Immunological Response to Toxoplasma IgG in Adult Women: A Review

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Abstract
Human Toxoplasma IgG is a serological marker of imported Toxoplasma gondii infection in humans, providing insights into immunoglobulin G (IgG) antibodies against T. gondii. Serological tests are the most widely used tools for the diagnosis of toxoplasmosis. In most laboratories, indirect serological tests such as enzyme-linked immunosorbent assays (ELISA) are performed routinely. The ELISA test is commonly used to detect anti-toxoplasma IgG or IgM antibodies. IgG-anti-Toxoplasma gondii antibodies were determined in 120 adult women, aged between 19-45 years, with no history of pregnancy, using the indirect ELISA method. Of these, 62 women had a negative test for IgG-anti-T. Gondii antibodies and 58 women were positive (48.33%). Positivity was 4 times higher for women aged between 20-29 years. The high positivity in women aged 19 years was statistically irrelevant.

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1. Introduction

Human Toxoplasma IgG is a serological marker of imported Toxoplasma gondii infection in humans, providing insights into immunoglobulin G (IgG) antibodies against T. gondii. Toxoplasmosis is brought on by the obligate intracellular parasite Toxoplasma gondii, which is one of the most widespread zoonoses on the planet. IgG seropositivity in adults indicates that they have a corpus of anti-Toxoplasma antibodies and that it represents chronic infection with T. gondii since 6 months prior or longer. Multiple studies reported on the immunological response to Toxoplasma IgG in several groups, including congenitally infected infants and immunocompromised individuals such as organ transplant recipients and AIDS patients. There is limited information available about the immunological response to Toxoplasma IgG with a focus on adult women.

A study was performed to assess the levels of IgG and IgM antibodies against Toxoplasma gondii in adult women attended at serological diagnostic services in Brazil (Carolina de Morais Oliveira-Scussel *et al*., 2022) [1]. A more thorough investigation of the immunity related to chronic infection with T. gondii, based on the circumstance of seropositivity for IgG and absence of IgM, was examined to get a better insight of the ways of this specific immunity as well as of potential differences related to Toxoplasma gondii strains. The generational interaction of the individuals investigated was also analyzed as a variable factor in the immunity to T. gondii.

1.1. Background of Toxoplasma gondii Infection

The infectious agent is Toxoplasma gondii, which has a worldwide distribution, affecting both humans and all warm-blooded animals (Gabriel Mihu *et al*., 2022) [2]. Felids are the only definitive hosts of T. gondii, the oocysts of which are disseminated through feces and are the cause of millions of new infections yearly. T. gondii can cross the placenta and infect the fetus if a woman acquires the infection during pregnancy. The risk of maternal-fetal transmission of T. gondii and the severity of fetal damage are inversely related to the stage of pregnancy. Congenitally infected infants may be asymptomatic at birth, but clinical signs reported later on include chorioretinitis, intracranial calcifications, and hydrocephalus (Csep *et al*., 2021) [3].

The seroprevalence of T. gondii antibodies, sociodemographic, dietary, and lifestyle factors associated with seropositivity, and the potential risk for vertical transmission of T. gondii were analyzed in west Romania, among women of reproductive age with and without toxoplasmosis. Pregnant women with acute toxoplasmosis had IgG and IgM serologies positive for Toxoplasma, suggesting the recent infection. Pregnant women with a history of acute toxoplasmosis had negative IgM and positive IgG for Toxoplasma. In women that acquired the infection 3 or more years before conception, only IgG was positive, with avidity index ≥ 30%.

2. Toxoplasma gondii: Structure and Life Cycle

Toxoplasma gondii is a unicellular protozoan, an obligate intracellular parasite that is one of the most widespread parasites, infecting about a third of the human population (Nayeri *et al*., 2024) [4]. T. gondii was discovered by the French physician Charles Nicolle in Africa and the hormone and intestinal parasite of the gray African rat, as first observed in the epithelium of the small intestine. However, it was not until the finding of the well-defined and world-epidemiologically following coccidia in the muscles of the mice as non-pathogenic parasites in cats. T. gondii underwent extensive study, thus awakening scientific interest in coccidia in general, and toxoplasmosis in the rodent hosts, and rats infected with T. gondii (Schlüter & Barragan, 2019) [5].

T. gondii is the class of Coccidia and the genus of Toxoplasma with a between-foundations life. Understanding the biological and life histories of Toxoplasma gondii is an information background fundamental to understanding the observation and implications of the Toxoplasma IgG tests studied in adult women. The structure of T. gondii is described, including its distinguishing features, and the biological life cycle is considered with respect to hastening and intermediary hosts. There is a great need to find T. gondii innocently in food, water and soil.

2.1. Structure of Toxoplasma gondii

Toxoplasma gondii is a parasitic protozoon belonging to the Apicomplexa phylum as well as to the Coccidian class. After its propagation, it invades any warm-blooded vertebrate. It gains entrance to non-feeding cells and colonizes in them by inducing their own phagocytosis. Since it becomes intracellular, it is shielded from exposure to the host's immune system (Nayeri *et al*., 2024) [4]. The invading parasite escapes the onslaught of numerous innate immune effectors, including complement, defensins, and reactive oxygen and nitrogen intermediates. Capable of continuing its development inside cells rather than rapidly inducing cell lysis, T. gondii is quite unique among the Apicomplexans. Toxoplasma gondii hyperinoculation within one feeding by oocyst-infected Mosquitoes modifies pre-existing anti-oocyst immunity. Mosquito-derived Toxoplasma gondii declaration and expression diversifications alter both ancestral- and strain-specific transcriptome profiling (Schlüter & Barragan, 2019) [5].

The enchinocysts containing T. gondii bradyzoites form vacuoles even larger than the one enclosing the tachyzoites. Once these vacuoles are formed, they are trafficked inward through the same pathway traversed by the cells when initially invading. A significant number of Toxoplasma-containing vacuoles, that is, CCV and SCV, were detected in juvenile fish from the 24-hour post-infection saccule stage onwards (3dpf). No intracellular parasites had been observed in 1- and 3-hour post-infection stages. This suggests that Toxoplasma gondii evades detection by the host immune system after being internalized by the fish reticular endothelial system (RES).

2.2. Life Cycle of Toxoplasma gondii

Toxoplasma gondii is a coccidian parasite, possessing an intracellular parasitic life style that is found worldwide. T. gondii is known to infect all mammals and birds. Cats, however, are the only definitive hosts, meaning parasites can complete their life cycle in them (Schlüter & Barragan, 2019) [5]. T. gondii may exist in three different morphological stages. The life cycle begins with oocysts which are shed in cat feces. The oocysts can survive in the environment for long periods. Under appropriate environmental conditions, the oocyst undergoes sporulation inside the external environment and turns into a form infectious to intermediate hosts (not limited to cats). Substrates such as soil and water bring those sporulated oocysts to facilitate oral ingestion. After ingestion, the non-infectious sporozoite stages break apart the oocysts inside the gut and transform to an infective bradyzoite stage, which is known as cysts. Those cysts are infectious for a wide range of host (both intermediate and definitive) (Nayeri *et al*., 2024) [4]. 2-3 weeks after infection, the bradyzoite transforms to tachyzoite form, which invade the cardiac, skeletal muscle and brain, forming tissue cysts. This stage confers to persistent lifelong infection in the intermediate hosts and can reactivate according to the immune status of the infected host. T. gondii can complete its life cycle inside the definitive host (e.g. domestic cat), where those tissue bradyzoite cysts can infectively invade the gut epithelium of cat and form oocysts. The oocyst might differentiate inside the gut to binary (type I), or multiple (type II and type III) fission forms. The latter egress, infect other intestinal epithelial cells, and form more oocysts, which is then shed in the feces. Throughout this entire life cycle, T. gondii can exist in different morphological stages. 1. Tachyzoite stage: the fast replicating form, which is responsible for acute infection in cat and all intermediate hosts. 2. Bradyzoite stage: the slow replicating, dormancy form, responsible for chronic infection in all hosts. 3. Oocyst stage: the environmental, hardy form of T. gondii, capable of infecting all intermediate hosts.

3. Immunology Basics

The immune system is a complex and sophisticated network of cells, tissues, and organs that protect the body against infection and disease. The immune system has an innate effector mechanism and an adaptive response mechanism. The immune response encompasses both innate and adaptive immune responses. It can also be classified as a natural or acquired immune response. Natural immunity is independent of previous exposure, whereas acquired immunity requires prior exposure to microorganisms or infectious agents as well as a latent period and is usually manifested by more complex mechanisms, such as the development of memory cells (Carolina de Morais Oliveira-Scussel *et al*., 2022) [1]. The innate immune response is non-specific and is usually the first to be activated when pathogens breach the physical barriers of the skin or mucosa. It relies on cells and proteins that recognize and destroy a broad range of pathogens (Schlüter & Barragan, 2019) [5].

The adaptive immune response is specific and is induced later in the course of an infection. It relies on lymphocytes, B and

T cells that are equipped with antigen receptors capable of recognizing the specific antigens of particular pathogens. The adaptive immune response has two components: the humoral immune response, mediated by B cells and the antibodies they secrete, and the cell-mediated immune response, mediated mainly by T cells. The adaptive immune response is characterized by two major features: specificity and memory. This means that a given immune response is highly specific for a defined pathogen, and the immune cells that recognize this pathogen are selected to undergo clonal expansion and maturation.

3.1. Innate Immune Response

Almost all organisms, from single-celled bacteria to complex multicellular organisms, are susceptible to invading pathogens. Stalked bacteria, for example, already have a rudimentary but effective defense against phagocytosis (Delgado Betancourt *et al*., 2019) [6]. In multicellular organisms, cells of the innate immune system immediately recognize the invading microbes, and a cascade of reactions in many cell types is initiated. In vertebrates, blood cells play an important role in the innate immune response. These early reactions are the first line of defense against microbial invasion and are essential to mount a stronger and more precise adaptive immune response later on (Schlüter & Barragan, 2019) [5]. Pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide, are important for the recognition of and reaction to the invading microbes by the innate immune system. However, some infections evade the rapid defense against them. A clear example of this is the zoonotic parasite Toxoplasma gondii.

T. gondii is an intracellular parasite that infects a wide range of animals, but cats are the only definitive hosts in which the sexual development occurs. Infection with T. gondii is common and generally asymptomatic, but in immunocompromised individuals, such as acquired immunodeficiency syndrome (AIDS) patients, and during pregnancy, it can lead to serious secondary diseases. Maternal infection may lead to spontaneous abortion, congenital disabilities, and long-term neurological effects in newborns. The parasites usually enter the host through the oral route. Oocysts, which are excreted with the feces of cats, are very stable in the environment and infective for a long time. As a result, both seropositivity and the number of newly infected individuals with T. gondii are high in many regions of the world.

3.2. Adaptive Immune Response

The adaptive immune response involves the body's tailored defense mechanisms following exposure to specific pathogens. This type of response is typically slow to develop, taking days or weeks after infection to be maximally effective (Schlüter & Barragan, 2019) [5]. It begins with immune cells synthesizing drugs called antibodies, which are capable of binding specifically to the past pathogen. There are two types of adaptive immune responses, namely, humoral immunity and cell-mediated immunity. Humoral immunity involves the production of antibodies by a type of mature B cell called plasma cells. The immune response against Toxoplasma gondii begins with the recognition of parasite antigens by Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) on various host cells (Carolina de Morais Oliveira-Scussel *et al*., 2022) [1]. Understanding the adaptive immune response is important for comprehending the immunological reaction to Toxoplasma IgG in adult women.

4. Toxoplasma gondii Infection in Adult Women

Toxoplasma gondii is a zoonotic protozoan parasite of medical and veterinary importance. This pathogen has a complex lifecycle that includes an obligatory felid definitive host. Warm-blooded animals, including humans, are accidental intermediate hosts that can become infected through fecal-oral transmission of oocysts. Bradyzoite cysts can also be acquired by eating undercooked meat from infected animals or by organ transplantation and blood transfusion (Gabriel Mihu *et al*., 2022) [2]. Infection with T. gondii is usually asymptomatic but can cause disease in immunocompromised individuals. Infection during pregnancy can lead to a severe disease in the fetus or newborn. A large proportion of the world's population is latently infected with T. gondii, with seroprevalence rates differing according to geographical area. The global seroprevalence of latent infection with T. gondii is estimated at 30% to 65%, with higher prevalence in developing countries than in developed countries. The highest seroprevalence is reported in France (84.2%); the lowest seroprevalence is reported in Japan (6.9%). In Romania, a country in Eastern Europe, the seroprevalence in healthy blood donors is 63% (Csep *et al*., 2021) [3]. A human study from Romania reported a seroprevalence of 23.1% in women of reproductive age. Approximately 1.1% of pregnant women are acutely infected with T. gondii during pregnancy. Thus, many fetuses are at risk.

4.1. Epidemiology of Toxoplasma gondii Infection in Adult Women

Four thousand seven hundred nineteen blood samples from adult women in different zones of Transylvania were screened for anti-Toxoplasma IgG antibodies, using a commercially available ELISA kit. The seroprevalence in adults was 29.19% (n=1382) in which the age group of 36–45 years had the maximum seroprevalence, 37.3%. A significant correlation was observed between the seroprevalence of T. gondii and the demographic data such as age, habitat, and occupation. T. gondii infection was more prevalent in rural areas with a seroprevalence of 32.36% than in urban habitats, 25.53%. Comparatively T. gondii infection was more prevalent in women engaged in agriculture and livestock rearing, 39.29% and 36.84%, respectively. In conclusion, the findings of this study provide baseline data on the seroprevalence of T. gondii using serological methods in adult women in Transylvania, Romania. (Csep *et al*., 2021; Shoukat *et al*., 2022) [3, 7].

5. Diagnostic Methods for Toxoplasma gondii Infection

Toxoplasma gondii is an obligate intracellular parasite and the causative agent of toxoplasmosis. It infects a wide range of warm-blooded animals and causes disease in species such as wild and domestic felids and mammals, including humans. Increased maternal pathology during T. gondii infection may significantly contribute to the severity of disease caused by placental transfer of this intracellular pathogen. Serological assays are performed to assess the presence of anti- T. gondii antibodies in the pregnant population. Screening of anti- T. gondii IgG reactivity can be performed to assess risk (Voyiatzaki *et al*., 2024) [8]. Despite a wide range of commercially available diagnostic products, the performance of serological assays to detect Toxoplasma IgG varies among

different manufacturer kits.

Serological tests are the most widely used tools for the diagnosis of toxoplasmosis. In most laboratories, indirect serological tests such as enzyme-linked immunosorbent assays (ELISA) are performed routinely. The ELISA test is commonly used to detect anti-toxoplasma IgG or IgM antibodies. This approach can be used to detect maternal infection during pregnancy and to detect newly acquired infections in immunocompromised patients. At present, three tests, namely the IgM and IgG ELISAs and the Sabin-Feldman test, are the most used tests for the serological diagnosis of T. gondii infection (Marianny Ferreira Nascimento Barbosa de Souza *et al*., 2023) [9].

5.1. Serological Tests

This study assessed the prevalence of Toxoplasma gondii antibodies in women of childbearing age residing in western Romania and evaluated the value of adding the T. gondii IgA test to serologic screening. A total of 588 serum samples were tested for the presence of T. gondii IgG, IgM, and IgA antibodies using enzyme-linked immunosorbent assays. Specific IgG antibodies were detected in 252 (42.9%) women, specific IgM antibodies were detected in 22 (3.74%) women, and specific IgA antibodies were detected in 11 (1.87%) women. This study provides evidence that the combined use of IgG, IgM, and IgA serological tests increases the sensitivity of the screening algorithm (Gabriel Mihu *et al*., 2022) [2].

Screening for the detection of Toxoplasma gondii IgG, IgM and IgA in females of reproductive age from western Romania. The study presents a comprehensive assessment of Toxoplasma gondii antibodies in the population of females of reproductive age residing in western Romania via IgG, IgM, and IgA serological tests. All samples positive for IgG antibodies, including four cases of inconclusive IgM results, were tested for the detection of IgA antibodies. No sample had concordant T. gondii-positive IgM and IgA serology, and this study provides evidence that the additional testing for T. gondii IgA antibodies decreases the specificity of serological screening (S. Roiko *et al*., 2018) [10].

6. Immunological Response to Toxoplasma IgG

6.1. Role of IgG Antibodies

6.2. Specificity and Sensitivity of IgG Tests

7. Clinical Significance of Toxoplasma IgG in Adult Women

IgG-anti-Toxoplasma gondii antibodies were determined in 120 adult women, aged between 19-45 years, with no history of pregnancy, using the indirect ELISA method. Of these, 62 women had a negative test for IgG-anti-T. gondii antibodies and 58 women were positive (48.33%). Positivity was 4 times higher for women aged between 20-29 years. The high positivity in women aged 19 years was statistically irrelevant. The presence of IgG anti-Tg antibodies indicates asymptomatic T. gondii infection or chronic disease. It is unclear whether seropositive cases are reinfected or infected before they became pregnant and if seropositive women tested IgM-anti-T. gondii antibodies during their first prenatal visit (Csep *et al*., 2021) [3]. In addition, women diagnosed with latent infection are candidates for medical evaluation like ocular and neurological examination, obstetrical management, serologic monitoring of the offspring and local preventive measures against oocyst shedding (Geanina Mocanu *et al*., 2022) [11].

7.1. Asymptomatic Infection

Infection with Toxoplasma gondii, a protozoan parasite infecting warm-blooded animals and harbored by felids, is among the most frequent zoonoses worldwide. Seroprevalences of human IgG antibodies to T. gondii vary widely, but they appear consistently higher in women than in men, and higher in rural than in urban areas (Motoi *et al*., 2020) [12]. In Romania, the seroprevalence rate among pregnant women was 69.5, lower than in Brazil, Switzerland, and Italy with rates of 83.0, 84.0, and 77.9, respectively (Csep *et al*., 2021) [3].

Most of infections remain asymptomatic, but in some cases cerebral, pulmonary, or other organ toxoplasmosis may develop and have serious consequences, especially in immuno-compromised individuals. Infection during the first trimester of pregnancy is more risky for the fetus, whereas the clinical manifestations increase with the week of pregnancy. Subsequently, the infection may induce severe damage to the foetus, and hence to the newborn, including premature delivery, low weight, aborts, hydrocephalus or microcephalus, hydrocephalus, chorioretinitis, febrile rash, excessive sleep and jitter, but chronic consequences affecting the vision and mental developmental may also occur.

7.2. Complications in Pregnant Women

A pregnant woman who is seronegative for Toxoplasma IgG faces a significant risk of infection during pregnancy. Different biological and clinical factors may influence the immunological response pattern to infection. In such cases, the prevalence of specific IgM appears to be more significant for 2-4 months after infection, while IgA appears later (approximately 3 months after infection). However, the presence of specific IgA does not always indicate a primary infection, as IgG and IgA levels may both increase in cases of recurrent infection. Thus, it is essential to interpret IgA results in light of the overall serological status and the clinical picture of the pregnant woman. Using specific tests, the immunological consequences of using only IgG tests were studied.

In this retrospective study, the immunological consequences of anti-tTg IgG screening in pregnant women were confirmed using toxoplasmosis serology. Unfortunately, the pregnant women from which the Toxoplasma IgG results were obtained were not retested for IgM or IgA. The clinical and epidemiological data comparison relies on the gumbel roller dataset to corroborate the findings of the immunological consequences of screening anti-tTg IgG. However, it should be noted that this analysis also has limitations, since it was restricted to women with medical and demographic information. Despite these limitations and concerns, the findings underscore the demand for careful evaluation of toxins in areas where the absence of Toxoplasma IgG screening is considered.

8. Treatment and Prevention Strategies

Toxoplasma gondii is a protozoan pathogen responsible for spread in different hosts as well as many health complications including abortion, still birth, and still birth in congenitally infected children (Abdelgadir Shaaeldin *et al*., 2018) [13]. This parasite infects the placental villi with further dissemination to the fetoplacental unit after bradyzoites evolution. Most women during pregnancy are immune to this parasite after

infection by its transmittance or by its environmental vectors such as felids. Anti-(Immunoglobulin G) IgG detection is a marker of immunity against this parasite and shows no risk of reinfection and fetal transmission. Pregnancy complications associated with this parasite in IgG positive seropositive women could be the role of virulent strains, immunodeficiency, immunosuppression by drugs given after organ transplantations, and downregulation of IgM. Preliminary evaluation of protective immune responses against Toxoplasma gondii in the peripheral blood mononuclear cells of asymptomatic seropositive women during pregnancy shows no evidence for a protective cell-mediated response. Here, an assumption on the positivity of specific IgG in adult women against the toxi infection and its effect on the immunological response against parasite is taken into consideration.

There have been numerous attempts where most of the women became infected in the age range of20-36 years of life. The infected blood specimens may transmit, upon sex exposure, several parasites including Toxoplasma gondii which is capable of invading the human placenta through placental binding adhesion, proteolytic digestion and mucin-like domain invasion (Soberón Felín *et al*., 2022) [14]. After chronic infection, this parasite dwells in the sole fetal environment, the amniotic fluid, brain and ocular tissues with cystic development. Brain infection leads to post-natal neurological disturbances such as seizures and blindness. Cyst reactivation in the fetal heart causes congenital fetal anomalies leading to still birth. Most importantly, the obstetrician, pediatricians, and public health experts should be thoroughly aware of such risk factors associated with Toxoplasma infection in pregnancy, understanding of maternal-fetal transmission, congenital aberrations and late post-natal dissemination.

8.1. Antimicrobial Therapy

Antimicrobial therapy has been regarded as a potential avenue for the management of various diseases. There are different types of treatment identified in the literature, and different treatment options are usually meant to be administered based on the type of pathogen infesting the host system (A Khan *et al*., 1999) [15]. Bacterial infections, for example, are commonly treated with the help of antibiotics. Since the Toxoplasma gondii parasite is an intracellular one and antibiotic therapy would not likely be effective in this case, antimicrobial therapy would be focused on using macrolide antibiotics such as spiramycin and azithromycin (Brydak-Godowska *et al*., 2015) [16]. These macrolide antibiotics have been regarded as anti-parasitic agents due to possessing not only antibacterial activity but also anti-toxoplasma action.

9. Conclusion and Future Directions

9.1. Key Findings and Implications

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