

Toxoplasmosis in Pregnancy: Prevention, Screening, and Treatment

This clinical practice guideline has been prepared by the Infectious Disease Committee, reviewed by the Family Practice Advisory Committee and the Maternal Fetal Medicine Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure statements have been received from all members of the committee.

Objective: To review the prevention, diagnosis, and management of toxoplasmosis in pregnancy.

Outcomes: Outcomes evaluated include the effect of screening on diagnosis of congenital toxoplasmosis and the efficacy of prophylaxis and treatment.

Evidence: The Cochrane Library and Medline were searched for articles published in English from 1990 to the present related to toxoplasmosis and pregnancy. Additional articles were identified through references of these articles.

Values: The quality of evidence is rated and recommendations made according to guidelines developed by the Canadian Task Force on Preventive Health Care (Table 1).

Benefits, harms, and costs: Guideline implementation should assist the practitioner in developing an approach to screening for and treatment of toxoplasmosis in pregnancy. Patients will benefit from appropriate management of this condition.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

Recommendations

1. Routine universal screening should not be performed for pregnant women at low risk. Serologic screening should be offered only to pregnant women considered to be at risk for primary *Toxoplasma gondii* infection. (II-3E)
2. Suspected recent infection in a pregnant woman should be confirmed before intervention by having samples tested at a toxoplasmosis reference laboratory, using tests that are as accurate as possible and correctly interpreted. (II-2B)
3. If acute infection is suspected, repeat testing should be performed within 2 to 3 weeks, and consideration given to starting therapy with spiramycin immediately, without waiting for the repeat test results. (II-2B)
4. Amniocentesis should be offered to identify *Toxoplasma gondii* in the amniotic fluid by polymerase chain reaction (a) if maternal primary infection is diagnosed, (b) if serologic testing cannot confirm or exclude acute infection, or (c) in the presence of abnormal ultrasound findings (intracranial calcification,

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Key Words: Toxoplasmosis, pregnancy, congenital, prenatal, disease transmission, mass screening, counselling

Abstract

Background: One of the major consequences of pregnant women becoming infected by *Toxoplasma gondii* is vertical transmission to the fetus. Although rare, congenital toxoplasmosis can cause severe neurological or ocular disease (leading to blindness), as well as cardiac and cerebral anomalies. Prenatal care must include education about prevention of toxoplasmosis. The low prevalence of the disease in the Canadian population and limitations in diagnosis and therapy limit the effectiveness of screening strategies. Therefore, routine screening is not currently recommended.

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.³²

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.³²

microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction). (II-2B)

5. Amniocentesis should not be offered for the identification of *Toxoplasma gondii* infection at less than 18 weeks' gestation and should be offered no less than 4 weeks after suspected acute maternal infection to lower the occurrence of false-negative results. (II-2D)
6. *Toxoplasma gondii* infection should be suspected and screening should be offered to pregnant women with ultrasound findings consistent with possible TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes, and other) infection, including but not limited to intracranial calcification, microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction. (II-2B)
7. Each case involving a pregnant woman suspected of having an acute *Toxoplasma gondii* infection acquired during gestation should be discussed with an expert in the management of toxoplasmosis. (III-B)
8. If maternal infection has been confirmed but the fetus is not yet known to be infected, spiramycin should be offered for fetal prophylaxis (to prevent spread of organisms across the placenta from mother to fetus). (I-B)
9. A combination of pyrimethamine, sulfadiazine, and folic acid should be offered as treatment for women in whom fetal infection has been confirmed or is highly suspected (usually by a positive amniotic fluid polymerase chain reaction). (I-B)
10. Anti-toxoplasma treatment in immunocompetent pregnant women with previous infection with *Toxoplasma gondii* should not be necessary. (I-E)
11. Women who are immunosuppressed or HIV-positive should be offered screening because of the risk of reactivation and toxoplasmosis encephalitis. (I-A)
12. A non-pregnant woman who has been diagnosed with an acute *Toxoplasma gondii* infection should be counselled to wait 6 months before attempting to become pregnant. Each case should be considered separately in consultation with an expert. (III-B)

13. Information on prevention of *Toxoplasma gondii* infection in pregnancy should be made available to all women who are pregnant or planning a pregnancy. (III-C)

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TOXOPLASMA GONDII: MAIN MICROBIOLOGIC CHARACTERISTICS

Toxoplasma gondii (*T. gondii*) is an obligate intracellular protozoan parasite.¹ It has a complex life cycle with asexual reproduction taking place in diverse tissues of mammals and birds (secondary hosts) and sexual reproduction taking place in digestive epithelium of cats (primary host).^{1–3} Cats mainly become contaminated by ingesting animal flesh (mouse, bird) encysted with *T. gondii* and rarely by ingesting oocysts directly from the feces of other cats.^{2,3} Infected cats are usually asymptomatic and begin to shed unsporulated (non-infectious) oocysts (up to one million per day) in their feces 1 to 2 weeks after exposure.^{3,4} Most cats shed oocysts only once in their lives.^{2,4} Within days to weeks, the oocysts sporulate and become infectious.^{2,3} Oocysts survive best in warm and humid conditions (garden, sand box, litter) and can remain infectious for many months.^{3,5,6} Oocysts also withstand exposure to freezing for up to 18 months, especially if they are covered and out of direct sunlight.³ After ingestion by a secondary host (human, bird, rodent, domestic animal), oocysts release sporozoites, which change into tachyzoites.^{1,3} Tachyzoites are present during acute infection and are capable of invading

cells and replicating.^{1,3} They are disseminated widely and circulate from 3 to 10 days in the immunocompetent host before changing into bradyzoites and forming cysts in tissues.^{1,3} These cysts remain present during latent infection.^{1,3} Once infected, humans are believed to remain infected for life. Unless immunosuppression occurs and the organism reactivates, human hosts usually remain asymptomatic.⁷

EPIDEMIOLOGY AND RISK FACTORS

Toxoplasmosis is the third leading infectious cause of food-borne death, after salmonellosis and listeriosis.^{5,7} Seroprevalence varies considerably with high seroprevalence (> 50%) occurring in countries where raw meat is commonly eaten (France, 54%) and in tropical regions of Latin America or Sub-Saharan Africa where cats are numerous and the climate is favourable to oocysts survival.^{4,5,8} In the United States, 15% of childbearing age women (15 to 44) are infected with *T. gondii*, with the incidence of congenital toxoplasmosis estimated at 400 to 4000 cases per year.⁵ In Canada, only a few serologic surveys or prospective studies of women of childbearing age have been carried out.⁹ On the basis of these studies, Carter and Frank⁹ have extrapolated a seroprevalence between 20% and 40% for Canadian women of childbearing age. However, their conclusion was based on studies with many important biases.⁹ High seroprevalence (59.8%) is documented in Inuit populations of Nunavik and other northern communities, associated with drinking contaminated water and consuming raw or undercooked seal meat and wild fowl.¹⁰

The 3 main routes of transmission are ingestion of raw or undercooked meats, exposure to oocyst-infected cat feces, and vertical transmission.^{1,2,5} In pregnancy, the most common mechanisms of acquiring infection are through consuming raw or very undercooked meats or contaminated water, or exposure to soil (gardening without gloves) or cat litter.^{1,2,5} Transfusion or organ transplantation from an infected person can also transmit the organism.⁷ Data from a European multicentre case-control study show that raw or undercooked meat accounts for more than 30% to 63 % of *T. gondii* seroconversions during pregnancy.⁴ Similar results (60%) were observed in the United States.^{4,11} Several studies have shown that owning a cat poses little risk for human infection.^{2,4,7} A study of 24 106 cats in European countries reported a detection rate of *T. gondii* oocysts of 0.11%.⁷ The risk of infection from cats is related to exposure to feces from a cat that is shedding oocysts.^{2,4} Indoor cats that do not hunt and are not fed raw meat are unlikely to acquire *T. gondii* infection.^{2-4,6} Prevalence rates vary according to geographic location, and pregnant women who travel to areas with higher prevalence rates may be at increased risk of infection.^{4,5}

CLINICAL MANIFESTATIONS

Most pregnant women (> 90%) with acquired *T. gondii* infection do not experience obvious signs and symptoms, and spontaneous recovery is the rule.^{12,13} Only a small proportion will develop clinical signs of the disease.^{8,12} The clinical presentation in pregnant women is not more severe than in non-pregnant women, and most often occurs as an influenza-like illness (low-grade fever, malaise, lymphadenopathy), with an incubation period of 5 to 18 days following exposure.^{11,12,14} Pregnant women will rarely show visual changes due to toxoplasmic chorioretinitis.^{15,16} In immunocompromised pregnant women, *T. gondii* can cause severe encephalitis, myocarditis, pneumonitis, or hepatitis via acute infection or reactivation of a latent infection.^{1,17}

DIAGNOSIS

T. gondii infection can be identified with serologic testing or amniocentesis, or by the presence of abnormal ultrasound findings (discussed in the Toxoplasmosis in Pregnancy section below).

Serologic Testing

Serologic testing is often the first step in diagnosis, using IgG and IgM antibodies. The diagnostic challenge is differentiating between a primary and a chronic infection, and results of IgG and IgM testing can often be difficult to interpret. For this reason, it is important to consult with an expert in this area when confirming the diagnosis. The presence of IgM antibodies cannot be considered reliable for making a diagnosis of acute toxoplasmosis infection. IgM antibody titres rise from 5 days to weeks following acute infection, reaching a maximum after 1 to 2 months and decline more rapidly than IgG.¹⁴ Although IgM antibodies can decrease to low or undetectable levels, in many cases they may persist for years following the acute infection.^{14,18} IgG antibodies appear later than IgM and are usually detectable within 1 to 2 weeks after the infection, with the peak reached within 12 weeks to 6 months after acute infection. They will be detectable for years after acquired infection and are usually present throughout life.¹⁸

If IgG and IgM are both negative, this indicates the absence of infection or extremely recent acute infection.¹⁹ If testing reveals a positive IgG and negative IgM, this indicates an old infection (infection greater than 1 year ago). If both IgG and IgM are positive, this indicates either a recent infection or a false-positive test result.¹⁸ If acute infection is suspected, repeat testing is recommended within 2 to 3 weeks.^{11,14} A 4-fold rise in IgG antibody titres between tests indicates a recent infection.²⁰ Commercial serologic diagnostic test kits can be unreliable (with unacceptable

false-positive and false-negative results).^{18–20} Therefore, it is very important that positive antibody results be confirmed by a toxoplasmosis reference laboratory (available in Montreal, QC, and Palo Alto, CA).^{18–20} Specific assays are used in reference laboratories to more accurately measure antibody levels, such as Sabin-Feldman dye test and indirect fluorescent antibody test.^{14,18}

Knowing when infection occurred during pregnancy is important in evaluating the risk of fetal transmission, initiating antibiotic therapy, and ensuring appropriate prenatal counselling.¹⁹ Reference laboratories use additional specific tests, including IgG avidity, to assist in determining the timing of the infection.^{8,19} The IgG avidity test measures the strength of IgG binding to the organism.²⁰ Avidity, in most cases but not all, shifts from low to high after about 5 months. If the avidity is high, this suggests infection occurred at least 5 months before testing.²⁰

Amniocentesis

Amniocentesis should be offered to appropriate patients, in consultation with maternal fetal medicine specialists, to identify *T. gondii* in the amniotic fluid by polymerase chain reaction (sensitivity 81% to 90%, specificity 96% to 100%). Whether or not diagnostic testing is performed will be influenced by when maternal primary infection is diagnosed, if serologic testing cannot confirm or exclude acute infection, and if there are abnormal ultrasound findings suggestive of toxoplasmosis infection.

Amniocentesis for the identification of *T. gondii* infection should not be offered at less than 18 weeks' gestation because of the high rate of false-positive results, and it should be offered no less than 4 weeks after the time of suspected acute maternal infection.²¹

Fetal blood sampling (cordocentesis), which was previously the gold standard for diagnosing fetal infection, should no longer be offered as a diagnostic test because of reported high sensitivity and specificity of the amniotic fluid polymerase chain reaction test and because of the associated higher fetal risk with cordocentesis.^{20–23}

Recommendations

1. Routine universal screening should not be performed for pregnant women at low risk. Serologic screening should be offered only to pregnant women considered to be at risk for primary *Toxoplasma gondii* infection. (II-3E)
2. Suspected recent infection in a pregnant woman should be confirmed before intervention by having samples tested at a toxoplasmosis reference laboratory, using tests that are as accurate as possible and correctly interpreted. (II-2B)

3. If acute infection is suspected, repeat testing should be performed within 2 to 3 weeks, and consideration given to starting therapy with spiramycin immediately, without waiting for the repeat test results. (II-2B)
4. Amniocentesis should be offered to identify *Toxoplasma gondii* in the amniotic fluid by polymerase chain reaction (a) if maternal primary infection is diagnosed, (b) if serologic testing cannot confirm or exclude acute infection, or (c) in the presence of abnormal ultrasound findings (intracranial calcification, microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction). (II-2B)
5. Amniocentesis should not be offered for the identification of *Toxoplasma gondii* infection at less than 18 weeks' gestation and should be offered no less than 4 weeks after suspected acute maternal infection to lower the occurrence of false-negative results. (II-2D)

TOXOPLASMOSIS IN PREGNANCY

Transmission to the fetus occurs predominantly in women who acquire their primary infection during pregnancy.¹⁶ Congenital transmission, in certain rare cases, has been detected in chronically infected pregnant women whose infection was reactivated because of their immunocompromised condition.^{15,18} Maternal-fetal transmission occurs between 1 and 4 months following placental colonization by tachyzoites. The placenta remains infected for the duration of the pregnancy, and therefore may act as a reservoir supplying viable organisms to the fetus throughout pregnancy.^{3,14} Historical studies (before the availability and use of anti-toxoplasma medication in pregnancy) have shown that the risk of vertical transmission increases with gestational age, with the highest rates (60% to 81%) in the third trimester compared with 6% in the first trimester.^{23,24} Disease severity, however, decreases with gestational age, with first trimester infection resulting in fetal loss or major sequelae.^{17,23,24} The overall risk of congenital infection from acute *T. gondii* infection during pregnancy ranges from 20% to 50% without treatment.^{11,14,24}

Classic congenital toxoplasmosis is characterized by the tetrad described by Sabin in 1942: chorioretinitis, hydrocephalus, intracranial calcification and convulsion.¹⁴ Signs such as intracranial calcification, microcephaly, hydrocephalus, and severe intrauterine growth restriction strongly suggest in utero infection in the presence of documented maternal infection.^{7,11} Ultrasound findings

are not sufficient for a definitive diagnosis. Termination of pregnancy should be considered in the case of severe morphological lesions.²⁴ Over 90% of neonates with congenital infection show no clinical signs of infection at birth.²⁵ Neonates, when no treatment is given, are at substantial risk of developing long-term sequelae, including chorioretinal disease (up to 85% of infected children) and major neurological abnormalities, as well as psychomotor and mental impairments.^{7,8,11,12,25} Acute maternal infection has also been implicated as a cause of intrauterine fetal death.¹⁷ Numerous studies have demonstrated that early treatment can favourably alter the development of these sequelae (already present but not clinically evident) in neonates and affect long-term outcomes.^{8,12,25}

Recommendation

6. *Toxoplasma gondii* infection should be suspected and screening should be offered to pregnant women with ultrasound findings consistent with possible TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes, and other) infection, including but not limited to intracranial calcification, microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction. (II-2B)

TREATMENT

A Cochrane Review of 3332 studies published in the past 30 years concluded that prenatal treatment in the presence of seroconversion during pregnancy does not lower transmission risk but could reduce congenital toxoplasmosis severity.^{26,27} Current evidence is insufficient to confirm that treating mothers who seroconvert during pregnancy prevents fetal infection.^{26,27}

There are 2 goals of drug therapy for toxoplasmosis, depending on whether or not fetal infection has occurred. If maternal infection has occurred but the fetus is not infected, spiramycin is used for fetal prophylaxis (to prevent spread of organisms across the placenta from mother to fetus).¹⁶ Spiramycin is a macrolide antibiotic that is concentrated in but does not readily cross the placenta, and therefore is not reliable for treatment of fetal infection.¹⁶ Use is aimed at preventing vertical transmission of the parasite to the fetus, and it is indicated only before fetal infection. Its use during pregnancy has been recommended by many investigators in Europe and North America.¹⁶ It is given at a dose of 1 g (3 million U) orally every 8 hours.¹⁶ It will be prescribed for the duration of the pregnancy if the amniotic fluid polymerase chain reaction is reported negative for *T. gondii*.

If fetal infection has been confirmed or is highly suspected, pyrimethamine and sulfadiazine are used for treatment. Pyrimethamine is a folic acid antagonist that acts synergistically with sulfonamides. This drug should not be used in the first trimester because it is potentially teratogenic. It produces a reversible, dose-related depression of the bone marrow and therefore must be combined with folinic acid.¹⁶ The combination of pyrimethamine and sulfadiazine results in a significant decrease in disease severity.²⁸

Recommendations

7. Each case involving a pregnant woman suspected of having an acute *Toxoplasma gondii* infection acquired during gestation should be discussed with an expert in the management of toxoplasmosis. (III-B)
8. If maternal infection has been confirmed but the fetus is not yet known to be infected, spiramycin should be offered for fetal prophylaxis (to prevent spread of organisms across the placenta from mother to fetus). (I-B)

PREVENTION

Screening

Routine screening of women at low risk should not be performed. Screening poses challenges, and it is important to take into account the cost, risks factors, availability of appropriate tests, relatively low incidence of acute infection, low sensitivity of screening (false-positive test results) and treatment effectiveness during gestation. Universal screening is provided in many European countries, although the benefits and costs have not been adequately assessed.²⁴ In most countries (including the United States and the United Kingdom) where the incidence of toxoplasmosis infection is low, universal screening is not recommended.^{16,27} Screening is recommended for those at high risk (for example, women who are immunosuppressed or HIV-positive) or those with ultrasound findings such as hydrocephalus, intracranial calcifications, microcephaly, fetal growth restriction, ascites, or hepatosplenomegaly.¹⁶ Because of the lack of certainty regarding the effect of treatment during pregnancy, Denmark and some American states have recently opted for screening based on detection of infected neonates at birth rather than prenatal screening.^{16,27} This strategy may identify some subclinically infected infants but does not prevent congenital infection. In Canada, only Nunavik and northern Quebec have screening programs for the detection of *T. gondii* antibodies during pregnancy because of their high seroprevalence.¹⁰

Table 2. Specific hygienic and dietary recommendations for pregnant women to avoid primary *T. gondii* infection

- Wear gloves and thoroughly clean hands and nails when handling material potentially contaminated by cat feces (sand, soil, gardening).
- Reduce the exposure risk of pet cats by (1) keeping all cats indoors (2) giving domestic cats only cooked, preserved, or dry food.
- Change litter and get rid of cat feces (wearing gloves) on a regular basis (every 24 hours).
- Disinfect emptied cat litter tray with near-boiling water for 5 minutes before refilling.
- Eat only well-cooked meat (> 67°C/153°F).
- Freezing meat to at least -20°C/-4°F also kills *T. gondii* cysts.
- Clean surfaces and utensils that have been in contact with raw meat.
- Do not consume raw eggs or raw milk.
- Wash uncooked fruits and vegetables before consumption.
- Prevent cross-contamination: thoroughly clean hands and utensils after touching raw meat or vegetables.
- Do not drink water potentially contaminated with oocysts.
- Be aware that
 - the process of curing, smoking, or drying meat does not necessary result in a product free of parasite cysts.
 - refrigeration does not destroy the parasite (still viable after 68 days at +4°C).
 - microwave oven cooking does not destroy parasites.

Recommendations

9. A combination of pyrimethamine, sulfadiazine, and folinic acid should be offered as treatment for women in whom fetal infection has been confirmed or is highly suspected (usually by a positive amniotic fluid polymerase chain reaction). (I-B)
10. Anti-toxoplasma treatment in immunocompetent pregnant women with previous infection with *Toxoplasma gondii* should not be necessary. (I-E)
11. Women who are immunosuppressed or HIV-positive should be offered screening because of the risk of reactivation and toxoplasmosis encephalitis. (I-A)
12. A non-pregnant woman who has been diagnosed with an acute *Toxoplasma gondii* infection should be counselled to wait 6 months before attempting to become pregnant. Each case should be considered separately in consultation with an expert. (III-B)

Despite evidence from observational studies that prenatal education is effective in reducing congenital toxoplasmosis, this has not been confirmed with randomized controlled trials. Health education materials containing information on the prevention of *T. gondii* infection in pregnancy may lead to a decreased rate of seroconversion. However, this intervention requires further study using more rigorous research and design methodology.^{14,29–31} Providing written recommendations to women at risk is insufficient to change behaviour, and personal interaction is more successful.²⁹ Ideally women would be made aware of these guidelines before their first pregnancy (pre-conception care). Pregnant women should have information regarding the

specific hygienic and dietary recommendations to prevent primary *T. gondii* infection (Table 2) as well as other food-borne infections.

Recommendation

13. Information on prevention of *Toxoplasma gondii* infection in pregnancy should be made available to all women who are pregnant or planning a pregnancy. (III-C)

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