second trimester may result in less severe manifestations, including splenomegaly, hepatomegaly, cerebral calcifications, pneumonitis, anemia, epilepsy, thrombocytopenia-induced petechiae, rash, and retinochoroiditis. *T. gondii* infection can also disrupt ovarian cycles and potentially reduce fertility. In normal rats, infection may inhibit ovulation [25]. Given that toxoplasmosis is a systemic infectious disease, it may likewise disrupt normal ovarian function. Chronic infection can also influence noradrenergic mechanisms in the hypothalamus, contributing to decreased reproductive activity [26]. Histological analyses of infected female mice have demonstrated significant hypertrophy of the

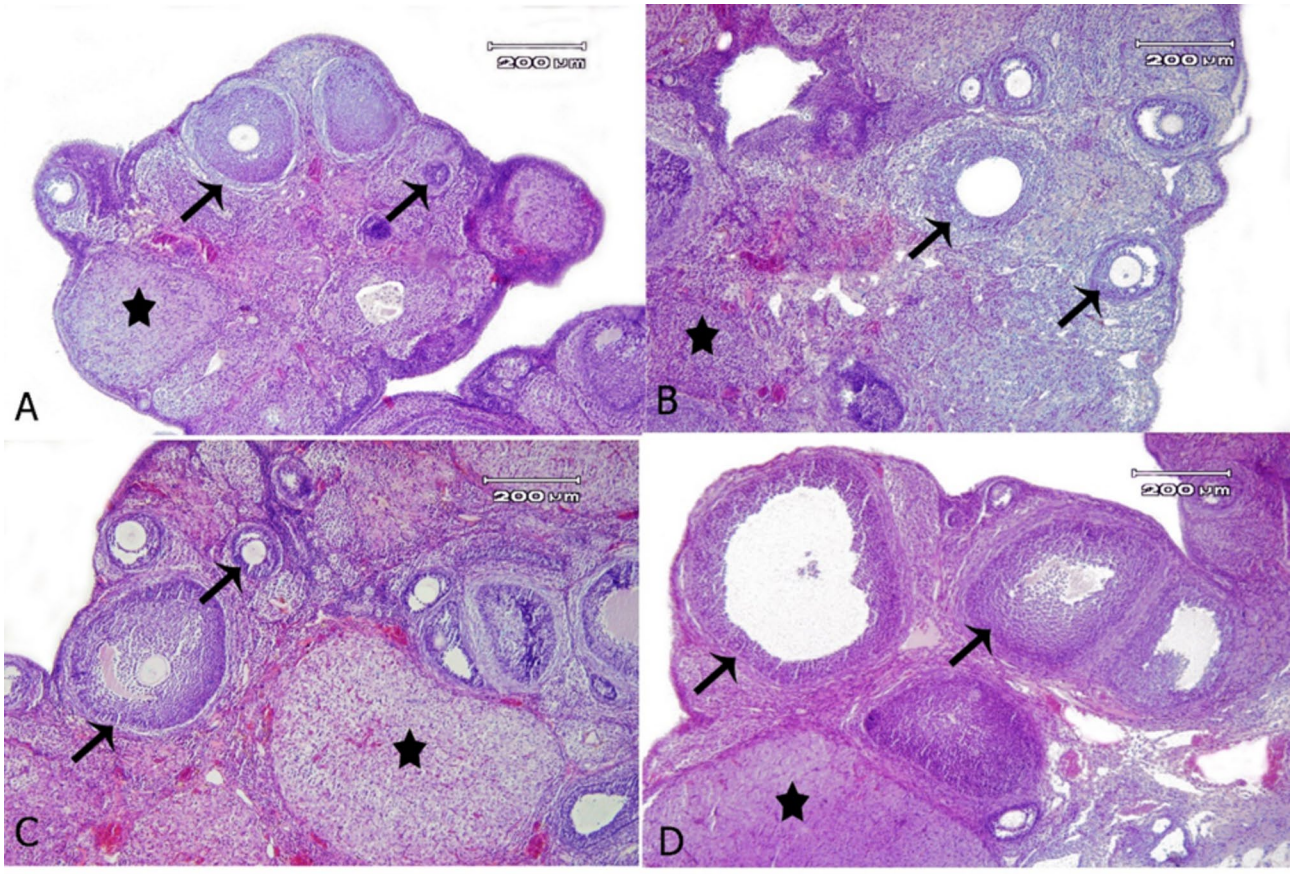

Fig. 5 Histological analysis of ovarian tissue in experimental groups (H&E stain). **A**: Sham group displaying a normal ovarian parenchymal structure. **B**: Control group exhibiting a normal ovarian parenchymal structure. **C**: RH-recipient group showing a normal ovarian architecture. **D**: VEG-recipient group presenting a normal ovarian structure. Arrows indicate developing follicles, varying in number and size. The RH group shows an increased number of growing follicles, while the VEG group is characterized by larger growing follicles. Asterisks indicate the corpus luteum

endometrium and myometrium. Fux et al. reported that *T. gondii*-infected mice exhibited reduced folliculogenesis and a decreased number of corpora lutea in the ovaries compared to uninfected controls [27]. Coutinho et al. identified placental damage, rather than direct fetal injury, as the principal cause of fetal death in infected animals [28]. Blader and Saeij [29] reported that IFN-γ is produced in response to parasite-induced IL-12 expression, a critical cytokine for resistance to both acute and chronic *T. gondii* infections. Shiono et al. demonstrated that IFN-γ produced following *T. gondii* infection could lead to abortion in wild-type pregnant mice [23]. Our results show a clear distinction between the effects of the highly virulent RH strain and the less virulent VEG strain on cytokine expression. The highly virulent RH strain significantly suppressed anti-inflammatory IL-10 mRNA expression while markedly upregulating pro-inflammatory IFN-γ mRNA expression. In contrast, the VEG strain did not significantly alter IL-10 levels but induced a moderate increase in IFN-γ, suggesting a less intense Th1-type immune response. These findings align with previous research indicating that *T. gondii* strains with different virulence profiles distinctly modulate host immune responses. Type I strains like RH are hypervirulent, often provoking severe inflammation and acute disease, while Type III strains such as VEG typically induce chronic, latent infections with milder immune responses [23]. Assessment of oxidative stress and antioxidant defense mechanisms further enhances our understanding of *T. gondii* strain effects. Evaluating enzyme activities, such as GPX and SOD, alongside measurements of MDA and TAC levels, provides insights into the oxidative stress status of ovarian tissues. Although specific values were not presented, elevated oxidative stress is known to cause tissue damage and reproductive dysfunction. The RH strain's pro-inflammatory profile likely correlates with increased oxidative stress, resulting in greater ovarian tissue injury than observed with the VEG strain. Hormonal analysis focusing on FSH, LH, and E2 levels is essential for understanding the reproductive implications of *T. gondii* infection. Alterations in these hormones can indicate disruptions in normal ovarian function and reproductive cycles. While specific data on hormonal levels were not provided, it is plausible that the inflammatory

responses and oxidative stress induced by different *T. gondii* strains suggest that the RH strain may lead to greater hormonal imbalance. Chronic inflammation and oxidative stress can lead to hormonal imbalances, affecting folliculogenesis, corpus luteum function, ultimately impairing fertility. Reduced IL-10 levels associated with the RH strain might contribute to persistent inflammation, potentially leading to more pronounced hormonal disruptions compared to the VEG strain. Overall, the differential effects on cytokine expression and oxidative stress correlate with strain-specific impacts on reproductive health. The pro-inflammatory and oxidative stress-inducing properties of the RH strain may lead to more severe reproductive consequences, including impaired folliculogenesis, altered ovarian function, and potential disruptions in reproductive cycles. Conversely, milder response may result in less pronounced reproductive impairment. These findings underscore the importance of considering strain-specific effects when evaluating the impact of *T. gondii* infections on reproductive health. The potential for varying degrees of reproductive impairment based on the virulence of different strains highlights the need for tailored approaches in managing and treating *T. gondii* infections, particularly concerning reproductive health.

Estradiol is essential in various aspects of pregnancy, emphasizing its critical importance during gestation. Qiu et al. demonstrated that the reduction in Treg cells induced by *T. gondii* infection is attributed to Treg apoptosis, which is mediated by the parasite [30]. During the early stages of embryonic development, cytotoxic processes can lead to an increase in follicular atresia. If steroid concentrations increase in infected mice, it may lead to physiological imbalances in the hypothalamic-hypophysial axis of the ovary, eventually inhibiting the secretion of GnRH, LH, and FSH, hormones necessary for ovarian steroid synthesis [31] An increase in steroid synthesis may cause hypertrophy of granulosa and theca1 cells, leading to both physiological and morphological alterations in the follicle. These changes can ultimately result in follicular cell apoptosis [32] Cell adhesion and interactions among granulosa cells are crucial for effective cell signaling, intracellular substrate transfer, and the maintenance of homeostasis. Disruption in these processes increases intercellular space among granulosa cells, contributing to deficiencies in proliferation and maturation [33]. Additionally, macrophages populations may be increased in the uterus and ovaries in of hosts during toxoplasmosis infection [31].

Conclusion

This study provides a comprehensive analysis of the distinct effects of different *T. gondii* strains, specifically Type I (RH) and Type III (VEG), on Wistar rats. Our findings reveal that the highly virulent RH strain elicits a significant pro-inflammatory response, evidenced by a marked increase in IFN-γ expression and a reduction in IL-10 levels, indicating a pronounced inflammatory state. In contrast, the less virulent VEG strain induces a more moderate IFN-γ increase without significantly altering IL-10 levels, suggesting a milder inflammatory response. These strain-specific immunomodulatory differences are likely associated with variations in oxidative stress and tissue damage, with the RH strain potentially leading to greater oxidative stress and reproductive disruption compared to the VEG strain. These results underscore the importance of considering strain-specific effects in the management of *T. gondii* infections and emphasize the need for further research to elucidate the precise mechanisms by which different strains impact oxidative stress and hormonal balance. Overall, this study enhances our understanding of how *T. gondii* strain virulence influences immune responses and reproductive health, providing a basis for more targeted therapeutic strategies.

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Author contributions

Conceptualization, E.A, M.M, J.R, and A.P.; methodology, R.M, K.M, N.N.Y, M.K, and B.G; software, M.M, A.P, J.R, M.K and A.N; validation, E.A, M.M, A.N, and J. R.; investigation, M.M, N.N.Y, A.P, A.N, M.K, and B.G; writing—original draft preparation, R.M, K.M, N.N.Y, M.K, A.N, and B.G; writing—review and editing, E.A, A.P, M.M and J.R.; supervision, E.A; funding acquisition, E.A.; All authors have read and agreed to the published version of the manuscript.

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Data availability

Data supporting the conclusions of this article are included within the article.

Declarations

Ethics approval and consent to participate

All the protocols of the present study were ethically approved by Iran National Science Foundation (No. 4020748) and local ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.AEC.1403.051).

Consent for publication

Not applicable.**Availability of data and materials**.

Competing interests

The authors declare no competing interests.

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