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Original article

The Relationship Between Toxoplasmosis and Concentration of Prolactin and Progesterone in Pregnant Women

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Abstract

Toxoplasma gondii (T.gondii) is an intracellular protozoon that causes toxoplasmosis in one-third of the world's population. During pregnancy, the prevalence of toxoplasmosis rises during the second and third trimesters causing abortion and a mild mononucleosis-like syndrome. Normally, progesterone rises during pregnancy, but in the case of toxoplasmosis, the body raises prolactin to inhibit T. gondii. The present study investigated the relationship between Toxoplasma gondii infection (toxoplasmosis) and the concentration of both prolactin and progesterone in infected pregnant women. A systematic review approach was conducted to research the aim of this study. PubMed, Scopus, Web of Science, and Google Scholar were searched using the following keywords “Toxoplasma gondii” or “T.gondii” AND “protozoon” OR “toxoplasmosis” OR “animals” OR “prolactin” OR “progesterone.” Only primary studies were included, whereas reviews and non-experimental studies were excluded. Six studies met the inclusion criteria and were, therefore, reviewed in the present study. The six studies showed a reverse relationship between prolactin and progesterone, such that if one increases the other drops. Furthermore, Toxoplasmosis increased progesterone levels, which results in the suppression of prolactin levels. Thus, toxoplasmosis-induced progesterone secretion has an antagonistic effect on prolactin levels. Since prolactin strongly elicits innate and adaptive immune responses, toxoplasmosis-induced progesterone release dampens the immune response of the host and enhances susceptibility to severe toxoplasmosis.

Keywords: ***Toxoplasma infection, toxoplasmosis, progesterone, prolactin, hyperprolactinemia, hypoprolactinemia.***

Introduction

Toxoplasmosis, caused by the intracellular protozoan parasite Toxoplasma gondii, is a widely distributed infectious disease that can be acquired through the consumption of contaminated food [1], water, and raw vegetables containing oocysts shed in cat feces [2]. This disease is prevalent in humans, with an estimated worldwide prevalence of 30%-50% [3]. However, some regions such as North America, Southeast Asia, Northern Europe, and Sahelian countries of Africa have reported a lower seroprevalence ranging between 10%-30% [4].

Various studies and surveys have reported significant differences in the prevalence of T.gondii infection among diverse ethnic groups, even when living in the same geographical area. These regional variations in infection rates may be attributed to climate changes and cultural variations in the type and quantity of raw meat consumption, as well as the sources of meat [5]. Age has been identified as the most common risk factor for the development of Toxoplasmosis gondii infection, with the prevalence of the infection increasing as age advances. Additionally, the level of hygiene, absence of a history of abortion, awareness of the mode of transmission of toxoplasmosis, and the origin of animals have also been reported as risk factors [6].

Approximately 80%-90% of Toxoplasmosis cases are asymptomatic, while 10%-20% of cases develop the systematic form, and the chronic infection can persist throughout the host's life. In HIV patients, bradyzoites can reactivate, leading to cerebral toxoplasmosis [7]. Toxoplasmosis infection during pregnancy poses a significant risk to pregnant women, as it increases the likelihood of adverse pregnancy outcomes, including spontaneous abortion, premature birth, and birth defects. Among these, congenital toxoplasmosis is the most severe manifestation of the disease, resulting from the transplacental contamination of the fetus with Toxoplasmosis gondii during pregnancy [8]. Recent research has demonstrated that early maternal and post-natal standard anti-parasitic treatment is the most effective strategy for preventing Toxoplasmosis gondii-associated injuries [9]. Therefore, it is strongly recommended that all pregnant women, especially those in the first trimester, undergo serological screening tests to detect IgG and IgM antibodies against T. gondii infection as a preventive measure to minimize or avoid any possible complications during childbirth. Nonetheless, certain diagnostic methods may not be effective in immunocompromised patients, which requires careful consideration in clinical practice [10].

Progesterone (P4 or Prog)

Progesterone known as the “pregnancy hormone, is a hormone produced in early pregnancy by a cyst on the ovary called the Corpus Luteum. This cyst continues to produce progesterone for 10 weeks during pregnancy. After these initial weeks, the placenta takes over producing progesterone. During the first trimester, progesterone levels rise exponentially, but plateau shortly after. Progesterone is key to creating a perfect environment for the ovaries to harbor the fetus by keeping the uterus muscle relaxed and helping the immune system tolerate foreign DNA [11]. The relationship between progesterone and pathogens is complicated. It is currently known that progesterone can affect the infection of parasites by modulating innate and acquired immune responses. To create a suitable environment for the growth and development of the embryo, sex hormones need to regulate the host’s immunity, and provide favorable conditions for the invasion of pathogens [12].

Prolactin (PRL)

The pituitary gland, located beneath the cerebral cortex, secretes the hormone prolactin (PRL), which is found at low levels in both male and female blood. Prolactin secretion is regulated by inhibitory factors, including dopamine [13]. Hyperprolactinemia, a condition characterized by elevated levels of PRL, is observed in pregnant women [14]. Prolactin receptors are present on the surface of B and T lymphocytes and macrophages, indicating the hormone's role in the immune system. Prolactin induces the production of cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon γ (IFNγ), and interleukin-12 (IL-12), in addition to its immune function [15].

The objective of this investigation is to explore the correlation between Toxoplasma gondii (T. gondii) infection and the levels of prolactin and progesterone in pregnant women who have been infected.

Materials & Methods

In order to conduct an updated literature review of the connection between Toxoplasma gondii (T.gondii) infection and the concentration of prolactin and progesterone in pregnant women who have been infected, various specialized databases such as PubMed, Scopus, Web of Science, and Google Scholar were utilized. To accomplish this, the following terms were used: Toxoplasma gondii (T.gondii); protozoon; toxoplasmosis; Animals; prolactin; progesterone.

All clinical and preclinical studies that highlighted the relationship between T. gondii infection and the concentration of both prolactin and progesterone were included. Only English-language patient reports were considered. Articles were chosen for review based on their title or abstract indicating similarities and excluded otherwise.

Eligibility Criteria

A systematic review of cross-sectional and case-control studies related to Toxoplasma gondii (T. gondii) was conducted to identify relevant research. In order to avoid potential bias, an independent investigator performed all stages, including the search process, study selection, quality assessment, and data extraction.

Study Characteristics

Exclusion criteria include sample size, lack of relevance to the topic, and case report.

Data collection methods

We carefully studied all selected studies. The full text of selected original articles was obtainedand reviewed. The inclusion criteria for this analysis were explicit data of all independent variables and at least one dependent variable; data collection and criteria eligibility were established for determining the frequency or proportion of each study. The independent variables were T. gondii strain, hormones, study design, stage of infection and developmental stage of the parasite, post-infection evaluation time, age, host, and technical analysis. Dependent variables were increased or decreased infection and number of parasites. Reference lists of full-text publications were examined for identifying studies not originally selected.

Results and Discussion

Toxoplasmosis is an infection caused by the parasite Toxoplasma gondii. It can be transmitted to humans through contact with infected cat feces, contaminated soil or water, or undercooked meat from infected animals. In pregnant women, toxoplasmosis can be transmitted to the fetus, potentially causing serious health problems. It's important to note that the relationship between toxoplasmosis and prolactin as well as progesterone hormones levels in pregnant

women is not yet fully understood, and more research is needed to better understand such relationship. Therefore, current study aimed to explore the link between the frequency of T.gondii infections and the level of the prolactin and progesterone hormone among the pregnancy women.

Toxoplasmosis is a widely prevalent but neglected disease that poses a chronic infection risk to pregnant women and their fetuses. The disease results from transmission of T. gondii from a seronegative pregnant woman infected with T. gondii to her fetus. The severity of fetal or newborn disease depends on multiple factors, including gestational age, parasitic load, strain virulence, and maternal immune system Symptoms range from mild to severe, including retinochoroiditis, hydrocephalus, microcephaly, mental retardation, and even death. Late-onset clinical symptoms can develop in some cases where there is no evidence of infection at birth, leading to neurological and ocular sequelae [16]. Multiple factors, including eating habits, climate, and awareness of the different modes of transmission, are associated with the occurrence of congenital toxoplasmosis. Public education is important, despite doubts about its effectiveness [17].

The changes in the endocrine system that occur during pregnancy, as well as the size and maturity of the placenta and the embryonic/fetal immune response, all have an impact on the ability to defend against invasion or fight infection. It is well known that the progesterone hormone increases in pregnant women to protect the fetus during development, while the body's immunity decreases to prevent miscarriage. As pregnancy is associated with suppressed immunity, the risk of infection with pathogenic bacteria and parasites tends to increase [18].

Besides their role in gender identity, sex hormones play essential roles in the development and activity of the adaptive and innate immune systems. Both innate and adaptive immune systems have receptors for sex hormones, and therefore, are modulated in response to hormonal cues. This could explain the observed gender-related differences in immune responses [19]. Pregnant women are at increased risk of toxoplasmosis-induced abortion and stillbirths, especially during the second and third quarters of gestation [20-21]. Interestingly, the prevalence of toxoplasmosis has been positively correlated with progesterone and negatively correlated with prolactin levels [21-22]. This suggests that progesterone and prolactin levels determine the reproduction and survival of T.gondii in pregnant women.

A total of 37 articles were initially identified as potentially relevant to the relationship between T. gondii and hormones. However, only six studies satisfied the predetermined criteria for inclusion in this systematic review. These studies were categorized into three groups: (A) effects of progesterone on serum prolactin concentrations, (B) human studies, and (C) animal studies.

However, the present study was enthused by the literature findings suggesting a possible modulatory relationship between prolactin and progesterone. Female sex hormones, estrogen, and progesterone levels increase steadily during pregnancy and reach their peak in the third trimester [23]. Apart from their primary function of promoting mammary tissue growth [24], estrogen and progesterone have marked effects on the secretion of other sex hormones, especially gonadotrophins, and prolactin. A previous experimental study by Minakami et al. (1985) tested the hypothesis that progesterone is involved in the regulation of estrogen-induced prolactin release in hypogonadal women. Twelve female subjects received 50 mg of progesterone intramuscularly and their blood samples were monitored every 15 min for prolactin levels. Eight of the 12 subjects (66.7%) had lower prolactin levels, indicating that progesterone suppresses estrogen-induced prolactin secretion [21]. Prolactin strongly elicits innate and adaptive immune responses, by promoting the maturation of Clusters of Differentiation 4 (CD4), and CD8 on surfaces of immune cells including monocytes, T helper cells, macrophages and dendritic cells, into CD4+ and CD8+ cells. Furthermore, serum prolactin levels (PRL) can alter Th1 and Th2 type cytokine production to favor interleukin (IL)-6 and interferon-gamma (INF-γ) secretion and also enhance immunoglobulin (Ig) production [25-26]. This could explain why pregnant women generally have weaker immunity compared to their non-pregnant counterparts.

Interestingly, infection with T.gondii, the causal agent of toxoplasmosis, can also alter serum levels of pregnancy-related sex hormones, especially prolactin, and progesterone [27]. Indeed, toxoplasma infection has a modulatory effect on serum prolactin levels (PRL) [25]. A recent cross-sectional study by Mohammadpour et al. (2019), tested PRL levels and performed anti-Toxoplasma IgG antibody ELISA (enzyme-linked immunosorbent assay) analysis on 343 serum samples of patients (240 women; 103 men) with suspected toxoplasma infection referred for serology [22]. Sixty-eight women tested positive for anti-T gondii IgG antibody; where the toxoplasma infection prevalence was significantly associated with hyperprolactinemia - high PRL levels (P=0.016). However, hyperprolactinemic women were associated with reduced T. gondii infection prevalence. This finding is consistent with a similar previous experimental study by Al-Warid and Al-Qadhi (2012) which measured serum anti-Toxoplasma IgG and IgM (using ELISA technique), estrogen hormones (using VIDAS Estradiol 11 -E2 11 kit) and progesterone (using progesterone kit) in 41 pregnant (1-4 months gestation) women attending an antenatal or gynecological clinic [28]. The prevalence of chronic toxoplasmosis was substantially high (31.7 %) compared to acute and sub-acute phases. However, acute toxoplasmosis was associated with lower serum levels of progesterone and estrogen. Though not significant, this finding suggests that T. gondii infection may suppress serum progesterone and estrogen levels, among pregnant women, especially in the acute phase of toxoplasmosis.In the chronic phase, progesterone and estrogen levels increase, which can be attributed to established adaptive and innate immunity against the parasite.

Furthermore, a previous experimental animal study by Golcu et al. (2014) demonstrated that toxoplasmosis increased serum progesterone levels in rats, which subsequently altered the cyclic appearance of behavioral sexual activity (estrus) in female rats [29]. T.gondii-infected female rats disliked rabbit urine and preferred spending time near bobcat urine and preferably in a lit chamber. The behavior was exactly the opposite of uninfected rats, suggesting that the aversive behaviors in female rats are due to hormone-dependent effects.

The infectivity and pathogenicity or virulence potential of T.gondii in humans could be influenced by the host's progesterone levels [27,30]. This was demonstrated in a recent in vitro study by Wu et al. (2022), where T. gondii treated with progesterone resulted in the inhibition of the invasion and proliferation level of otherwise, a rapidly growing life stage of T. gondii [27,30]. When cultured for 48 h with different concentrations of progesterone in vitro, T. gondii's daughter cells exhibited altered morphology (cytoskeleton) and budding patterns (an abnormal division of the apicoplast) and enhanced autophagy in a concentration-dependent manner [30].

Moreover, a bioinformatics analysis of the whole T. gondii's genomeled to the identification of the TgPGRMC (TGGT1_276990) gene, similar to the progesterone receptor membrane component 1 (PGRMC1). The TgPGRMC gene motif contained a conserved hormone-binding site, six Casein Kinase II (CK2) phosphorylation sites, three Protein kinase C (PKC, EC 2.7. 11.13) phosphorylation sites, and four myristyl sites [30]. T. gondii alters the expression of

hormonal receptors, by decreasing prolactin receptor (PRLR), estrogen receptor beta (Erβ), and progesterone receptor (PR), which leads to increased circulating levels of PRL, estrogen, and progesterone [27]. A recent study has also shown that membrane progesterone receptors (mPRα) mediate the progesterone inhibitory effect on PRL secretion by decreasing Cyclic Adenosine Monophosphate(cAMP) and activating Transforming Growth Factor (TGF-β1) pituitary secretory cells, lactotrophs [31].

This now leads to the hypothesis that increased serum levels of PRL, estrogen and progesterone promote the infectivity of T. gondii. According to Galván-Ramírez et al. (2019), elevated serum levels of estrogen and progesterone increase T. gondii infectivity by mediating anti-inflammatory response in T helper1 cells [27]. This occurs because estrogen suppresses the secretion of pro-inflammatory cytokines, interleukin (IL)-10, IL-12, and IL-1β [32]. As the name suggests, T helper cells provide helper functions to other immune cells, especially macrophages, dendritic cells, and B cells, in establishing adaptive immunity against infections [33]. Adaptive immunity is essential in eliminating pathogens or parasites and preventing their growth. Thus, by increasing serum estrogen and progesterone levels, T.gondii dampens the host's adaptive immunity, thereby enhancing its infectivity, survival, and persistent infection. This explains why pregnant women who test positive for chronic toxoplasmosis have elevated progesterone, estrogen, and PRL levels, which dampens the host's immunity against the parasite [27].

During pregnancy, maternal hormones can modulate the maternal immune response and activate macrophages and lymphocytes [34-35]. Progesterone is one of the maternal hormones produced by the ovary that plays a role during pregnancy by regulating immune cells to prevent the rejection of the developing fetus [34,36]. Several studies have demonstrated that Progesterone is capable of selectively regulating the expression of different genes that are involved in the activation of macrophages [37]. Progesterone has been shown to selectively reduce the transcription of the MCR1 while increasing the transcription of the YM1 in murine macrophages, indicating the possibility of plasticity in alternative macrophage activation. Additionally, progesterone has been shown to negatively regulate the differentiation of Th1 and Th17 cells by murine fetoplacental tissues, and it contributes to the local production of Th2-associated cytokines [38]. Progesterone can also influence the Th1/Th2 balance and stimulates the release of IL-4 and IL-10 during pregnancy by enhancing the production of progesterone-induced blocking factors by lymphocytes expressing progesterone receptors [39]. Therefore, dysfunctional immune regulation caused by extrinsic factors, such as infection, impairs pregnancy maintenance and adversely impacts pregnancy outcome.

It is known that an altered immune system caused by pregnancy may increase the risk of acquiring a T. gondii infection. However, the relationship between T. gondii infection and progesterone levels is complex and requires further study to fully understand.

Some studies have suggested that higher levels of progesterone during pregnancy may increase susceptibility to T. gondii infection by suppressing the immune system. A study found that pregnant women with higher levels of progesterone were more likely to be infected with T. gondii compared to those with lower levels of progesterone [35]. However, other studies have suggested that progesterone may have a protective effect against T. gondii infection.

Taken together, the available evidence suggests that progesterone levels may play a role in T. gondii infection during pregnancy, but the relationship is not straightforward and may depend on various factors such as the timing of infection, the route of transmission, and the individual immune response. Further research is needed to clarify the relationship between T. gondii infection and progesterone levels and to determine whether progesterone has a protective or harmful effect on T. gondii infection during pregnancy.

Prolactin hormone is secreted by the pituitary gland. Dopamine and other prolactin inhibitory factors control the secretion of this hormone in the blood of females and males [14]. There is evidence that prolactin plays a role in the immune system because its receptors appear on B and T lymphocytes and macrophages. Such hormone stimulate the production of cytokines such as tumor necrosis factor alpha, interferon beta, and interleukin-12 [15]. Previously, it was shown that high levels of prolactin inhibited T. gondii proliferating in mononuclear cells. Dzitko et al. suggest that a significant increase in the serum prolactin level during pregnancy might significantly limit the risk of Toxoplasma spreading and could play an important role in natural protection against toxoplasmosis [40]. It has been shown that prolactin has capability to inhibit multiplication of Toxoplasma in murine microglial cell cultures [41]. This is due to prolactin has the ability to bind to live RH tachyzoites (type I) and ME49 (type II) strains in a specific way [27].

Conclusion

According to our findings, progesterone stimulates T. gondii while prolactin inhibits the parasite during pregnancy. This study has some limitations, existing studies on hormones and T. gondii are incomplete and contradictory. In addition to that, further anti-inflammatory research is necessary to understand their mechanisms of action and the impact of hormones on the immune system.

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