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Review Article

The Impact of Toxoplasmosis Infection on the Reproductive ability of Men

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Abstract

Toxoplasma gondii infection spreads systemically, leading to cyst formation in organs including the brain, eyes, and testicles. To ensure its survival, reproduction, and dissemination, the parasite alters host substance production and concentration and produces compounds that damage host tissues and support stable cyst formation. Toxoplasmosis infection is prevalent among men, although women exhibit higher infection rates. The presence of different parasite stages, such as Bradyzoite or Tachyzoites, can result in significant host complications, including impaired fertility. These complications arise due to alterations in sex hormone concentrations, destruction of testicular tissue, and negative impacts on sperm composition and vitality. Additionally, indirect effects have been observed through interactions between the parasite and medications administered to enhance male sexual function. Monitoring changes in sex hormone and stimulant levels reveals a close alignment with the stages of the parasite's life cycle. This pattern often weakens the host's immune defences and, in many cases, adapts them to support the parasite's survival and reproduction. Even when the host's immune capacity is high, the parasite may still control the transition to dormant phases. The mechanism by which T. gondii change reproductive parameters is not precisely determined, and the first proposed pathway is the effect of hormonal regulation through the concentrations of gonadotropin-stimulating hormones (LH and FSH), which regulate the entire spermatogenesis process. The second pathway, through epigenetic pathways, which alter the methylation of certain specific genes that regulate spermatogenesis, and thus gene expression.

Keywords: toxoplasmosis; sex hormones; reproductive ability; fsh; lh

Introduction

T. gondii is a zoonotic parasite where cats are the final host and the main vector of the parasite that inhabits different habitats of birds and mammals and infects different parts of the body, where it is a slow-reproducing dormant (Bradyzoite) phase, which can cause many pathological complications (Kim et al., 2024). While most individuals infected with T. gondii do not exhibit overt health consequences, latent and chronic toxoplasmosis can result in involuntary changes in behaviour, personality, and hormone concentrations (Sanchez and Besteiro, 2021). These behavioural changes appear to differ by gender. For instance, infected men may demonstrate increased suspicion, jealousy, and control (Bahreini et al., 2022), whereas infected women may exhibit higher moral values and perseverance. These observations indicate a potential influence of infection on personality traits (Lyons et al., 2024).

Molecular and pathogenic responses to chronic infections exhibit sex-specific differences. Females typically develop a greater number of parasite cysts and demonstrate reduced responsiveness to treatment compared to males, suggesting increased tolerance to parasite infections. Conversely, males tend to present with more necrotic lesions, higher parasite burdens, and lower mortality rates, indicating greater resistance to infection (El-Sayed et al., 2025). These distinctions are attributed to differences in immune response, as males are capable of producing higher and more rapid levels of interferon-gamma (IFN-γ) and interleukin-12 (IL-12) (Moghaddami et al., 2024). T. gondii infection may impair several indicators of reproductive capacity. It can decrease the ratio of testicular weight to body weight, as well as reduce sperm motility and viability rates. Infection with T. gondii also enhances the expression of genes involved in the production of male hormones. This effect may influence foetal sex determination during early pregnancy, as the male hormone testosterone mediates sexual differentiation (Al-Ardi, 2022). Although the exact mechanism by which Toxoplasma alters reproductive parameters is unknown, the first pathway that has been suggested is the effect of hormonal regulation through the concentrations of gonadotropin-

stimulating hormones (LH and FSH), which control the entire spermatogenesis process (Hussein and Mohammed, 2022). Long-term stress caused by infection inhibits the activity of the hypothalamic axis by secreting stress hormones that lead to decreased LH secretion, and thus to decreased spermatogenesis (Hussein, 2023). Infection may increase (through peripheral cytokines) the secretion of corticotropin-releasing factor (CRF, a neuropeptide that regulates stress response) by hypothalamic neurones and, in response, inhibit the secretion of gonadotropin-stimulating hormone (GnRH) from the h This cascade directly causes hypogonadism in the pituitary gland. However, this putative mechanism has not been investigated further, and no link has been found to toxoplasmosis. with a reduced level of gonadotropin stimulant (Al-Ardi, 2021). The second pathway involves epigenetic mechanisms that modify the methylation of specific genes regulating spermatogenesis, thereby influencing gene expression. Pathogens and eukaryotic host cells have co-evolved, enabling pathogens to exploit host cells for survival, reproduction, and immune evasion (Li et al., 2024). Through manipulation of epigenetic processes, pathogens can alter the host cell's immune response, which may result in chronic infections. Notably, certain epigenetic pathological changes may be reversible or preventable if thoroughly understood, offering considerable therapeutic potential (Tabares Tejada and Cardona Maya, 2025).

The effect of infection on the concentrations of sex hormones

Testosterone levels

Testosterone and its derivatives, dihydrotestosterone and dehydroepiandrosterone, are androgens primarily produced in the male gonads, adrenal glands, and brain. Testosterone exerts its effects by binding directly to androgen receptors in various target tissues. Androgens are essential for the development of male secondary sexual characteristics, reproductive function, and foetal testicular maturation. Additionally, in the brain, testosterone functions as a neuroprotective hormone (Abdoli et al., 2024). Testosterone levels are markedly correlated with antibody concentrations (IgG) of the T. Gondii, which fluctuate based on the parasite strains or the infected individuals (Hegazy et al., 2024). Infection with parasites has been noted to enhance testosterone production and induce the overexpression of messenger RNA (mRNA) for luteinising hormone receptor (LHR) (Latifi et al., 2025).

Serum lactate dehydrogenase levels rise, and seminal vesicle fructose concentrations fall in tandem with this sharp rise in the male hormone's concentration. The rise in light fat (cholesterol) concentrations is one of the key findings (Flegr et al., 2008). Acute and new parasite infections, as well as the presence of the parasite antibody IgG in the blood serum, are accompanied by these fluctuations in levels and concentrations, but these effects quickly reverse, and the sugar returns to normal. Male hormone levels and their derivatives fall during late and chronic infection, with a normal level occurring on the twentieth day following infection (Eslamirad et al., 2013).

Luteinizing hormone (LH) level

The hypothalamus, a part of the brain, produces a stimulating hormone known as gonadotropin-releasing hormone (GnRH). GnRH signals the pituitary gland to release luteinizing hormone (LH), one of the main gonadotropins (Galván-Ramírez et al., 2014). LH plays a crucial role in the reproductive systems of both males and females. In females, it regulates the release of estrogen and progesterone from the ovaries, while in males, it stimulates testosterone production in the testicles and supports spermatogenesis. Additionally, LH helps regulate germ cell differentiation and, through increased testosterone, contributes to the development of male secondary sexual characteristics, such as beard growth and a deepened voice (Al-Masoudi et al., 2018). LH secretion increases in several physiological and pathological conditions, including Klinefelter syndrome, testicular tissue damage, and chemotherapy. Elevated FSH and LH levels have also been reported during chronic infection, often with reduced male hormone levels (Jabbar et al., 2023). This may result from primary hypogonadism, as T. gondii infection can activate the adrenal-pituitary-hypothalamus (HPA) axis, which in turn alters the gonad-pituitary-hypothalamus axis and adjusts gonadotropin levels. This is further supported by higher concentrations of luteinizing hormone in urine compared to serum (Oduwole et al., 2021).

Follicle-stimulating hormone (FSH) levels

Follicle -stimulating hormone levels can be elevated by a number of reasons, all of which are linked to a reduction in the testicles' functional capacity. Chronic infection with T. gondii has also been shown to abruptly increase FSH levels (Altemeemi et al., 2021).

Cortisol hormone levels

Cortisone (glucocorticoid) is secreted by the adrenal cortex and works through a signal-inducing pathway that begins when the hormone binds to specific cell receptors, stimulating or inhibiting proteins manufactured by the glucocorticoid response of specialised tissues (Andreou et al., 2025). Cortisone (a glucocorticoid) is secreted by the adrenal cortex. It acts as a signal by binding to specific cell receptors. This process stimulates or inhibits the production of proteins through the glucocorticoid response in specialized tissues (Andreou et al., 2025).

Studies have shown that infection raises cortisone levels. Cortisone stimulates the formation of slow-reproducing tachyzoites and cysts. This process releases large quantities of parasite antigens, especially when the brain is attacked (Shirbazou et al., 2011).

Structure of testicular tissue

Sertoli cell proliferation mainly occurs during prenatal and prepubertal mammalian development, then stabilizes after puberty. Recent studies show that mature Sertoli cell bundles can still increase in number through hormonal modification. Gonad-inducing hormones control both Sertoli cell proliferation and when it stops. Additionally, before maturity, Sertoli cells retain the capacity to proliferate and respond to low levels of inducible gonadotropins (Hegazy et al., 2024).

Males show mild testicular damage with a change in sperm count. As the injury continues, the testicular lumen contains fewer sperm (Hegazy et al., 2024). Afterward, the testicular tissue can regain its ability to regenerate and reproduce cellularly (Dvorakova-Hortova et al., 2014). Lim et al. (2013) state that the severity of the infection determines the impact: acute infection induces improvement. Testicular function improves as male hormone levels increase. When infection continues, symptoms such as collapse of the seminiferous tubules and tissue distortion begin to appear. T. gondii infection stimulates programmed cell death in testicular tissue, destroying it. This coincides with a switch from Tachyzoites to Bradyzoites phases, preparing the parasite for spread outside the testicle (Abdoli et al., 2012).

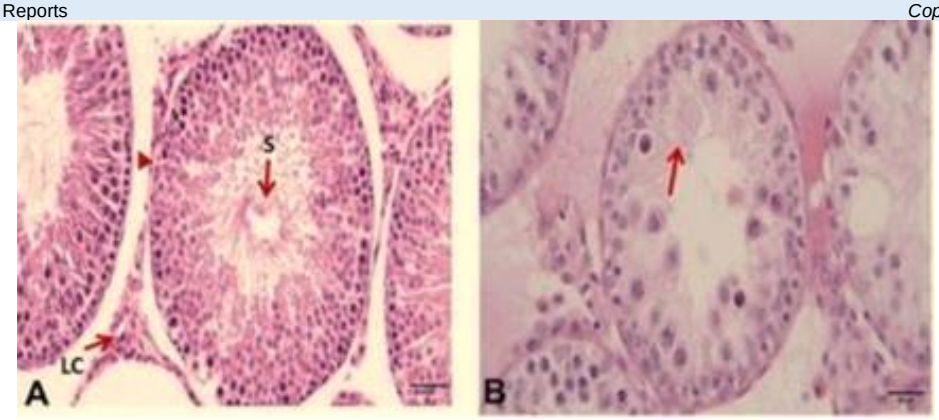

Figure 1: Histological analysis of mouse testis (H&E, ×200). A: control group, B: testis infected with toxoplasmosis (Hegazy, et al., 2024).

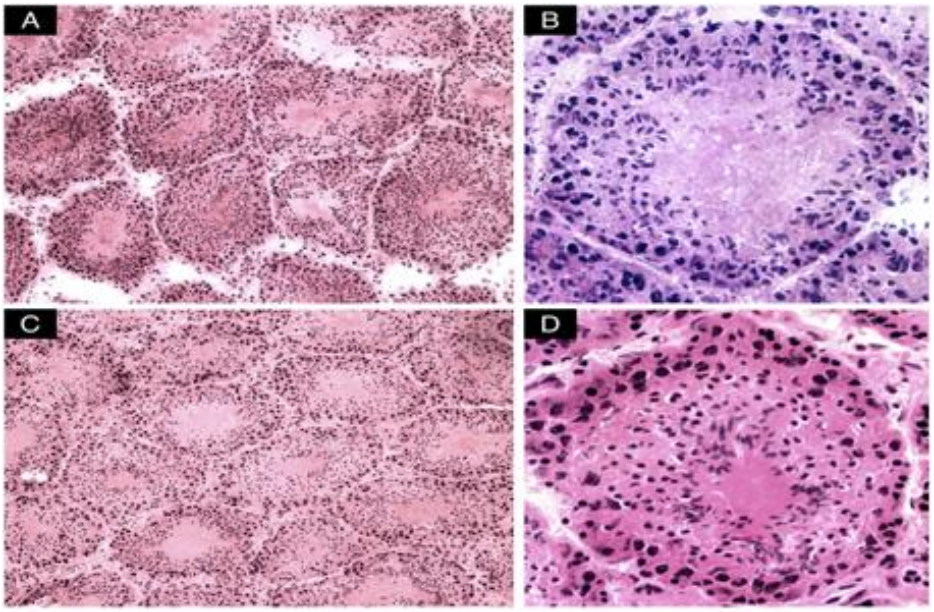

Figure 2: Cross-sections of seminiferous tubes from a mouse testicle infected with toxoplasmosis. No significant effect on the tissue structure of the affected mouse testicle was observed compared to the control group. Magnification 20x (a) and 40x (b), and control group samples 20x (c) and 40x (d) (Dvorakova-Hortova, et al., 2014).

Characteristics of semen

Local and systemic hormonal balance plays a crucial role in regulating spermatogenesis, as the gonadal-hypothalamus-pituitary axis represents the axis of the systemic hormonal environment, while the balance of the testicular testosterone to estradiol (T:E2) ratio represents local hormonal regulation. The precise balance between testosterone (T) and estradiol (E2) is essential for normal spermatogenesis, and this is reinforced by the detection of decreased T levels and increased E2 levels. In both semen (Luboshitzky et al., 2002) and serum (Schlegel, 2012) of infertile men, studies have indicated a possible effect of acute and chronic toxoplasmosis on serum hormone balance in men, regardless of semen characteristics (Hlaváčová et al., 2021).

Vitality and number of sperm

Toxoplasmosis is one of the most significant types of infection that can negatively impact reproductive function. This has resulted in a large percentage of sperm losing their heads. Scanning electron and transmission electron microscopy revealed structural defects in sperm, such as their twisted tails and destruction of the plasma membrane. T. gondii infection stimulates programmed cell death (apoptosis) of sperm in all males (sterile and fertile) (Tyebji et al., 2020). Research shows a negative correlation between apoptosis rates and the ratio of sperm density to anterior motility (Dass et al., 2011). In relation to this, T. gondii causes a loss of mitochondrial membrane potential in sperm, but does not change reactive oxygen species levels, which points to mitochondrial dysfunction as a possible cause of sperm damage. Furthermore, studies have found that men with infertility linked to T. gondii infection can have a mutation in the ND1 gene in their sperm mitochondria (Arantes et al., 2009). Finally, a recent study found that latent toxoplasmosis affects sperm motility and count, but not sperm shape or semen volume (Moura et al., 2007). Toxoplasma's ability to cross the blood-testis barrier could affect the reproductive cycle or sperm maturation. When sperm were exposed to rapidly growing cells, they showed twisting, sliding, and conical protrusions, which are early signs of invasion. These changes appeared within 5 minutes, suggesting the parasite tried to invade sperm at the same speed seen in somatic cells (Carruthers and Boothroyd, 2007).

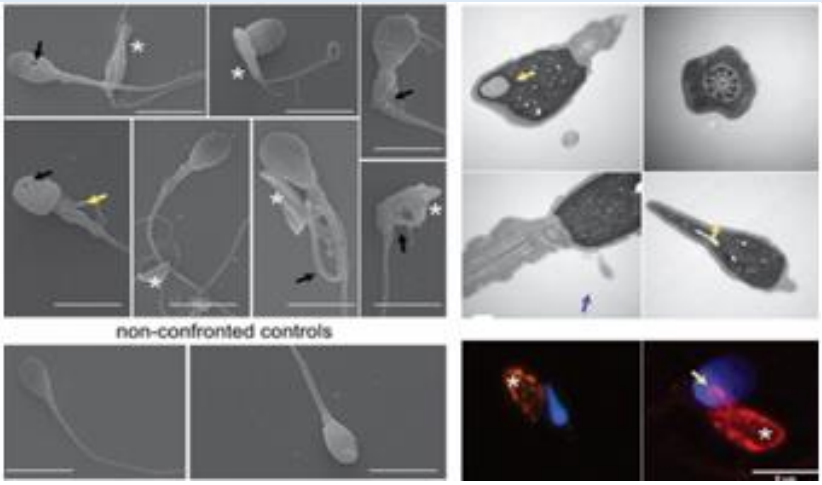

Figure 3: Defects in the safety of human sperm exposed to Toxoplasma gondii parasites (Rojas-Barón, et al., 2025).

The use of medications to treat toxoplasmosis affects male reproductive function People with normal immune systems are usually treated for toxoplasmosis with pyrimethamine, sulfadiazine, and folic acid for 4 to 6 weeks. For those with weakened immunity, trimethoprim/sulfamethoxazole is a very effective preventive antibiotic (Krassas et al., 2008). Several reports have shown that anti-toxoplasma drugs, especially pyrimethamine, can negatively affect male reproductive function (Prasil et al., 2023). Experimental studies on male mice and rats found that animals treated with pyrimethamine had lower sperm motility and sperm count. The structure of the testes and epididymis also changed in treated animals compared to the control group (Węglińska et al., 2022). Other studies have suggested that pyrimethamine has mutagenic effects in the germ cells of rat testes and can cause a decrease in DNA synthesis in sperm cells (Gholami et al., 2025). Various studies have suggested that drugs with anti-folate or anti-dihydrofolate reductase (DHFR) effects affect the availability of purines and pyrimidines for DNA synthesis and may have anti-fertility effects (Vanichtanankul et al., 2022). The anti-fertility effects of other anti-toxoplasmosis drugs, such as sulfadiazine and the combination of trimethoprim/sulfamethoxazole, have also been considered in other studies (de Lima Bessa et al., 2023). Although the anti-fertility effects of toxoplasmosis and anti-toxoplasmosis drugs have been reported in various studies, there is no report revealing whether the combination of toxoplasmosis and drugs has a synergistic negative effect on male reproductive functions.

Discussion

The link between T. gondii infection and alterations in host hormone levels arises from two main mechanisms. The first is direct: localised abscesses disrupt specific brain regions, modifying the host's physiology and behaviour. The second is indirect: the immune response to infection, marked by elevated cytokine production, induces changes in neural and systemic functions and behaviour (Laubach et al., 2022). The cascade of immune action against Toxoplasma infection is not precisely defined, but it has been found that infection with Toxoplasma gondii stimulates the production of pro-inflammatory cytokines, including IFN-ɣ and IL-1β. Likewise, the transcription-regulating expression of the MIP-1a and MIP-1b B genes (Sana et al., 2022) is stimulated. T. gondii appears to have the ability to stimulate pro-inflammatory cytokine production from neutrophils, and thus the levels of High MIP-1a and MIP-1b resulting from parasite presence result in part from stimulation of autocrine secretion via TNF-α, and this may indicate that the efficiency of immune mechanisms and IL-1b induction are not linked to parasite presence but instead to a dysregulation of the cytokine network (Li, et al., 2025).

Elevated IL-1b in hypogonadism, along with its relationship to sex hormones, suggests a pathophysiological role for IL-1b in hypogonadism development (Ali et al., 2025). IL-1b modulates GnRH release from the hypothalamus. This process is likely mediated by increased release of noradrenaline and dopamine from brainstem neurons. The hypothalamus inhibits gonad-stimulating hormones (GnRH), and cytokines influence several endocrine glands by altering anterior pituitary release. Cytokines also suppress the hypothalamus-pituitary-gonadal (HPG) axis. They act directly or indirectly by increasing the secretion of corticotropin-releasing hormone (CRH), stimulating cortisol release (Pérez-Osorio et al., 2025). Sex hormone receptors are present on the membranes of various immune cells, including lymphocytes, macrophages, granulocytes, and mast cells. This indicates direct links between endocrine glands and the immune system, allowing endocrine factors to modulate the expression of target genes in immune cells (Mohammed et al., 2022). These hormones also target the amygdala and related brain regions, including the hippocampus and hypothalamus, which regulate circulating steroid hormone levels and influence both behaviour and immune response (Pérez-Osorio et al., 2025). During chronic infection, T. gondii converts cholesterol from low-density lipoproteins into cholesterol esters, which are subsequently stored in lipid bodies. Elevated levels of low-density lipoproteins are associated with the parasite's adaptive response to changes in serum lipoproteins, mediated by alterations in lipid receptors and apolipoproteins (Milovanovic et al., 2009). Additionally, certain metabolic products of dehydroepiandrosterone (DHEA), particularly 7-hydroxy derivatives, increase in brain tissue following acute infection with the parasite. These compounds demonstrate preservative and neuromodulatory properties (Morfin and Stárka, 2001). Additionally, levels of these derivatives decrease as antibodies to the parasite decline, and the infection persists. Importantly, there is strong evidence that steroid hormones influence the progression of toxoplasmosis in humans and mice. For instance, estradiol enhances the invasion of PRU and VEG strains into host cells, thereby increasing the parasite's pathogenicity (Galván-Ramírez et al., 2014). Specifically, estradiol enters the parasite cytoplasm and rapidly stimulates intracellular calcium influx. It also increases secretion of the main protein mediating parasite movement (Tg-MIC2) and accelerates parasite motility, further enhancing activity and pathogenicity in mice (Kaňková et al., 2011). Supporting these findings, Al-Ardi (2021) found significant

differences in estradiol concentrations between T. gondii infected and uninfected samples, as well as between acute, chronic, and non-infected groups in infertile men. Persistent infection leads to increased cortisone levels. This explains the resulting immunosuppression, as cortisone is an immunosuppressive hormone. Indirect evidence suggests that 'asymptomatic' latent toxoplasmosis acts as a mild but chronic stressor (Lindová et al., 2010). Chronic stress from underlying injury, along with elevated cortisone, may directly weaken immune function. Prolonged injury and hypothalamic dysfunction can result in secondary hypogonadism due to hypogonadotrophic damage. Damage to the thalamus and hypothalamus may delay the secretion of GnRH-stimulating hormones. Repair of the pituitary and restoration of the pituitary-gonadal axis can improve hormone production. This also supports parasite elimination. Alternatively, administration of male hormones can achieve similar results (Pérez-Osorio et al., 2025). Abnormal DNA methylation in male germ cells causes issues in testicular tissue and alters the formation of sperm in both mice and humans (Cui et al., 2016). Genes such as Crem and Creb1, which help make cAMP and turn on other genes through DNA elements called CRE, are controlled by hormones and methylation. These genes are important for sperm development (El Omri-Charai et al., 2023). The CREM and CREB genes are the transcription factors involved in the cAMP signalling pathway, which regulate the expression of many genes specific to spermatogenesis, and these elements act as an important regulator in the hormone response for mammalian cell growth, differentiation, and survival during spermatogenesis. These genes undergo sequential regulation, being activated or inhibited through mechanisms such as alternative exon binding and excitatory usage. Their expression is modulated by cAMP signaling pathways in multiple directions. Furthermore, abnormal CREM gene methylation has been observed in men with azoospermia, which is associated with reduced sperm motility and quality (Siebert-Kuss et al., 2024). A similar result is likely for the function of the transgenic Hspa1 gene. This gene encodes a protein similar to the testis-specific heat shock protein Hsc70T, part of the Hsp70 family. Hsc70T is expressed in germ cells during post-meiotic differentiation I. Its deficiency reduces sperm motility. Creb314-deficient mice also show increased male germ cell apoptosis. Creb314 belongs to the CREB family. These phenotypic defects resemble those seen after T. gondii infection. They could link infection to its mechanism (Siebert-Kuss et al., 2023). The acrosome is a membrane-bound organelle found at the front of the sperm nucleus. The acrosome reaction is important for male fertility because it causes the acrosome membrane to fuse with the sperm's plasma membrane when calcium enters the cell. Problems with this process can make it harder for sperm to join with zone pellucid. Studies have shown that both live and dead sperm do not show increased acrosome rupture after being incubated with T. gondii for 10 minutes (Rojas-Barón et al., 2025). Sperm are highly motile cells that rely on mitochondrial-derived ATP energy to sustain their motility (Park and Pang, 2021). Sperm mitochondria are not only involved in sperm motility, but are essential for hyperactivation, pluripotency, acrosome interaction, and fertilisation. Mitochondria are also a major source of ROS, and human sperm are particularly sensitive to ROS in semen, hypothesising that the decapitation phenotype could be mediated by an oxidative stress (OS)-induced response leading to ROS production (Moraes CR & Meyers, 2018).

Conclusion

Toxoplasmosis infection is prevalent among men, although women exhibit higher infection rates. The presence of various parasite stages, whether quiescent or rapidly reproducing, can cause significant complications for the host, including impaired fertility. The infection alters sex hormone concentrations, damages testicular tissue, and negatively impacts sperm composition and vitality. Additionally, medications used to treat toxoplasmosis may indirectly affect male sexual function.

Monitoring changes in sex hormone and stimulant levels reveals a close alignment with the stages of the parasite's life cycle. This pattern often weakens the host's immune defences and, in many cases, adapts them to support the parasite's survival and reproduction. Even when the host's immune capacity is high, the parasite may still be able to control the transition to dormant phases.

Scientists remain uncertain how Toxoplasma alters reproductive functions. One hypothesis is that it disrupts hormone levels, particularly LH and FSH, which regulate spermatogenesis. Another hypothesis is that it triggers epigenetic modifications, specifically methylation changes in genes crucial for spermatogenesis and gene expression.

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