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Toxoplasmosis

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Summary Infections with *Toxoplasma gondii* occur worldwide, but are especially prevalent in Europe, South America and Africa. The primary problem for the diagnosis of *T. gondii* infection is long-lasting IgM-antibodies, thus the presence of *T. gondii*-specific IgM-antibodies do not necessarily indicate an acute infection. The use of a *Toxoplasma*-specific IgG-avidity ratio, differentiated Western blots and two-dimensional immunoblots usually resolves diagnostic problems. There is no consensus on the best strategy to control congenital toxoplasmosis. Recent European prospective, but descriptive, studies including a meta-analysis of existing cohorts have found a surprisingly small effect on maternal—fetal transmission and clinical signs in children treated for *T. gondii* infection diagnosed by pre- and neonatal screening programmes. No randomised studies exist on the treatment of *T. gondii* infection in pregnant women and newborn children with congenital toxoplasmosis. Atovaquone is the most promising new drug available, but is not yet approved for use in pregnant women and small children.

Prevalence of infection with *Toxoplasma gondii*

Toxoplasma gondii occurs worldwide, but its incidence is higher in tropical areas and decreases with increasing latitude. Seroprevalence in Europe is high, up to 54% in Southern European countries and it decreases with increasing latitude to 5—10% in northern Sweden and Norway.[1,2] The age-specific prevalence has been decreasing in Europe over the past three to four decades.[3,4] The study National Health and Nutrition Examination Study (NHANES: 1999—2000) and the NHANES III (1988—1994) from the USA found a *T. gondii* seroprevalence of 15.8% in the 12—49 years age-group.[5,6] *Toxoplasma gondii* is a common infection in South America and a study from Brazil found that seroprevalence was high in people from poor socio-economic conditions probably due to water-borne transmission.[7]

The seroprevalence is low in most Asian countries and a study of human immuno-deficiency virus (HIV)-positive patients from Taiwan found a seroprevalence of 10.2%.[8] A recent study from India found a seroprevalence of *Toxoplasma*-specific IgG antibodies of 45%,[9] while a study from Malaysia found a seroprevalence in Malays of 55.7%.[10] Another study from Sudan found a seroprevalence in pregnant women from Khartoum of 34.1%.[11] Out of 1828 HIV-positive patients from Bobo-Dioulasso, Burkina Faso, 25.4% had positive *T. gondii* serology.[12] Immigrants to the UK born in West Africa had a 100-fold higher incidence of symptomatic eye disease due to *T. gondii* compared to white people born in Britain.[13]

T. gondii infection in pregnancy

If a pregnant woman acquires primary infection in pregnancy, *T. gondii* may be transmitted to the fetus and cause

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inflammatory lesions that may lead to permanent neurological damage, with or without hydrocephalus, and chorioretinitis with visual impairment. The pregnant woman and the infected newborn are often asymptomatic but the child is at risk of recurring chorioretinitis later in life.

How to best prevent damage due to congenital toxoplasmosis is a matter of debate and recent collaborative studies have elucidated the current state of knowledge, but prospective, randomised trials are needed.

Risk factors for infection with *T. gondii*

There is no biological test that can distinguish infections due to oocysts transmitted from felines, from tissue cysts ingested from infected meat.[14,15] Therefore, epidemiological surveys examining risk factors in infected and non-infected persons remain the most useful way of assessing the relative importance of different sources of *T. gondii* infection in humans.

A prospective case—control study from Norway in 1992—1994 found that eating raw or undercooked meat and meat products, poor kitchen hygiene, cleaning the cat litter box and eating unwashed raw vegetables or fruits were associated with an increased risk of *T. gondii* infection.[16] From 1991 through to 1994 a prospective risk factor study in pregnant women infected during pregnancy and controls was performed in Italy. Eating cured pork or raw meat at least once a month increased the risk of *T. gondii* infection threefold.[17]

A European multicentre, case—control study in six centres included 252 cases and 708 controls.[18] That study found that contact with raw or undercooked beef, lamb, or other sources of meat, as well as with soil, were independent risk factors for *T. gondii* seroconversion during pregnancy. In addition, travel outside Europe, the USA and Canada was a risk factor for seroconversion. The population attributable fraction showed that 30—63% of seroconversions were due to consumption of undercooked or cured meat products and 6—17% were a result of soil contact, but ownership of a cat was not a risk factor.[19] Information about how to avoid toxoplasmosis in pregnancy could be a cost—effective approach to preventing congenital toxoplasmosis.[19,20] Based on this knowledge of these identified risk factors for primary toxoplasmosis, pregnant women should be appropriately advised by their obstetricians and primary care providers on how to lower the risk of congenital toxoplasmosis by avoiding risk factor exposure.

T. gondii genotypes, distribution and pathogenicity

Toxoplasma gondii can be divided into three main genotypes.[21,22] Genotype II is the most prevalent type in Europe.[23] It has been proposed that the different genotypes may be partly responsible for the different pathogenicities observed in the infection. Recent work, however, suggests a more complicated picture in Brazil, with both pathogenic and apathogenic isolates overall belonging to genotype I.[24,25] One study has reported an unusual abundance of type I and recombinant strains in patients with retinochoroiditis,[26] while in a recent study from Brazil of ocular disease caused by *T. gondii*, analysis of lesions found only type I and III strains and no type II strains.[26] In Europe, a study of 86 pregnant women from France found predominantly type II,[27] which confirms previous study results which also primarily found type II.[28] Recently, methods have been developed that allow *T. gondii* in patients to be, at least partially, typed using genotype-specific markers.[29]

Diagnosis of *T. gondii* infections in pregnant women

The majority of maternal infections are subclinical and serological methods form the basis for diagnosis. In countries where pre-natal screening programmes are in place a test of the first blood sample from the pregnant women for *Toxoplasma*-specific IgM- and IgG-antibodies is performed. Conversion from seronegative to IgM/IgG-positive forms a solid basis for diagnosis. The interpretation of a finding of specific IgM and IgG may be more difficult as approximately 5% of seropositive women in the first trimester have *Toxoplasma*-specific IgM-antibodies, but only approximately 4% of these give birth to a child with congenital *Toxoplasma* infection. Low levels of *Toxoplasma*-specific IgM antibodies may be found for up to several years after acute infection and the mere demonstration of low levels of *Toxoplasma*-specific IgM-antibodies is, therefore, not regarded as a sign by itself of acute infection with *T. gondii*.[30,31]

It is, therefore, a problem to diagnose whether women with specific IgM antibodies are infected before or after conception. This problem has been partly solved by obtaining repeat samples from pregnant women to see if there is any development of the immune response. It is generally agreed that there is a development of the *Toxoplasma*-specific IgG-antibody response within the first 8 weeks after infection, after which time the IgG levels are maintained at a high level, with or without declining IgM antibodies.[32,33]

Combined, two-test strategies

The questions of why there are so many low-level *Toxoplasma*-specific IgM-positive patients and whether the diagnostic performance could be improved by repeating the same tests 2 weeks apart were investigated in a European multicentre study.[34] All highly sensitive assays were found to have a low specificity and single tests were unable to reliably distinguish between acute and past infections. Only the sequential analysis of sera by a highly sensitive IgM assay in combination with IgG avidity testing, i.e. measuring the antibody binding capacity (avidity index), gave excellent diagnostic performances in the diagnosis of acute and recent infection. In contrast, IgA or IgM assays were less useful for diagnosing acute infections by confirming positive IgM results.[37]

The increased use of the *T. gondii* IgG-avidity test has, however, highlighted an inherent problem with that test: the maturation of the IgG-response after a primary toxoplasma infection, as reflected by binding capacity (avidity index), varies considerably between individuals. In one