

Toxoplasmosis and pregnancy

Shahnaz Akhtar Chaudhry MD Nanette Gad Gideon Koren MD FRCPC FACMT

Abstract

Question Congenital toxoplasmosis is a dangerous fetal infection. Why is routine screening for *Toxoplasma gondii* infection during pregnancy not available for most Canadians?

Answer Low prevalence of the infection, high cost associated with testing, low sensitivity of screening tests, false-positive test results, and limitations of treatment effectiveness are all cited as reasons for not routinely screening for *T gondii* infection in Canada. Currently, screening for the detection of *T gondii* is only performed in Nunavik and other parts of northern Quebec owing to the high prevalence of infection in this region. Congenital toxoplasmosis causes neurologic or ocular disease (leading to blindness), as well as cardiac and cerebral anomalies.

Toxoplasmose et grossesse

Résumé

Question La toxoplasmose congénitale est une dangereuse infection congénitale. Pourquoi le dépistage systématique d'une infection aux *Toxoplasma gondii* durant la grossesse n'est-il pas accessible à la plupart des Canadiennes?

Réponse La faible prévalence de l'infection, les coûts élevés associés aux analyses, la faible sensibilité des tests de dépistage, les résultats d'analyses faux-positifs et l'efficacité limitée des traitements sont tous des motifs cités pour justifier de ne pas offrir de dépistage systématique des infections aux *T gondii* au Canada. À l'heure actuelle, les tests de dépistage des *T gondii* ne se font qu'au Nunavik et dans d'autres parties du Nord québécois en raison de la forte prévalence de cette infection dans cette région. La toxoplasmose congénitale cause des maladies neurologiques et oculaires (menant à la cécité), ainsi que des anomalies cardiaques et cérébrales.

Toxoplasmosis is a disease caused by the intracellular protozoan parasite *Toxoplasma gondii*.¹ Most immunocompetent individuals who contract the parasite do not develop symptoms, or might experience nonspecific flulike symptoms including fever, headache, muscle pain, and lymphadenopathy.²⁻⁴ Although one-third of the world's population is infected with the parasite, it often remains unrecognized, as most patients do not exhibit symptoms.⁵ Critically, when a *T gondii* infection is acquired in pregnancy, the parasite can be transmitted across the placenta to the fetus, resulting in congenital toxoplasmosis, which can have grave consequences.⁶

Toxoplasma gondii has 2 life cycles: the sexual cycle occurs exclusively in the small intestines of cats, whereas the asexual cycle takes place in infected animals and humans.^{7,8} In humans, infection is usually acquired by consumption and manipulation of raw or undercooked meat. Infection can also be acquired through eating unwashed vegetables and fruit, drinking water containing oocytes excreted in the feces of infected cats, or contact with cat litter or soil.

Effect on pregnancy

Infection with *T gondii* before pregnancy confers little or no risk to the fetus except in women who become infected up to 3 months before conception.^{9,10} In the neonate, manifestations of congenital toxoplasmosis might include hydrocephalus, microcephaly, intracranial calcifications, retinochoroiditis, strabismus, blindness, epilepsy, psychomotor and mental retardation, petechiae due to thrombocytopenia, and anemia.^{11,12}

While infection in early pregnancy poses a small risk of fetal transmission (less than 6%), rates of transmission range between 60% and 81% in the third trimester.¹³ Conversely, although the transmission of *T gondii* during embryogenesis is rare, it results in far more serious effects on the fetus.¹⁴ In contrast, maternal infection in the third trimester often results in asymptomatic newborns. However, if not treated appropriately, these newborns might develop retinochoroiditis and neurologic deficits in childhood or early adulthood.¹⁴⁻¹⁶

There is no evidence of *T gondii* transmission through breastfeeding or via direct human-to-human contact.³

Diagnosis

The greatest challenge in diagnosing toxoplasmosis is to establish the acute (primary) infection and distinguish it from past (chronic) infection. *Toxoplasma gondii* infection can be diagnosed using serologic tests, ultrasound scans, and amniocentesis. Results of serologic tests measuring immunoglobulin (Ig) M and IgG are often difficult to interpret when differentiating between acute and chronic infections. Following acute infection, IgM antibody titres rise starting on day 5 and reach the maximum level at 1 to 2 months. At this point, IgM antibodies decline more rapidly than IgG antibodies.¹⁷ However, in many cases the IgM antibodies persist for years following acute infection. In contrast, IgG antibodies are usually detectable within 1 to 2 weeks after acute infection, peak within 12 weeks to 6 months, and usually remain detectable throughout life.¹⁸ The absence of IgG and IgM antibodies before or early in pregnancy indicates no previous infection and identifies women at risk of acquiring the infection during pregnancy.¹⁹ The detection of IgG antibodies and absence of IgM antibodies indicates an old infection. However, if test results are positive for both IgG and IgM, interpretation is difficult, as the positive results might be owing to either a recent infection or low levels of IgM antibodies from a previous infection.²⁰ If acute infection is suspected, repeat testing is recommended within 2 to 3 weeks.¹⁷ A 4-fold rise in IgG antibody titre between tests indicates a recent infection.²¹

Confirming primary infection is of utmost importance in evaluating the risk of fetal transmission, initiating antibiotics, and providing appropriate counseling. To more accurately determine the likelihood of a recently acquired infection, more specific tests, such as IgG antibody avidity testing, are helpful.²² The IgG avidity assay measures the strength of IgG binding to *T gondii*.²¹ In most cases IgG avidity shifts from a low to a high index about 5 months after the infection. Thus, patients with acute infection exhibit a low avidity index, suggesting that infection occurred within 5 months of testing, whereas those with previous infection have a high IgG avidity index.²³

Up to two-thirds of cases of congenital toxoplasmosis do not exhibit any abnormality on ultrasound scans.²⁴ Positive sonographic findings for *T gondii* infection include intracranial calcifications, microcephaly, hydrocephalus, ventricular dilations, hepatosplenomegaly, ascites, and severe intrauterine growth retardation.³

As maternal infection does not always result in fetal infection, it is critical to determine whether fetal infection has occurred. The diagnosis of congenital toxoplasmosis in the fetus is currently done by polymerase chain reaction analysis of the amniotic fluid.⁶ Amniocentesis is offered only if maternal primary infection is confirmed, if maternal serologic test results do not confirm or exclude acute infection, or if ultrasonographic features are

consistent with congenital toxoplasmosis.²⁵ It should be offered after 18 weeks' gestation and at least 4 weeks after the suspected acute maternal infection to decrease the risk of false-negative results.²⁵

Management

While there is insufficient evidence to prove that treating mothers with seroconversion during pregnancy prevents fetal infection, treatment might reduce the severity of congenital toxoplasmosis.^{26,27} If primary *T gondii* infection is confirmed during pregnancy, treatment is used for fetal prophylaxis or to decrease the disease severity.^{28,29} In case of maternal infection without fetal infection, spiramycin is the drug of choice to prevent vertical transmission.²⁸ Spiramycin is a macrolide antibiotic that cannot cross the placenta but remains concentrated in it. According to the Society of Obstetricians and Gynaecologists of Canada guidelines, it is prescribed at a dosage of 1 g orally every 8 hours for the duration of pregnancy if amniotic fluid polymerase chain reaction analysis results are negative for *T gondii*.²⁵

Pyrimethamine and sulfadiazine are administered in cases of confirmed fetal infection, but not in cases of suspected infection, especially in the first trimester, owing to potential teratogenicity and bone marrow toxicity to both mother and fetus.^{26,28} Both prenatal and postnatal treatment have shown evidence of reducing the risk and severity of long-term symptoms. However, even after treatment has been discontinued, clinical and ophthalmologic examinations should be performed regularly for several years to screen for any sequelae that might arise.⁶

Prevention

In Canada, owing to the low prevalence of the disease and the aforementioned limitations in diagnosis and therapy, routine screening for toxoplasmosis is currently not recommended in low-risk populations.²⁵ Only Nunavik and other parts of northern Quebec have screening programs for *T gondii* during pregnancy owing to high endemic seroprevalence.³⁰ In many European countries, universal screening for *T gondii* is provided but benefit and costs have not been adequately assessed.¹³ Routine screening is not recommended in most countries where incidence of toxoplasmosis is low, including in the United Kingdom and United States.²⁷

Prevention of congenital toxoplasmosis is dependent on effective avoidance of infection during pregnancy.³¹ This involves avoidance of contact with litter boxes or soil, owing to the presence of *T gondii* oocytes that might have been excreted by cats. Pet cats are less likely to be a source of infection if they are kept indoors only and are provided with only cooked, preserved, or dry food.^{32,33}

It is also important to avoid undercooked, raw, or cured meat, and raw, unwashed fruits or vegetables.³¹

Proper hand hygiene is essential to decreasing the risk of infection.⁶

Counseling

Owing to the grave outcome of fetal toxoplasmosis, it is critical to counsel the parents and ensure that they understand the implications of positive and negative test results.

Conclusion

Primary infection with *T gondii* during pregnancy is rare, but poses challenges in establishing the diagnosis. The important consequence of primary infection is vertical transmission to the fetus, resulting in congenital toxoplasmosis. Vertical transmission and its effects on the fetus are dependent upon the gestational age at which the primary infection is acquired. After establishing the diagnosis, proper counseling of pregnant women regarding congenital toxoplasmosis and the need for invasive tests, such as amniocentesis, and antibiotic therapy should take place. As symptoms of congenital toxoplasmosis can occur years after birth, regular clinical and ophthalmologic examinations should be performed for several years. Prenatal counseling should include education regarding prevention of toxoplasmosis. Routine screening for *T gondii* is currently not recommended in Canada.

Competing interests

None declared

References

- Yamada H, Nishikawa A, Yamamoto T, Mizue Y, Yamada T, Morizane M, et al. Prospective study of congenital toxoplasmosis screening with use of IgG avidity and multiplex nested PCR methods. *J Clin Microbiol* 2011;49(7):2552-6. DOI: 10.1128/JCM.02092-10. Epub 2011 May 4.
- Jenum PA, Stray-Pedersen B, Melby KK, Kapperud G, Whitelaw A, Eskild A, et al. Incidence of *Toxoplasma gondii* infection in 35,940 pregnant women in Norway and pregnancy outcome for infected women. *J Clin Microbiol* 1998;36(10):2900-6.
- Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet* 2004;363(9425):1965-76. DOI: 10.1016/S0140-6736(04)16412-X.
- Saadatnia G, Golkar M. A review on human toxoplasmosis. *Scand J Infect Dis* 2012;44(11):805-14. DOI: 10.3109/00365548.2012.693197. Epub 2012 Jul 25.
- Bodaghi B, Touitou V, Fardeau C, Paris L, LeHoang P. Toxoplasmosis: new challenges for an old disease. *Eye (Lond)* 2012;26(2):241-4. DOI: 10.1038/eye.2011.331. Epub 2012 Jan 6.
- Kieffer F, Wallon M. Congenital toxoplasmosis. *Handb Clin Neurol* 2013;112:1099-101. DOI: 10.1016/B978-0-444-52910-7.00028-3.
- Dubey JP. History of the discovery of the life cycle of *Toxoplasma gondii*. *Int J Parasitol* 2009;39(8):877-82.
- Lebech M, Andersen O, Christensen NC, Hertel J, Nielsen HE, Peitersen B, et al. Feasibility of neonatal screening for toxoplasma infection in the absence of prenatal treatment. Danish Congenital Toxoplasmosis Study Group. *Lancet* 1999;353(9167):1834-7.
- Vogel N, Kirisits M, Michael E, Bach H, Hostetter M, Boyer K, et al. Congenital toxoplasmosis transmitted from an immunologically competent mother infected before conception. *Clin Infect Dis* 1996;23(5):1055-60.
- Gavinet MF, Robert F, Firtion G, Delouvrier E, Hennequin C, Maurin JR, et al. Congenital toxoplasmosis due to maternal reinfection during pregnancy. *J Clin Microbiol* 1997;35(5):1276-7.
- McAuley J, Boyer KM, Patel D, Mets M, Swisher C, Roizen N, et al. Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial. *Clin Infect Dis* 1994;18(1):38-72.
- Swisher CN, Boyer K, McLeod R. Congenital toxoplasmosis. The Toxoplasmosis Study Group. *Semin Pediatr Neurol* 1994;1(1):4-25.
- Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet* 1999;353(9167):1829-33. DOI: 10.1016/S0140-6736(98)08220-8.
- Berrébi A, Assouline C, Bessières MH, Lathière M, Cassaing S, Minville V, et al. Long-term outcome of children with congenital toxoplasmosis. *Am J Obstet Gynecol* 2010;203(6):552.e1-6. DOI: 10.1016/j.ajog.2010.06.002. Epub 2010 Jul 15.

- Wilson CB, Remington JS, Stagno S, Reynolds DW. Development of adverse sequelae in children born with subclinical congenital toxoplasma infection. *Pediatrics* 1980;66(5):767-74.
- Baquero-Artigao F, Del Castillo Martín F, Fuentes Corripio I, Goncé Mellgren A, Fortuny Guasch C, de la Calle Fernández-Miranda M, et al. The Spanish Society of Pediatric Infectious Diseases guidelines for the diagnosis and treatment of congenital toxoplasmosis [article in Spanish]. *An Pediatr (Barc)* 2013;79(2):116.e1-16. DOI: 10.1016/j.anpedi.2012.12.001. Epub 2013 Jan 23.
- Stray-Pedersen B. Toxoplasmosis in pregnancy. *Baillieres Clin Obstet Gynaecol* 1993;7(1):107-37.
- Liesenfeld O, Press C, Montoya JG, Gill R, Isaac-Renton JL, Hedman K, et al. False-positive results in immunoglobulin M (IgM) toxoplasma antibody tests and importance of confirmatory testing: the Platelia Toxo IgM test. *J Clin Microbiol* 1997;35(1):174-8.
- Hedman K, Lappalainen M, Seppäälä I, Mäkelä O. Recent primary toxoplasma infection indicated by a low avidity of specific IgG. *J Infect Dis* 1989;159(4):736-40.
- Iqbal J, Khalid N. Detection of acute *Toxoplasma gondii* infection in early pregnancy by IgG avidity and PCR analysis. *J Med Microbiol* 2007;56(Pt 11):1495-9. DOI: 10.1099/jmm.0.47260-0.
- Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis* 2002;185(Suppl 1):S73-82. DOI: 10.1086/338827.
- Petersen E, Borobio MV, Guy E, Liesenfeld O, Meroni V, Naessens A, et al. European multicenter study of the LIAISON automated diagnostic system for determination of *Toxoplasma gondii*-specific immunoglobulin G (IgG) and IgM and the IgG avidity index. *J Clin Microbiol* 2005;43(4):1570-4. DOI: 10.1128/JCM.43.4.1570-1574.2005.
- Pour Abolghasem S, Bonyadi MR, Babaloo Z, Porhasan A, Nagili B, Gardashkhani OA, et al. IgG avidity test for the diagnosis of acute *Toxoplasma gondii* infection in early pregnancy. *Iran J Immunol* 2011;8(4):251-5. DOI: IJIV814A8.
- Merz E. *Ultrasound in obstetrics and gynecology. Vol. 1: obstetrics*. 2nd ed. New York, NY: Thieme; 2004.
- Paquet C, Yudin MH. Toxoplasmosis in pregnancy: prevention, screening, and treatment. *J Obstet Gynaecol Can* 2013;35(1):78-9.
- Wallon M, Liou C, Garner P, Peyron F. Congenital toxoplasmosis: systematic review of evidence of efficacy of treatment in pregnancy. *BMJ* 1999;318(7197):1511-4.
- Peyron F, Wallon M, Liou C, Garner P. Treatments for toxoplasmosis in pregnancy. *Cochrane Database Syst Rev* 2000;(2):CD001684. DOI: 10.1002/14651858.CD001684.
- Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis* 2008;47(4):554-66. DOI: 10.1086/590149.
- McLeod R, Kieffer F, Sautter M, Hosten T, Pelloux H. Why prevent, diagnose and treat congenital toxoplasmosis? *Mem Inst Oswaldo Cruz* 2009;104(2):320-44.
- Messier V, Lévesque B, Proulx JF, Rochette L, Libman MD, Ward BJ, et al. Seroprevalence of *Toxoplasma gondii* among Nunavik Inuit (Canada). *Zoonoses Public Health* 2009;56(4):188-97. DOI: 10.1111/j.1863-2378.2008.01177.x. Epub 2008 Sep 22.
- Cook AJ, Gilbert RE, Buffolano W, Zufferey J, Petersen E, Jenum PA, et al. Sources of toxoplasma infection in pregnant women: European multicentre case-control study. European Research Network on Congenital Toxoplasmosis. *BMJ* 2000;321(7254):142-7.
- Elmore SA, Jones JL, Conrad PA, Patton S, Lindsay DS, Dubey JP. *Toxoplasma gondii*: epidemiology, feline clinical aspects, and prevention. *Trends Parasitol* 2010;26(4):190-6. DOI: 10.1016/j.pt.2010.01.009. Epub 2010 Mar 2.
- Jones JL, Krueger A, Schulkin J, Schantz PM. Toxoplasmosis prevention and testing in pregnancy, survey of obstetrician-gynaecologists. *Zoonoses Public Health* 2010;57(1):27-33. DOI: 10.1111/j.1863-2378.2009.01277.x. Epub 2009 Sep 10.

MOTHERISK Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Dr Chaudhry is a member of, Ms Gad is a medical student with, and Dr Koren is Director of the Motherisk Program. Dr Koren is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the Canadian Family Physician website (www.cfp.ca) and also on the Motherisk website (www.motherisk.org).