



## The Uncharted Territory

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### ABSTRACT

Determining acute *Toxoplasma gondii* infection in pregnant women, due to the risk of congenital toxoplasmosis is of particular interest 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.

### 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, infection, IgG and IgM antibodies generally rise within 1 to 2 weeks of infection. 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 have 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 falsepositive reaction.

### 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 titre 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.

### 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].

### 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.

### 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].

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