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**Review Article**

# Clinical approaches to diagnosing and managing congenital toxoplasmosis

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## ABSTRACT

*Toxoplasma gondii* is a globally prevalent intracellular parasite, which is the causative agent of congenital toxoplasmosis, a disease that may lead to neonatal and fetal complications. Infection by *Toxoplasma* occurs through ingesting raw or undercooked meat containing still viable cysts. Accurate diagnosis and timely intervention during pregnancy are crucial for mitigating adverse effects. This review aims to summarize current clinical approaches for the diagnosis and management of congenital toxoplasmosis. Different diagnostic methods such as polymerase chain reaction (PCR), immunosorbent agglutination assay (ISAGA), Western blot, and enzyme-linked immunosorbent assay (ELISA) show varying degrees of specificity and sensitivity. Additionally, combined methods improve diagnostic accuracy. Prenatal treatment spiramycin or pyrimethamine-sulfonamide regimens show effectiveness in reducing vertical transmission and disease severity, particularly when started early. Management of congenital toxoplasmosis postnatally needs regular monitoring and prolonged therapy due to high risk of side effects. Recently, multiple tools have emerged like recombinant antigens, microRNAs, and vaccine candidates and seemed promise but require further validation. Congenital toxoplasmosis remains a diagnostic and therapeutic challenge. While current strategies improve outcomes, global implementation of standardized screening and the development of safer, more effective interventions are needed to further reduce disease burden.

**Keywords:** Congenital toxoplasmosis, *Toxoplasma gondii*, Clinical approaches, Diagnosis, Management

## INTRODUCTION

*Toxoplasma gondii* is an intracellular protozoan parasite and the causative agent of congenital toxoplasmosis. It is one of the most successful parasites globally, since it infects over 30% of the human population.[1] The seroprevalence of *Toxoplasma* is about 30% in the American, European, and Asiatic regions. While it reaches more than 60% in the African continent.[2,3]

Humans mainly get infected by *Toxoplasma* by ingesting raw or undercooked meat containing viable cysts, contaminated water, vegetables, fruit, shellfish, or by contact with soil contaminated by oocysts excreted in the feces of infected cats. It also may be transmitted via blood or leukocytes from immunocompromised and immunocompetent donors. Typically, *Toxoplasma* persists lifelong as cysts in intermediate host.[4] The life cycle of *Toxoplasma* is shown in Figure 1.

*Toxoplasma gondii* is mainly asymptomatic, however, primary infection in pregnant women may result in congenital toxoplasmosis.[5] Congenital toxoplasmosis occurs due to the vertical transmission of the parasite

across the placenta and can lead to disabling disorders in the developing fetus and newborn.[6] The risk and severity of fetal infection vary depending on gestational age. The risk of fetal infection increases with gestational age, while severity inversely proportional to gestational age.[7] Fetal infection occurring in early pregnancy may lead to various complications such as spontaneous abortion or brain damage, while fetal infection occurring in the late stages of pregnancy is usually subclinical.[8]

It is crucial to diagnose maternal *Toxoplasma* infection accurately for timely intervention to prevent side effects on both the mother and the fetus. Advanced diagnostic methods and effective screening tests are required to manage *Toxoplasma* infection appropriately. Currently, various serological (e.g. enzyme-linked immunosorbent assay (ELISA), immunosorbent agglutination assay (ISAGA)) and molecular tests (e.g. polymerase chain reaction (PCR)) are available.[9] Despite the advancement in early laboratory diagnosis of congenital toxoplasmosis, many assays are still limited, and comprehensive prenatal screening programs are still not widely implemented in many countries. Additionally, current therapeutic approaches are mainly focused on the acute phase of the disease, with no focus on chronic *Toxoplasma* infection, consequently, a cure is still not available. The significant toxicity and prolonged duration of treatment often lead to high rates of discontinuation. Nonetheless, findings from French studies indicate that both preventive and therapeutic interventions during pregnancy may lower the likelihood of symptoms and long-term complications in affected children.[1] The aim of this review is to summarize the recent clinical approaches to diagnosing and managing congenital toxoplasmosis, highlighting the effectiveness and safety of these approaches.

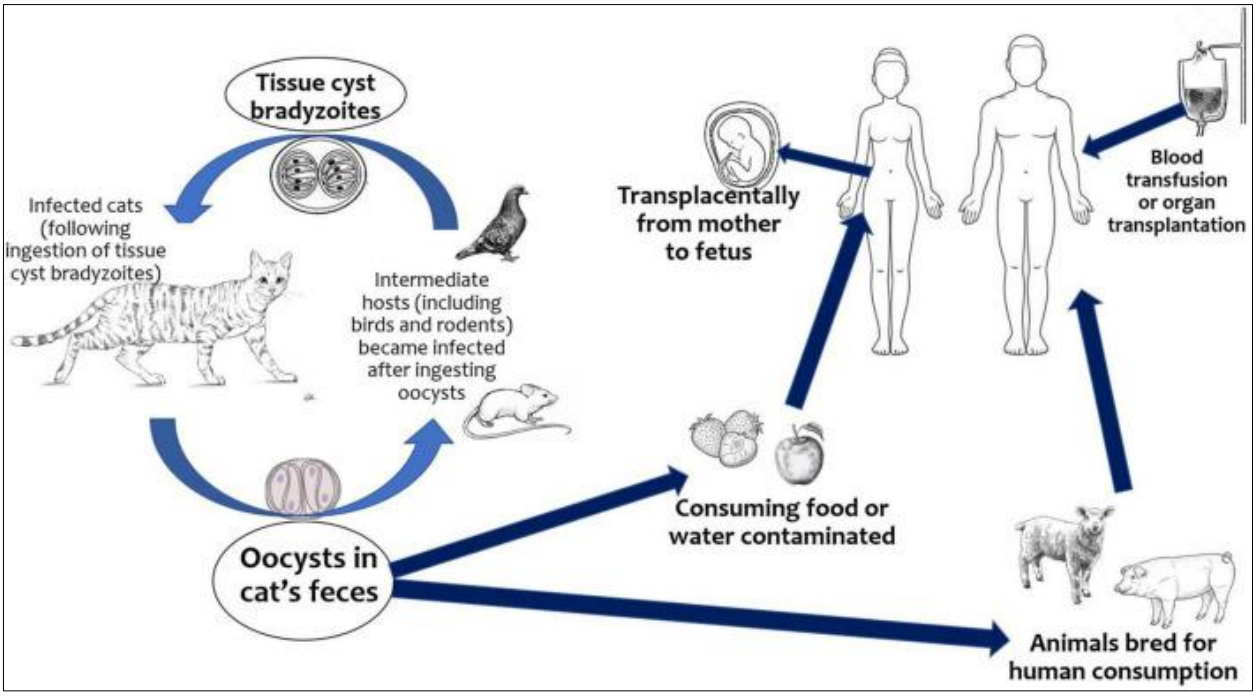


**Figure 1: Life cycle of *Toxoplasma gondii*.[4]**

## METHODS

A comprehensive literature search was conducted in Medline (via PubMed), Scopus, and Web of Science databases up to 12 May 2025. Medical Subject Headings (MeSH) and relevant free-text keywords were used to identify synonyms. Boolean operators ('and', 'or') were applied to combine search terms in alignment with guidance from the Cochrane Handbook for Systematic Reviews of Interventions. Key search terms included: "congenital toxoplasmosis" and "diagnosis" and "management". Summaries and duplicates of the found studies were exported and removed by EndNoteX8. Any study that discusses clinical approaches to diagnosing and managing congenital toxoplasmosis and published in peer-reviewed journals was included. All languages are included. Full-text articles, case series, and abstracts with the related topics are included. Case reports, comments, and letters were excluded.

## DISCUSSION

### *Diagnosis of congenital toxoplasmosis*

In order to effectively manage and prevent side effects of *Toxoplasma gondii* on both the fetus and the mother, an accurate diagnosis should be reached. Advanced diagnostic methods along with effective screening tests are crucial for managing the infection appropriately. Currently, various diagnostic methods to detect *Toxoplasma* are available including serological assays, molecular essays, and imaging techniques. Direct

diagnostic methods which detect the parasite, or its constituents include PCR and immunohistochemistry. While indirect diagnostic methods, such as ELISA, ISAGA, immunochromatography, and Western Blot, recognize the infection by detecting host immunoglobulins produced in response to the parasite infection.[9,10] However, the difficult accessibility of sampling the fetus with suspected *Toxoplasma* infection and the tendency of amount of parasite DNA or antibody levels against *Toxoplasma* to be low complicate diagnosis.[11]

***Polymerase chain reaction***

PCR-based tests are the most common molecular diagnostic methods used in diagnosing congenital toxoplasmosis due its high sensitivity (97.4–100%).[12,13] Various samples can be used in this test including amniotic fluid, peripheral blood, and cerebrospinal fluid. Notably, taking an amniotic fluid during pregnancy carries a high risk of complications.[14] PCR has the ability to amplify DNA to detectable levels, while real-time PCR can amplify and quantify the parasite load even in samples with relatively low DNA loads.[15] Despite its advantages, PCR sensitivity can be affected by sample handling and storage conditions.[16] Additionally, the detection accuracy of PCR can be affected by gestational age.[17,18] Other molecular diagnostic methods include loop-mediated isothermal amplification and nucleic acid sequence-based amplification, however more studies should be done to improve their effectiveness.[19,20]

***Serological testing***

Serological tests are commonly used to diagnose *Toxoplasma* infections through detecting specific antibodies. These tests can detect IgG, IgM, IgA, IgE, and IgG by different methods such as ELISA, ISAGA, chemiluminescence immunoassay, and Western blot.[10]

IgG antibodies develop within 1–2 weeks after acute infection. They peak at 2 to 3 months and persist for life. Seroconversion in a previously seronegative pregnant woman is considered the gold standard for diagnosing primary infection.[21] However, acute and chronic infection cannot be distinguished by a single positive IgG test.

IgM antibodies typically appear within a week, peak at 4 to12 weeks, and usually decline in three months.[22] Notably, they may persist for over two years in 9–27% of patients, resulting in false positive results.[21,22] Occurrence of a recent infection or rapid decline of IgM can result in false negative results.[21] If IgM detection test is positive, it should be confirmed with IgG and avidity tests.

IgA antibodies appear shortly after infection, take one month to peak, and decline rapidly.[23] Although it is more specific than IgM, it has less sensitivity due to its rapid decline.[21] IgA detection can improve diagnostic accuracy during pregnancy.[23]

IgE antibodies also appear shortly after infection and persist for 3 to 5 months.[24] IgE antibodies were detected by immunocapture assays in 86% of pregnant women with documented IgG seroconversion or rising titers.[25] The IgE antibody ISAGA test demonstrated high specificity (82.7%) and sensitivity (94.4%).[26] Furthermore, both ELISA and ISAGA tests showed 100% specificity for detecting true negative results.[27]

The IgG avidity test evaluates the functional strength of IgG binding. A high avidity means that an infection occurred more than 3–5 months ago, while low or intermediate avidity does not exclude chronic infection.[28] Notably, antibody maturation can be delayed due to individual variation, treatment, or pregnancy-related immune changes.[29] High avidity has a positive predictive value near 100%, while low avidity has a negative predictive value of 61.1–77.7%.[29,30] Additionally, high avidity early in pregnancy indicates prior infection, but further testing may be required to exclude primary infection such as repeat serology and amniocentesis.[21,28] While very low avidity results may suggest recent infection within 2–3 months.[30]

***ISAGA***

ISAGA is a method that can immunocapture *Toxoplasma gondii* tachyzoites using IgM and IgA serum samples.[31] The sensitivity of ISAGA in newborns ranges from 52 to 93% which is higher than ELISA range 44 to 87%.[32] The disadvantages of ISAGA include the requirement for specialized personnel and the need to use the parasite to perform this test.[33]

***Western blot***

Western blot test is mainly used to confirm the detection of *Toxoplasma*-specific IgG, IgM, and IgA antibodies. Congenital toxoplasmosis is diagnosed by comparing the Western blot profiles of the mother and child. If more intense or unique bands are found in the child's sample, this finding confirms the diagnosis.[34] The sensitivity of Western blot varies according to the antigen preparation and patient selection criteria.[14] Sensitivity for detection of IgG ranges from 33% to 74%, and for IgM detection from 49% to 79%. However, specificity has been reported high for both antibodies, and ranges between 95% and 100%. Although relatively simple to perform, Western blot is expensive and unsuitable for large-scale screening, so it is primarily used for confirmatory testing.[32,34]

***Amniocentesis***

Congenital toxoplasmosis diagnosis can be confirmed prenatally by identifying *Toxoplasma* DNA in an amniotic fluid specimen. It is preferred to perform US-guided amniocentesis after 16 to 18 weeks of gestation and at least 4 weeks after confirmation of primary maternal infection to reduce the risk of false-negative results.[35] The sensitivity of PCR of amniotic fluid ranges between 64% and

98.3%.[36,37] A systematic review and meta-analysis reported that PCR of amniotic fluid has a sensitivity of 83% and specificity of 98.3%.[37] It was also reported that the sensitivity of PCR of amniotic fluid peaks between 17 and 21 gestational weeks and is increased in late pregnancy compared to the first trimester of pregnancy.[18,38]

### *Treatment of congenital toxoplasmosis*

*Treatment during pregnancy*

The effectiveness of prenatal treatment mitigating the incidence and severity of congenital toxoplasmosis was debatable in previous studies.[39] However, multiple observational studies demonstrated that starting therapy as early as possible can hinder vertical transmission and reduce the incidence and severity of fetal infection.[40,41] Typically, it should be started within three weeks of maternal seroconversion.

If a primary maternal infection occurs within the first 18 weeks of gestation, spiramycin should start as early as possible. Spiramycin is a macrolide that can reach placenta in high concentrations and decrease the risk of vertical transmission. However, it is not recommended in case of fetal infection.[42] It was also reported that the combination of spiramycin with trimethoprim-sulfamethoxazole seems to be more effective in mitigating transmission than spiramycin alone, since it can effectively cross the placenta and reach fetal tissues.[43] Furthermore, in case of maternal infection occurring after 18 weeks of gestation and is confirmed by positive PCR, pyrimethamine, sulfonamides, and folinic acid regimen is the current gold standard treatment. Notably, this therapy is contraindicated before 14 weeks of gestation due to the high risk of teratogenic side effects.[44]

In cases of primary maternal toxoplasmosis infection, ultrasound monitoring should be performed monthly throughout pregnancy to detect possible fetal defects. In case of positive amniocentesis for toxoplasmosis, ultrasound examination should be done every 2 weeks to monitor fetal brain development. Ventriculography and intracranial calcifications are the typical sonographic findings in cases of congenital toxoplasmosis.[44]

*Treatment in neonates*

Newborns who are at risk of congenital toxoplasmosis must receive full clinical and neurological examination at birth, whether a prenatal diagnosis is confirmed or not. Examination should include serological and immunological testing, transfontanellar ultrasound to detect cerebral defects such as cerebral calcifications and ventricular dilation, and direct and indirect dilated fundoscopy to exclude chorioretinitis or other eye abnormalities.[45] Brain computed tomography (CT) or magnetic resonance imaging (MRI), electroencephalography (EEG), and hepatic and cardiac ultrasound may also be helpful in severe cases. Various methods and tests are available to reach a postnatal diagnosis as mentioned before.

There is a lack of randomized clinical trials reporting effectiveness of early treatment in improving congenital toxoplasmosis outcomes and reducing its risk of long-term complications, in both pregnant women and infected neonates, however, multiple observational studies exist.[46,47] During the 1950s, pyrimethamine and sulfonamides combination therapy proved its efficacy and became the first-line treatment for neonates with congenital toxoplasmosis. Both drugs act through inhibiting folate metabolism in *Toxoplasma gondii*, thus preventing tachyzoite proliferation and cyst formation.[48] This combination should be supplemented with folinic acid to avoid the risk of folate acid deficiency.[48]

Although treatment protocols vary between centers, no definitive evidence favors one regimen over another.[4] In France, a multidisciplinary approach has led to comprehensive care and an optimized treatment algorithm.[44] Another protocol, developed by McLeod, uses varying doses of pyrimethamine based on disease severity.[47] Notably, treatment should last for at least 12 months to avoid recurrence or long-term disability.[42] Glucose-6-phosphate dehydrogenase (G6PD) deficiency should also be excluded prior to initiation of therapy and regular clinical and laboratory monitoring is needed to evaluate efficacy and identify adverse reactions.[48]

This combination therapy can lead to hematological adverse effects, such as anemia, neutropenia and thrombocytopenia, in up to 30% of treated infants, especially within the first two months of therapy. This is due to the bone marrow suppression effects of these drugs, thus folinic acid is crucial to reduce the risk of bone marrow suppression. Initially, blood examinations should be performed every 15 days, then it should be monthly. Notably, if neutrophils are below 800/mm³, therapy should be stopped resumed upon recovery.[44]

Long-term oncologic or hematologic complications have not been reported in previous studies. Gastrointestinal side effects such as diarrhea and vomiting and dermatologic reactions, such as rash may occasionally occur.[49] Sulfonamides may lead to severe skin conditions like Stevens-Johnson syndrome which require immediate and permanent cessation of therapy.[44]

### *New insights into congenital toxoplasmosis*

*Recombinant proteins in toxoplasmosis diagnosis*

The advancements in recombinant DNA technology have resulted in developing novel diagnostic tools for congenital toxoplasmosis that can differentiate between acute and chronic stages of infection.[38,39] For instance, specific antigens like pMIC8 are more reactive during the acute phase, while soluble *Toxoplasma gondii* antigens (STAg) are linked to chronic infection.[50] $CD8^+$ T-cells also differ

in response to various epitopes such as response to GRA4 epitope that peaks at 2 weeks and ROP7 that peaks at 6–8 weeks.[51]

Furthermore, antigens such as P35 (GRA8) and P22 (SAG2) lead to early induction of IgG antibodies.[52] ELISA using recombinant P22a (rP22a) and rp35a showed high specificity and sensitivity in differentiating between infected and non-infected pregnant women and in differentiating between early and late phases of toxoplasmosis.

*MicroRNAs as emerging biomarkers*

It has been reported that *Toxoplasma* can change host microRNA profiles in a strain-dependent and stage-specific manner.[53,54] MicroRNAs regulate gene expression and have demonstrated potential in diagnosing different diseases.[55] For example, miR-204 is downregulated during the acute phase, while miR-146a is upregulated during chronic infection in mice.[54] In addition, plasma miR-217-5p, miR-712-3p, and miR-511-5p levels were significantly increased in mice infected with both RH and ME49 strains.[53] Although these findings are promising, data in pregnant humans are lacking, and further research is needed to validate miRNAs as diagnostic biomarkers for acute toxoplasmosis in this population.

***Toxoplasma* vaccination**

Studies on *Toxoplasma* vaccination are mainly using vertical transmission models to evaluates immune responses through IgG isotypes and cytokine production. Elevation of IFN-γ, IL-2, IL-12, IL-10, and sometimes IL-4, was observed in non-pregnant mice up to 60–70 days post-vaccination.[56] However, pregnancy changes immune status, thus, findings from non-pregnant mice should be cautiously interpreted.[57] Currently, no vaccine has fully blocked *Toxoplasma* vertical transmission, even with multi-antigen strategies, mainly due to limited understanding of maternal-fetal immune mechanisms.[58]

One study using nanoparticle-based vaccines found protection correlated with decreased IFN-γ and increased IL-6, IL-10 at the placenta.[59] Another study showed a mixed Th1/Th2 response, associated with high survival and low brain cyst load.[60] This suggests fetal adaptive immunity can develop without direct infection. Live attenuated vaccines induced mixed maternal Th1/Th2 immunity, with Th1 crucial for parasite control and Th2 for fetal tolerance.[61]

## CONCLUSION

Despite improvements in diagnostic and therapeutic approaches, congenital toxoplasmosis remains a public health concern. Accurate and early diagnosis using a combination of serological and molecular methods is crucial for effective management. Although prenatal and neonatal therapies have demonstrated effectiveness in mitigating transmission and reducing complications, challenges such as the absence of a definitive cure, treatment toxicity, and limited access to screening persist. Emerging diagnostic markers and vaccine research have the potential to improve management and prevention, highlighting the need for further research and introduction of standardized global screening protocols.

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