Toxoplasmosis in pregnancy: often suspected, rarely convicted

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Toxoplasmosis during pregnancy is uncommon and usually asymptomatic but can cause catastrophic fetal disease. It is often suspected because of non-specific symptoms or positive serological tests. However, false-positive toxoplasma IgM tests are common and confirmatory tests not always reliable. The risk of fetal infection increases as pregnancy progresses; it should be diagnosed or excluded by amniotic fluid PCR, especially early in pregnancy when the risk of severe damage is high. Prompt antibiotic therapy of maternal infection probably reduces fetal infection and disease, but its efficacy has not been confirmed by randomised controlled trials.

The culprit – *Toxoplasma gondii*

Sexual reproduction of *T. gondii* (Figure 1) occurs in the intestines of felines. Infected cats excrete oocysts in faeces which are infective, after several days, if ingested by warm-blooded animals including food-producing livestock and humans. Toxoplasmas spread throughout the body until halted by the host immune response. A few organisms remain dormant but viable, in tissue cysts in muscle, eyes or brain, where they can reactivate if local or systemic immunity is compromised.

Epidemiology and risk factors

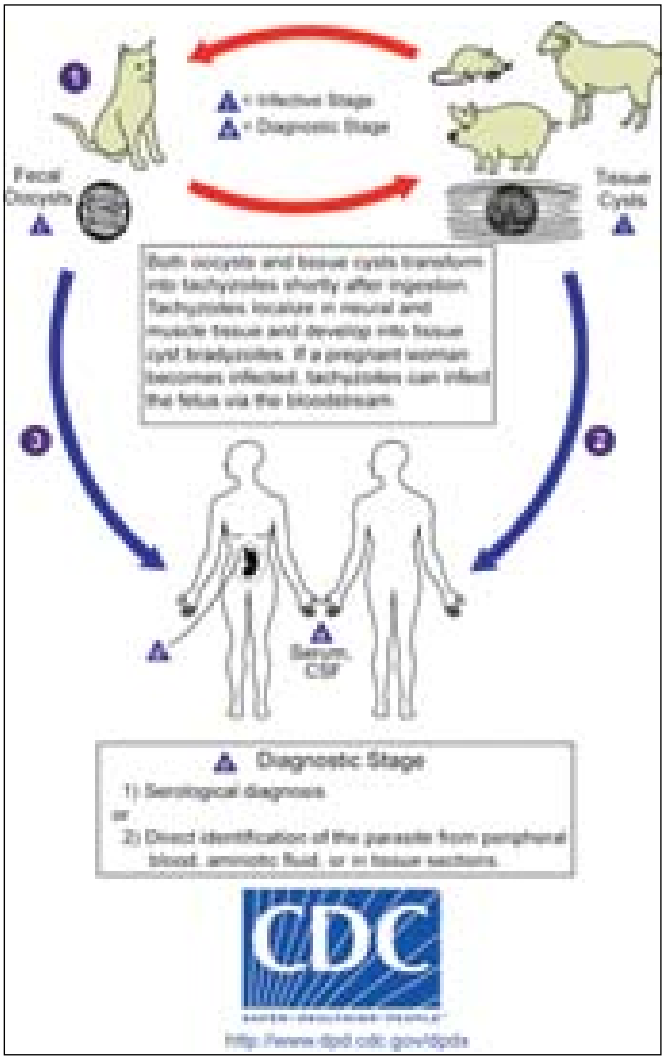
Faecal oocysts mature rapidly in warm, moist conditions; the geographic prevalence of toxoplasmosis is, roughly, inversely proportional to distance from the equator. Humans are infected by eating undercooked meat or by coming into contact with soil contaminated by cat faeces (e.g. on hands or unwashed vegetables) [1]. A case control study showed that consumption of undercooked or cured meat products (30-63% of cases), contact with soil (6-17%) and travel outside Europe and North America were the most common risk factors; contact with cats was not [2].

Clinical manifestations and presentation

Toxoplasmosis is usually asymptomatic or causes non-specific, self-limiting illness with malaise, mild fever and lymphadenopathy (commonly cervical). Severe, multi-system disease can occur in severely immunodeficient individuals. If toxoplasmosis occurs during pregnancy, the immunologically immature fetus is at risk. Maternal toxoplasmosis is often suspected because of symptoms or a positive toxoplasma IgM which often persists for months or years after acute infection.

At least 80% of intrauterine infections are asymptomatic and often unrecognised. Gross clinical features of fetal/congenital toxoplasmosis – hepatosplenomegaly, hydrocephalus liver and/or brain calcification (Figure 2) – are rare. The most common sign – *Toxoplasma chorioretinitis* (Figure 3) – is often missed

Figure 1. Life cycle of *T. gondii.*



at birth but can progress and first present as sight-threatening reactivation during childhood or early adult life. Progressive encephalitis can cause developmental and intellectual delay.

Vertical transmission

The risk of fetal infection increases from <15% when maternal infection occurs in the first trimester, to 44% in the second and 72% in the third trimester of pregnancy [3, 4]. Fetal infection in the first trimester causes symptomatic disease in about 75% of cases, compared with about 15% in the second and none in the third [5, 6].

Antenatal screening and diagnosis

Routine prenatal screening has been practised routinely in some European countries for many years, but is not recommended in Australia – maternal infection is uncommon and fetal disease rare, the sensitivity and specificity of screening tests are poor and the efficacy of treatment is doubtful.

Toxoplasma IgG can be measured by a variety of methods (some of which are historical). Enzyme-linked immunoassays (EIA) are now most commonly used. Seroconversion is the best serological evidence of recent infection, whereas toxoplasma IgM EIA has poor specificity [7]. If IgG and IgM are positive and unchanged when repeated with different kits or on another specimen, further tests are needed to improve specificity, for example:

- A quantitative antibody test – e.g. differential agglutination may show a rising titre in paired sera, as toxoplasma IgG titre continues to rise for about 3 months after acute infection.
- A double sandwich IgM EIA and IgM immunosorbent agglutination assay (ISAGA) are more specific than commercial IgM EIAs – levels rise and fall rapidly after infection, albeit at variable rates.
- IgG avidity is now the standard 'confirmatory' test.

Following acute infection, the affinity of IgG for specific antigen increases progressively, making disruption of serum antigen/antibody complexes, e.g. by treatment with 8M urea, increasingly difficult. The avidity index is the ratio of IgG levels (measured by EIA optical density values) in aliquots of treated and untreated serum, tested in parallel. In general, high avidity indicates past and low avidity recent infection.

IgG avidity tests are not standardised. A recent review of 11 published studies, involving six in-house and eight commercial IgG avidity tests, showed considerable variation in definitions of low avidity index (from <15% to <50%) and high avidity index (from >20% to >58%) and the maturation period, which defines recent infection (from 3-6 months). Generally, delayed IgG maturation was found in fewer than 5% of subjects but two methods showed poor sensitivity. Occasionally, low avidity persisted for years. In one study, the same method demonstrated

Figure 2. Severe fetal toxoplasmosis. Routine fetal ultrasound examination at about 16 weeks' gestation showed gross hydrocephalus and ascites and pregnancy was terminated. Toxoplasmosis was confirmed by histological examination of fetal tissues.

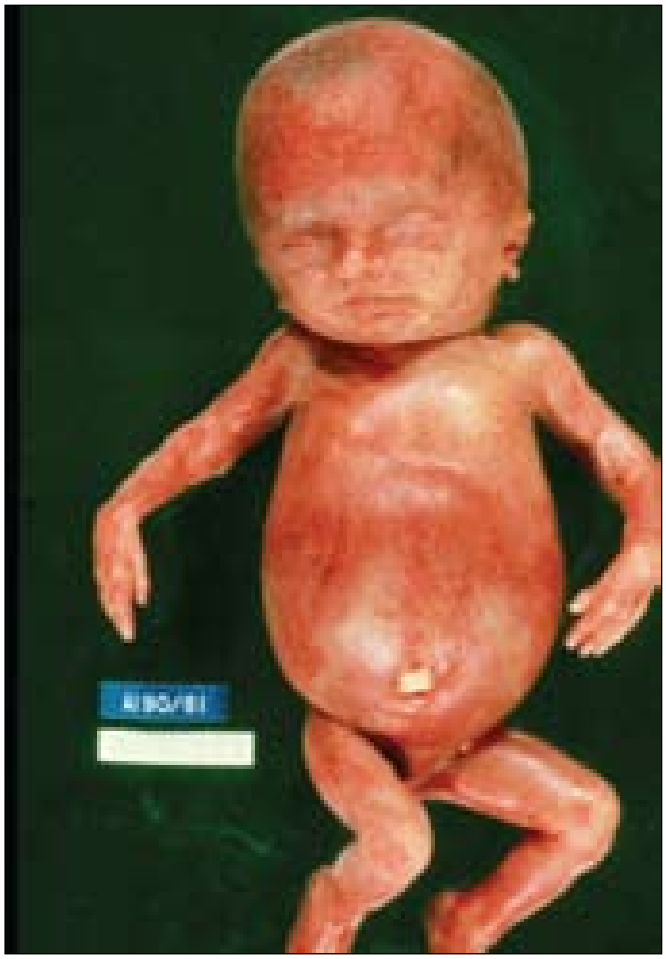
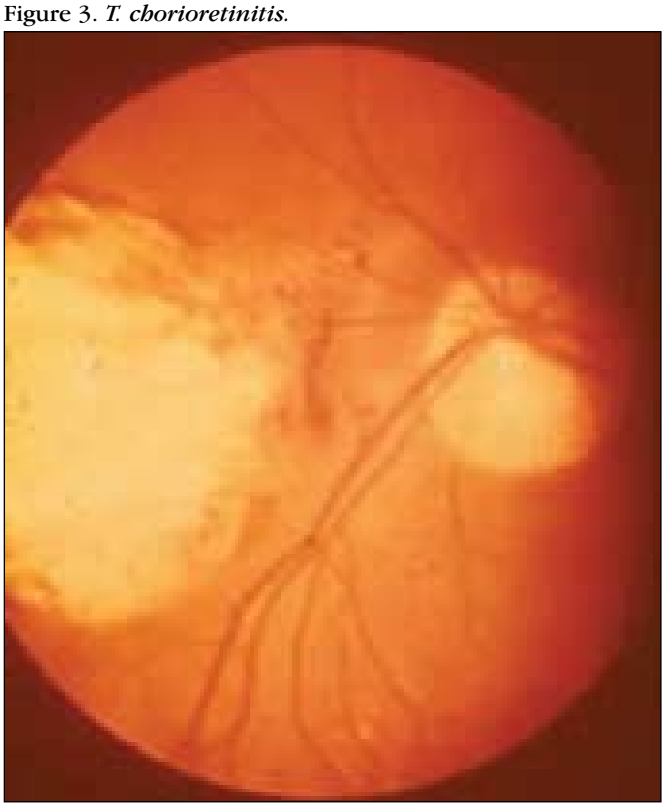


Figure 3. *T. chorioretinitis.*



delayed maturation in 9.5% of pregnant women compared with 0.9% of non-pregnant subjects. High avidity indices within the maturation period were reported with five methods [8]. Despite these limitations, properly validated IgG avidity tests can assist in diagnosis or exclusion of recent toxoplasmosis.

If recent toxoplasmosis is likely or cannot be excluded during pregnancy, intrauterine diagnosis is recommended, especially in the first half of pregnancy, because of the high risk of fetal damage. Amniotic fluid PCR, at 18 weeks' gestation or later, is highly specific and much more sensitive (97%) than mouse inoculation (64%), fetal blood IgM or non-specific inflammatory markers (30-40%) [9].

A study in nine European centres examined the effects of gestational age at maternal seroconversion, timing of amniocentesis and treatment, on the accuracy of PCR for diagnosis of congenital toxoplasmosis. The positive predictive values (PPVs) increased, from 0.75 to 0.94 and the NPVs fell, from 0.98 to 0.56 between the first and third trimesters. There was considerable variation in specificity centres [10].

Treatment

T. gondii is susceptible to several types of antimicrobial. Workers in some European countries, where routine antenatal screening has been compulsory for years, recommend treatment with spiramycin (a macrolide, which can be used safely in early pregnancy), as soon as possible after the diagnosis. Termination is often recommended for fetal infection in the first trimester because of the high risk of severe disease. Later in pregnancy, spiramycin may be continued or replaced by combined sulphadiazine and pyrimethamine (with folinic acid, to reduce side-effects) [7].

There have been no randomised controlled trials of treatment. Despite extensive experience and circumstantial evidence of efficacy [5, 6], a recent systematic review of published cohort studies [4] and a large case review [11], only weak evidence that treatment reduced placental transmission was found and none that it reduced clinical manifestations; there were, however, significant biases in selection of treated cases and controls. It is therefore likely that benefits are greatest in or limited to cases in which treatment is started within 3-4 weeks of maternal infection [4, 11].

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