

Diagnosis of toxoplasmosis in pregnancy: a review

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Abstract

Determining acute *Toxoplasma gondii* infection in pregnant women, due to the risk of congenital toxoplasmosis is of particular interest in Turkey, as well as worldwide. In recent years, a major effort has been made toward improving our ability to diagnose recently acquired infection in the pregnant woman and congenital infection in the fetus and newborn. We now have a number of new methods that are proving to be of great value towards this end. When ordering and interpreting maternal serological screening tests, providers should not assume quality testing and should question each individual lab regarding its methods of quality assurance; in addition, providers should not rely on a single sample test but seek confirmatory testing through a nationally recognized reference laboratory if results are positive.

Keywords: toxoplasmosis, toxoplasmosis gondii, diagnosis, toxoplasmosis in pregnancy

Background

Toxoplasmosis is caused by infection with the obligate intracellular protozoan parasite *Toxoplasma gondii* (*T.gondii*). It is one of the most prevalent chronic infections affecting one third of the world's human population [1]. The prevalence of *T. gondii* infection varies among different geographical regions. The infection is characterized by non-specific symptoms with the consequent formation of cysts that may remain in latent form in many organs [2]. Primary infection is usually subclinical but in some patients cervical lymphadenopathy or ocular disease can be present [3].

There are four groups of individuals in whom the diagnosis of toxoplasmosis is most critical: pregnant women who acquire their infection during gestation, fetuses and newborns who are congenitally infected, immunocompromised patients, and those with chorioretinitis [4-6]. Although these infections are usually either asymptomatic or associated with self-limited symptoms in adults [e.g., fever, malaise, and lymphadenopathy], infections in pregnant women can cause serious health problems in the fetus if the parasites are transmitted [i.e., congenital toxoplasmosis] and cause severe sequelae in the infant including mental retardation, blindness, and epilepsy. The most frequent challenge encountered by physicians the world over is how to determine if a pregnant woman acquired the acute infection during gestation. Women who acquired their infection prior to pregnancy are essentially not at risk for delivering an infected infant [unless the woman is immunosuppressed]. Practicing obstetricians may be confronted with a number of issues

regarding toxoplasmosis, including diagnosis, laboratory testing, screening practices, clinical presentation, and prevention.

Although congenital toxoplasmosis is not a nationally reportable disease, extrapolation from regional studies indicates that an estimated 400 to 4,000 cases occur in the U.S. each year [2,7,8]. The overall laboratory evidence of an infection of *T. gondii*, at a prevalence rate of 23%, emphasizes the scope of toxoplasmosis in a community, and it explains the heavy burden of morbidity due to this parasitic disease [1]. It was believed that congenital toxoplasmosis results from a primary infection acquired during pregnancy [9], but not from the reactivation of a latent infection in immunocompetent pregnant women [10]. In addition, it was believed that latent toxoplasmosis could reactivate and cause a congenital transmission of the parasite to infants who then become infected in utero [11].

In recent years, a major effort has been made toward improving our ability to diagnose recently acquired infection in the pregnant woman and congenital infection in the fetus and newborn. We now have a number of new methods that are proving to be of great value towards this end. Among these are the serum IgG avidity test, PCR with body fluids and tissues, and Western blots of serum from mother-baby pairs.

The focus of care in the United States is on primary prevention and recommends preconceptional and early pregnancy counseling to teach all women how to avoid personal exposure during pregnancy [12,13]. Countries with high disease prevalence have instituted successful secondary prevention programs via widespread maternal serologic screening [14], but universal

maternal serologic screening for toxoplasmosis is not currently recommended in the United States because of low disease prevalence [15-18]. Instead, current practice suggests maternal serological screening when abnormal fetal findings [often detected by ultrasound] indicate possible infection. Ultrasound findings that prompt testing may include hydrocephaly, anatomic abnormalities of the central nervous system, symmetric fetal growth restriction, and nonimmune hydrops [16]. Providers may also consider maternal testing for all HIV [human immunodeficiency virus]-infected pregnant women and for women with lymphadenopathy who have negative mononucleosis tests [12]. Positive screening is followed by confirmatory maternal testing, in utero fetal diagnosis, and in utero treatment as appropriate [12,13,19].

Infections with *T. gondii* during early pregnancy may frequently lead to many intrauterine malformations [22]. The detection of anti-toxoplasma antibodies by ELISA [enzyme-linked immunosorbent assay] methods is commonly performed in many medical centers. The results of such tests are generally well accepted by clinicians because of their excellent sensitivities and specificities, the rapid availability of results, and the relatively low costs of the tests. It is important to understand that a single serologic test is not enough for the diagnosis of toxoplasmosis. In worldwide, commercial test kits for *Toxoplasma*-specific IgG and IgM antibodies are readily available. Because IgM antibodies can be detected for many months or even years following the acute phase of an infection in some individuals, the presence of IgM antibodies is not always an indication of a recent infection [23]. On the other hand, the presence of specific *T. gondii* IgM antibodies in the chronic stage of an infection, and false-positive IgM positivity results can lead to and result in needless concern and a misdiagnosis [possibly affecting the decision to abort] particularly in pregnant women [9,24]. IgM test results are difficult to interpret and the reliability of test kits is variable. Some commercial IgM tests have had problems with specificity, resulting in unacceptably high rates of false-positive test results. In 1996, the Food and Drug Administration [FDA] and Centers for Disease Control [CDC] conducted extensive evaluations of the six most commonly used commercial IgM kits in the U.S. to determine the extent of the problem with the specificity of these kits. Sensitivity and specificity rates for these six kits ranged from 93.3% to 100.0% and from 77.5% to 99.1%, respectively [20]. Although the sensitivity and specificity seem acceptable, this study design could not determine the extent of false-positive results [21]. The Food and Drug Administration [FDA] has noted problems with false-positive results in some testing methods, and the CDC has responded by creating a toxoplasma serum panel with known positive and negative sera. The FDA now requires new commercial test kits to use this sera as the "gold standard" during quality assurance testing [12]. False positives are a major concern because they create anxiety-ridden pregnancies, expose fetuses to unnecessary procedural risks of diagnosis and side

effects of treatment, and may ultimately lead to termination of a non-infected pregnancy.

As a result of these findings, in 1997 FDA distributed an advisory to physicians in the U.S. highlighting these test limitations. The agency provided a guide for interpreting test results [Table 1] and issued a recommendation to laboratory personnel and physicians advising them to be aware of the specificity problems associated with some commercial test kits before making decisions about the clinical management of their patients. The complete document may be obtained at www.fda.gov/cdrh/toxopha.html [12].

In worldwide there is no systematic screening of pregnant women to detect seroconversion during gestation. Much of the literature is based on studies from France, where such screening is performed monthly to detect recently acquired infection. Thus, mostly, a single serum sample from each woman is submitted for evaluation, and from this sample the physician hopes to learn if the patient has recently been infected, thereby placing the fetus at risk. So, it is important to settle down a screening serology testing accomplished every month in seronegative pregnant in the beginning of the pregnancy. When ordering and interpreting maternal serological screening tests, providers should not assume quality testing and should question each individual lab regarding its methods of quality assurance; in addition, providers should not rely on a single sample test but seek confirmatory testing through a nationally recognized reference laboratory if results are positive [12].

Specific Laboratory Tests

IgM and IgG Detection

Initial maternal serological screening relies on identification of IgG and IgM antibodies using enzyme-linked immunosorbent assay [ELISA] [4]. The presence of elevated levels of *Toxoplasma*-specific IgG antibodies indicates infection has occurred at some point, but does not distinguish between an infection acquired recently and one acquired in the distant past. In acute infection, IgG and IgM antibodies generally rise within 1 to 2 weeks of infection [22]. Acute toxoplasmosis is diagnosed rarely by detecting the parasite in body fluids, tissue, or secretions; the most common method used worldwide in the attempt to determine if and when a pregnant woman has experienced acute infection with toxoplasmosis [4,20]. Determining when *T. gondii* infection occurred in a pregnant woman is important because infection before conception poses little risk for transmission of infection to the fetus; however, infection after conception does pose such risk. Detection of *Toxoplasma*-specific IgM antibodies has been used as an aid in determining the time of infection, but IgM antibodies have been reported to persist for up to 18 months postinfection [25]. A negative IgM with a positive IgG result indicates infection at least 1 year previously. A positive IgM result may indicate more recent infection or may be a false-positive reaction. A flow diagram for *T. gondii* testing and

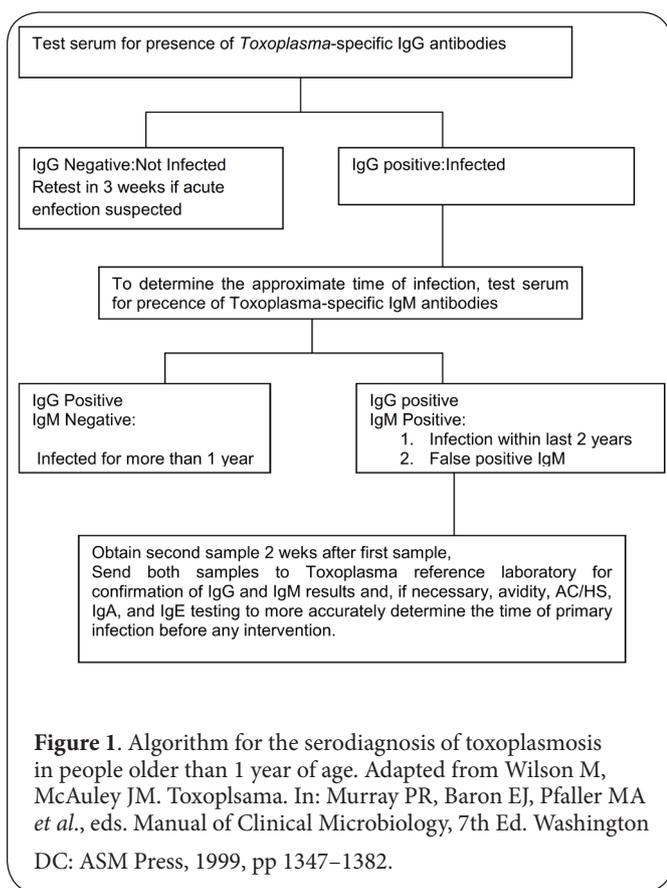


Table 1. Guide to general interpretation of *Toxoplasma gondii* serology results obtained with commercial assays.

Results		Report / Interpretation for humans (except infants)
IgG	IgM	
Negative	Negative	No serological evidence of infection with <i>Toxoplasma</i>
Negative	Equivocal	Possible early acute infection or false-positive IgM reaction. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same, the patient is probably not infected with <i>Toxoplasma</i> .
Negative	Positive	Possible acute infection or false-positive IgM result. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same, the IgM reaction is probably a falsepositive.
Equivocal	Negative	Indeterminate: obtain a new specimen for testing or retest this specimen for IgG in a different assay.
Equivocal	Equivocal	Indeterminate: obtain a new specimen for both IgG and IgM testing.
Equivocal	Positive	Possible acute infection with <i>Toxoplasma</i> . Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same or if the IgG becomes positive, both specimens should be sent to a reference laboratory with experience in the diagnosis of toxoplasmosis for further testing.
Positive	Negative	Infected with <i>Toxoplasma</i> for >1 year.
Positive	Equivocal	Infected with <i>Toxoplasma</i> for probably >.1 year, or false-positive IgM reaction. Obtain a new specimen for IgM testing. If results with the second specimen remain the same, both specimens should be sent to a reference laboratory with experience in the diagnosis of toxoplasmosis for further testing.
Positive	Positive	Possible recent infection within the last 12 months, or false-positive IgM reaction. Send the specimen to a reference laboratory with experience in the diagnosis of toxoplasmosis for further testing.

guide to interpretation of *T. gondii* tests are presented in **Figure 1** and **Table 1**.

Given the potential for false-positive results, the true value of IgM testing is in ruling out the presence of acute infection. In other words, negative IgM results are reassuring, whereas positive results should be interpreted carefully, confirmed in a toxoplasmosis reference laboratory, and followed by serial titers at least 3 weeks apart [4,21,25].

There are different *Toxoplasma* seropositivity reports from all over the world. The population of Turkish childbearing age women has the seropositivity of *T. gondii* as 1.34% for IgM and 24.6% for IgG [26]. In Maracaibo, Venezuela the overall prevalence of toxoplasmosis was 33%, while 18.2% were positive IgM [27]. In Qatar among 823 women of childbearing age the *T. gondii* IgG and IgM was 35.1% and 5.2% respectively [28]. In a study in Beirut the seroprevalence of IgG *T. gondii* antibodies from 2145 sera were examined in hospital and private laboratories and the seropositivity rates were found to be 55% and 67%, respectively. In addition, the IgM *T. gondii* antibodies from 1352 sera from hospital and 2074 sera from private laboratories were similar to each other 6.7% and 6.8%, respectively [29]. In India, 300 pregnant women were screened and anti *Toxoplasma* IgG antibodies were detected in 15.33% cases, while 3% had positive anti-*Toxoplasma* IgM with IgA

and/low avidity antibodies suggestive of acute infection during or just before pregnancy [30]. In another study in Iran, 247 of the 553 pregnant women were found to be positive for IgG *T. gondii* antibodies and the rate of seropositivity of latent *T.gondii* infection was 44.8 % [31].

Sabin-Feldman Dye Test

IgG antibodies are primarily measured by the Sabin-Feldman Dye Test [DT]. The DT is a sensitive and specific neutralization test in which live organisms are lysed in the presence of complement and the patient's IgG *T. gondii* -specific antibody. IgG antibodies usually appear within 1 to 2 weeks of the infection, peak within 1 to 2 months, fall at variable rates, and usually persist for life. The titer does not correlate with the severity of illness.

A positive DT establishes that the patient has been exposed to the parasite. A negative DT essentially rules out prior exposure to *T. gondii* [unless the patient is hypogammaglobulinemic]. However, in a small number of patients, IgG antibodies might not be detected within 2 to 3 weeks after the initial exposure to the parasite. In addition, rare cases of toxoplasmic chorioretinitis and toxoplasmic encephalitis in immunocompromised patients have been documented in patients negative for *T. gondii* -specific IgG

antibodies.

Confirmatory testing with a serologic profile including the Sabin-Feldman DT and IgM ELISA test has also been useful in distinguishing recently acquired infections [32,33]. If both the DT and the IgM-ELISA are negative, then the woman has no previous exposure to *T. gondii* and is susceptible to acute infection during pregnancy. If the DT is positive and the IgM-ELISA is negative, then the woman has been infected in the past. If both tests are positive, acute infection is possible, but tests should be repeated in 3 weeks to observe for rising titers [34,35].

Differential agglutination [AC/HS]

In the early 1980s, it was observed that the agglutination of AC [acetone]-treated *T. gondii* tachyzoites was remarkably and surprisingly different from that of HS [formalin]-fixed parasites [23,36]. Sera from patients with a recently acquired infection tended to agglutinate both the HS and AC parasite suspensions, whereas sera from patients with infection acquired in the distant past tended to have higher titers in the HS agglutination test and lower or negative titers in the AC agglutination test. This phenomenon has been attributed to the variation in IgG profiles in response to shifting *Toxoplasma* surface antigens as the infection progresses from an acute to a more chronic stage. The differential agglutination test [also known as the "AC/HS test"] uses two antigen preparations that express antigenic determinants found early following acute infection [AC antigen] or in the later stages of infection [HS]. Ratios of titers using AC versus HS antigens are interpreted as acute, equivocal, non-acute patterns of reactivity or non-reactive. It should be emphasized that the terms "acute" and "nonacute" refer solely to the interpretation of the agglutination pattern of the AC/HS test and not to whether the patient actually had a recently acquired infection [36]. The acute pattern may persist for one or more years following infection. This test has proved useful in helping differentiate acute from chronic infections but is best used in combination with a panel of other tests [e.g.: *Toxoplasma* serological profile].

In a recent study, data suggest that a nonacute pattern from the AC/HS test is unique in that it excludes infection acquired within the prior 13 months [37]. Thus, the AC/HS test's window for excluding a recently acquired infection appears to be remarkably longer than that for the avidity test [38]. This suggests that the AC/HS test may be of special value for women for whom the diagnosis of acute infection is being considered. Unfortunately, only two reference laboratories [one in the United States and one in Paris, France] perform the AC/HS test.

IgG Avidity Test

Since the U.S. Food and Drug Administration [FDA] has recommended that a solely positive IgM test result should undergo confirmatory testing, avidity specific *T. gondii* IgG tests have been presented to differentiate between recently

acquired and distant infections [9]. Recently, it has been discovered that IgG avidity tests can provide confirmatory evidence of an acute infection and they can distinguish reactivations from primary infections with a single serum specimen. This is of particular value for pregnant and immunosuppressed patients [39-43].

The IgG avidity test was developed to help discriminate between past and recently acquired infection. Results are based on the measurement of the avidity [functional affinity] of *Toxoplasma*-specific IgG antibodies [44]. Following an antigenic challenge, the antibodies produced usually have a low average affinity. During the course of the immune response, there is maturation of antibody affinity that increases progressively over weeks or months. Increase in IgG affinity results from an antigen-driven B-cell selection process, resulting in an increase in complementarity of the antigen-antibody-binding site. Tightness of the binding of the antibody to the antigen is established through chemical forces such as hydrogen bonding or electrostatic and van der Waals interactions. In the *Toxoplasma* IgG avidity enzyme-linked immunosorbent assay [ELISA], urea or another protein-denaturing agent is used to dissociate the antigen-antibody complex. The resulting titer reflects urea-resistant and total IgG and is determined using the ratios of optical densities of urea-treated and -untreated samples.

The method, originally developed by Hedman and his associates in Finland [45], is available in kit form in world. IgG avidity, or the strength with which IgG binds to *T. gondii*, usually shifts from low avidity to high avidity at about 5 months after infection. This is most useful in pregnant women in their first months of gestation who have a positive test for both IgG and IgM *Toxoplasma* antibodies. For example, a woman who has a high avidity test result in her first trimester did not acquire the acute infection in the preceding 3 months. It can be used to rule out primary *T. gondii* infection in early pregnancy in approximately three quarters of women with positive IgM serum tests [44]. Therefore, since her infection was acquired prior to gestation her fetus is essentially not at risk [the likelihood of congenital transmission as a result of an infection acquired in the weeks before or near the time of conception is extremely low, approaching zero [5,45]. In practice, the avidity method is particularly valuable in the common situation in which only a single serum sample, drawn during the first months of gestation, is available. As a matter of fact, antibodies characterize the initial IgG antibody response to an infection with low avidity, in which binding to the specific antigen sites is easily dissociated [34]. The maturation of the IgG response varies between individuals and may take months in pregnant, treated women, for whom one study found that a low IgG AI persisted up to 9 months postinfection [46]. A persistent, low IgG AI poses a diagnostic problem, at least in some pregnant women receiving treatment during pregnancy [47]. In one recent study, high-avidity antibodies were demonstrated retrospectively in 17.5% of 40 women for

whom spiramycin had been recommended because recently acquired infection could not be ruled out in the single serum samples available from each of them [39].

Health care providers and clinical laboratories involved in the care of pregnant women should be aware that avidity testing is a confirmatory test and not the ultimate test for decision-making. Its highest value is observed when laboratory test results reveal high IgG avidity antibodies and the serum is obtained during the time window of exclusion of acute infection for a particular method [*i.e.* 16 weeks for the VIDAS-bioMérieux method]. Low or equivocal IgG avidity antibody results should not be interpreted as diagnostic of recently acquired infection. These low or equivocal avidity antibodies can persist for months to one year or longer. An appropriate decision on how patients with low- or equivocal-avidity test results should be managed must be made using results of other serologic methods. For this purpose a panel of serologic tests consists of ELISA for IgM, IgA, and IgE, the Dye test [measures IgG antibodies], and the differential agglutination test should be performed [43]. Ashburn and colleagues have suggested the appropriate use of the avidity test to be as a confirmatory test along with a panel of other serologic tests as suggested by [48]. Indeed, the avidity test should not be used alone as a definitive test for decision making.

IgA Antibodies

Toxoplasma specific IgA has been measured both by enzyme linked immunosorbent assay [ELISA] and immunosorbent agglutination assay [ISAGA], in the sera of patients with acquired primary infection [49-52]. Following infection it is claimed that specific IgA production parallels that of specific IgM [51], or lags slightly behind IgM [49]. The increased sensitivity of IgA assays over IgM assays for diagnosis of congenital toxoplasmosis represents an advance in diagnosis of the infection in the fetus and newborn [54]. It has been claimed that specific IgA is detected early after infection but also disappears rapidly [55,56]. Ashburn and colleagues found that specific IgA was detected in the first post-seroconversion sample, confirming its rapid appearance after infection [48]. However, the IgA ISAGA was also positive in all other pregnancies.

IgE Antibodies

Beside its critical role in allergy, IgE is generally believed to play a physiological role in immunity towards helminthic parasites [57]. Immune response to parasite infection is often correlated with an increased expression of IgE in mammals, which is believed to play a protective role against worms. IgE antibodies are detectable by ELISA in sera of acutely infected adults, congenitally infected infants, and children with congenital toxoplasmic chorioretinitis. The duration of IgE seropositivity is less than with IgM or IgA antibodies and hence appears useful as an adjunctive method for identifying recently acquired infections.

Histologic Diagnosis

Demonstration of tachyzoites in tissue sections or smears of body fluid [*e.g.*, CSF, amniotic fluid or BAL] establishes the diagnosis of the acute infection. It is often difficult to demonstrate tachyzoites in conventionally stained tissue sections. The immunoperoxidase technique, which uses antisera to *T. gondii*, has proven both sensitive and specific; it has been successfully used to demonstrate the presence of the parasite in the central nervous system of AIDS patients. The immunoperoxidase method is applicable to unfixed or formalin-fixed paraffin-embedded tissue sections.

A rapid and technically simple method is the detection of *T. gondii* in air-dried, Wright-Giemsa-stained slides of centrifuged [*e.g.*, cytocentrifuge] sediment of CSF or of brain aspirate or in impression smears of biopsy tissue.

The presence of multiple tissue cysts near an inflammatory necrotic lesion probably establishes the diagnosis of acute infection or reactivation of latent infection.

Polymerase Chain Reaction [PCR]

Confirmed positive maternal serological screening should be accompanied by fetal diagnosis. Prenatal diagnosis of congenital toxoplasmosis is primarily based on ultrasonography and PCR with amniotic fluid [4,40]. The polymerase chain reaction [PCR] amplification of toxoplasmosis DNA from amniotic fluid has been deemed the most reliable and safe method of prenatal diagnosis and has basically replaced direct sampling of fetal blood [4,40,58,59]. Amniotic fluid testing by PCR is indicated in all pregnant women with serologic test results diagnostic or highly suggestive of acute infection acquired during gestation and also if there is evidence of fetal damage by ultrasound examination [*e.g.*, hydrocephalus and/or calcifications]. Amniocentesis for PCR is not recommended in pregnancies with maternal human immunodeficiency virus [HIV] infection due to procedural risks of fetal HIV transmission [4].

The most recent study of PCR reports an overall sensitivity of 64%, a negative predictive value of 87.8%, a specificity of 100%, and a positive predictive value of 100% [58]. This study also found that the sensitivity of PCR is significantly higher when maternal infection occurs between 17 and 22 weeks' gestation [58]. The reliability of PCR prior to 18 weeks' gestation remains essentially unknown [4,45,59]. Hohlfeld *et al.* reported the performance of a competitive PCR test performed on amniotic fluid from 339 consecutive women from Paris, France, who acquired acute *T. gondii* infection during pregnancy [60]. In this study amniocentesis was performed between 18 and 38 weeks. PCR with amniotic fluid had a PPV of 100% and an NPV of 99.7% [45]. In addition, PCR of amniotic fluid is more sensitive than fetal blood sampling and is safer [61]. The PCR can be performed as early as 18 weeks' gestation, whereas IgM tests of fetal blood are only positive after 22 weeks' gestation [4,45,62].

However, false-positive and false-negative tests do occur

with PCR [60]. In a subsequent and more recent study, Romand *et al.* reported the performance of the same PCR method used by Hohlfeld *et al.* for 271 pregnant women from Paris, Lyon, and Marseille, France, who were diagnosed with acute *T. gondii* infection during gestation [59]. In this study, amniocentesis was performed in most patients at least 4 weeks after the estimated date of infection [systematic serologic screening at monthly intervals is performed in all pregnant women in France] but not prior to 18 weeks of gestation. PCR with amniotic fluid had a PPV of 100%, a specificity of 100%, an NPV of 88%, and a sensitivity of 64% [58]. A negative PCR at any gestation cannot completely rule out congenital infection, and obstetric providers should consider continued follow-up via serial ultrasounds, prophylaxis with spiramycin therapy, and neonatal testing [58].

Children born to mothers who acquired the primary infection during gestation should be evaluated at birth for the possibility of congenital toxoplasmosis. Offspring of mothers chronically infected with the parasite but who are immunologically compromised [*e.g.*, those with human immunodeficiency virus infection or those receiving high-dose immunosuppressive drugs] should also undergo a thorough diagnostic workup to rule out the possibility of congenital toxoplasmosis. PCR with cerebrospinal fluid, whole blood, and urine has been successfully used and could be included in the evaluation of these newborns [5,63-65].

Competing interests

The authors declare that they have no competing interests.

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