



REVIEW

Toxoplasmosis in pregnancy

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ABSTRACT: Pregnant women who acquire infection from *Toxoplasma gondii* usually remain asymptomatic, although they can still transmit the infection to their fetuses with severe consequences. Given the asymptomatic nature of most *Toxoplasma* infections, primary prevention in pregnant women may lower the risk of congenital toxoplasmosis. Both consumption of undercooked meat and unprotected contact with soil are independent risk factors for *T. gondii* seroconversion during pregnancy, while contact with cat litter may pose a risk in certain situations. However, many pregnant women lack knowledge of these risk factors. This article reviews toxoplasmosis infection in pregnancy, with an emphasis on risk factors and appropriate counseling of pregnant women.

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Toxoplasma gondii is an obligate intracellular protozoan that can infect all mammals, who serve as intermediate hosts. In immunocompetent subjects, 90% of *T. gondii* infections are asymptomatic. Symptomatic infections usually cause a mononucleosis-like illness with low-grade fever, malaise, headache, and cervical lymphadenopathy. Other manifestations, such as encephalitis, myocarditis, hepatitis, and pneumonia, are rare but can complicate acute toxoplasmosis.¹ Primary infection in pregnant women, which is transmitted transplacentally, can cause congenital toxoplasmosis. Congenital toxoplasmosis can then lead to a wide array of manifestations, ranging from mild chorioretinitis, which can present many years after birth, to miscarriage, mental retardation, microcephaly, hydrocephalus, and seizures. Pregnant women and their primary care physicians and obstetricians need to be informed about the risk factors for toxoplasmosis to lower the risk of congenital infection.

Epidemiology

Evidence of prior infection with *T. gondii* is common throughout the world. In the United States, the overall age-adjusted seroprevalence is 22.5%,² and 15% among women of childbearing age (15 to 44 years). There are approximately 225,000 cases of *T. gondii* infection per year, which result in 5000 hospitalizations and 750 deaths, making *T. gondii* the third most common cause of fatal foodborne illness in the country.³ Although evidence of prior infection is common, congenital toxoplasmosis is relatively uncommon in the United States, with an estimated 400 to 4000 cases per year.⁴

Pathophysiology

There are three forms of *T. gondii* during its life cycle. Oocysts are the product of sexual reproduction, which occurs in the small intestine of a cat that has recently ingested tissue cysts, usually in uncooked meat. Oocysts, which contain infective sporozoites, are then produced in a cat for approximately 2 weeks after the initial infection. Once the oocysts are deposited by a cat, they become infective 1 to 5 days later.⁵ Tachyzoites are the rapidly dividing products of

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asexual reproduction, which occurs in macrophages following invasion of the host intestinal wall by either sporozoites (from oocysts) or bradyzoites (from tissue cysts). Macrophages then serve as the vehicle for hematogenous dissemination of the tachyzoites in an intermediate host until an adequate immune response occurs after 7 to 10 days. Once an immune response develops, the protozoan becomes contained within tissue cysts as bradyzoites, or slowly dividing *T. gondii*. These tissue cysts can remain dormant for the lifetime of the intermediate host in various tissues, including the lymph nodes, muscle, brain, retina, myocardium, lungs, and liver.⁶ If immunity wanes, such as with the use of immunosuppressive therapy or the acquired immunodeficiency syndrome, bradyzoites can resume rapid division and hematogenously disseminate as tachyzoites again.

There are three means of *T. gondii* infection in humans. First, humans can ingest tissue cysts in infected, undercooked meat. Bradyzoites can be found in up to 8% of beef, 20% of pork, and 20% of lamb.⁷ Cooking meat to an internal temperature of 67°C or freezing meat to below -12°C kills bradyzoites and eliminates the risk of this mode of infection.⁸ Second, infective oocysts can be ingested through fecal-oral contact, releasing sporozoites that cause infection following intestinal wall invasion. Third, although very uncommon, blood transfusions can cause infection if blood is transfused from an infected patient with circulating tachyzoites to a nonimmune recipient.

Congenital toxoplasmosis develops from the transplacental passage of tachyzoites to a fetus. Assuming a normal immune system, this form of infection only occurs when a pregnant woman develops a primary infection. Previously infected subjects only rarely are reinfected once they have had an adequate immune response. The risk of congenital toxoplasmosis infection from a mother with primary toxoplasmosis increases during pregnancy, from 0% to 9% in the first trimester to 35% to 59% in the third trimester.^{9,10} Fortunately, the later in pregnancy that congenital infection occurs, the less severe the consequences are to the fetus.

Risk factors

Since more than 90% of acute toxoplasmosis infections are asymptomatic, primary prevention is the best way to lower the risk of congenital infection. This section reviews studies of various risk factors for toxoplasmosis seroconversion (i.e., primary infection) during pregnancy to allow practitioners to counsel pregnant women appropriately on risk factor reduction.

A prospective case-control study involving 63 women in Norway revealed the following predictors for *T. gondii* seroconversion during pregnancy:¹¹ eating raw or undercooked mutton; washing kitchen knives infrequently after preparation of raw meat prior to handling another food item; cleaning the cat litter box; eating raw or undercooked minced meat products; eating raw or undercooked pork; and

eating unwashed raw vegetables or fruits. Four of these six risk factors involve contact with undercooked meat, which allows direct ingestion of tissue cysts. Cleaning the litter box allows contact with oocysts if the cat was infected in the past 2 weeks. Following exposure to contaminated cat litter, subjects must then touch their mouths for fecal-oral transmission to occur. Eating unwashed vegetables also allows fecal-oral transmission of oocysts, as outdoor cats are known to deposit their feces in gardens, a risk factor that is likely to be independent of cat ownership since many outdoor cats roam to neighboring sites to deposit their feces.

In a high-risk group of women aged 15 to 45 years in Belgrade, Yugoslavia, where the overall mean rate of *T. gondii* infection was 77%, only consumption of undercooked meat was found to be associated with *T. gondii* infection.¹² In a subgroup analysis of women below age 20 years, exposure to soil was also found to be associated with *T. gondii* infection, but cat ownership itself was not linked to *Toxoplasma* infection.

A case-control study in France involving 80 cases of *T. gondii* seroconversion during pregnancy also revealed consumption of undercooked beef and raw vegetables to be predictors of seroconversion.¹³ Cat ownership was of borderline importance, although handling cat litter was not found to be associated with *T. gondii* seroconversion.

A large multicenter European case-control study involving 252 cases and 858 controls also revealed contact with raw or undercooked beef, lamb, or other meat, as well as with soil, to be independent risk factors for *T. gondii* seroconversion during pregnancy.¹⁴ Further analysis of the data showed that up to 63% of seroconversions were due to consumption of undercooked or cured meat products and up to 17% were a result of soil contact. In addition, travel outside of Europe, the United States, and Canada was a risk factor for seroconversion, while tasting meat during cooking was of borderline importance. Multiple different cat exposures were assessed, but none were found to be risk factors for toxoplasmosis infection. Specifically, having a cat or kitten at home, cleaning the litter box, and owning a cat that hunts were not risk factors for *T. gondii* seroconversion.

In the United States, there are no published studies assessing the risk factors for seroconversion during pregnancy. A seroprevalence study found that 15% of women aged 15 to 44 years had *T. gondii* immunoglobulin G (IgG) antibodies.² Further analysis found the following risk factors to be associated with seroprevalence: increasing age, being foreign born, lower educational level, living in crowded conditions, and working in soil-related occupations. Since this study was not designed to assess new seroconversions during pregnancy, it is not known if these risk factors apply to pregnant women and the risk of congenital toxoplasmosis. Thus, although this study shows that 85% of women of childbearing age are at risk of primary *Toxoplasma* infection, it does not reveal risk factors for seroconversion and congenital disease.

Each study of *T. gondii* seroconversion during pregnancy independently links the consumption of undercooked meat and soil contact through gardening or consumption of unwashed vegetables with primary infection. Although uncooked meat products carry a risk of containing tissue cysts that are potentially infective, soil contact is a lesser-known risk factor. Soil contact through gardening allows contact with infective oocysts deposited by any recently infected cat. While oocysts take 1 to 5 days to become infective, they can remain infective in soil for up to 1 year.⁵ Thus, there need not be evidence of recent cat feces for a garden to remain a risk factor for pregnant women. Since this method of transmission also requires fecal-oral transmission, wearing gloves and washing hands after gardening or soil contact should eliminate this risk factor.

The risk of changing cat litter is less well established. Only one of the four studies of seroconversion found cleaning the litter box to be associated with *T. gondii* seroconversion.¹¹ One other study showed cat ownership to be of borderline importance, although handling cat litter was not found to be a risk factor.¹³ Cat ownership and changing the cat litter are less likely to be risk factors for seroconversion for several reasons. First, only outdoor cats that hunt or indoor cats that are fed raw meat are at risk of primary infection. Indoor cats that are fed canned and prepackaged food do not consume tissue cysts and thus will never produce oocysts. Second, transmission of *T. gondii* through oocysts requires fecal-oral transmission. Most persons who clean a cat's litter box are likely to practice good hygiene and wash their hands following handling cat litter regardless of their knowledge of toxoplasmosis.¹⁵ Finally, there is a narrow window when oocysts are produced and when they become infective. Oocysts are shed in a cat's feces for approximately 2 weeks after primary infection. Once a cat has been exposed to *T. gondii*, it develops immunity and is less likely to become reinfected. In addition, oocysts require at least 1 day to become infective after being deposited, allowing for safe removal of oocysts from a cat's litter through daily changing of the litter.⁵

Based on these established risk factors for primary toxoplasmosis, pregnant women (or women trying to become pregnant) should be appropriately advised by their obstetricians and primary care providers on how to lower the risk of congenital toxoplasmosis. Table 1 summarizes general recommendations for primary prevention of toxoplasmosis infection. In addition, since approximately 15% of women aged 15 to 44 years already possess *T. gondii* IgG antibodies, an anxious pregnant cat owner can also be offered an antibody test via indirect immunofluorescence assay to determine if she is at risk of primary infection. Evidence of prior exposure almost completely eliminates the risk of primary infection during pregnancy.²

Table 1 Recommendations for lowering the risk of primary toxoplasmosis infection among pregnant women

1. Avoid consumption of undercooked meat. Cook all meat until it is no longer pink and the juices run clear.
2. Always use gloves while, and wash hands thoroughly after, handling raw meat.
3. Thoroughly wash all utensils that are in contact with undercooked meat.
4. Wash all uncooked vegetables thoroughly.
5. Wear gloves when gardening or working in soil. Wash hands immediately after contact with soil.
6. If possible, keep cats indoors throughout pregnancy and do not feed cats uncooked meat.
7. Use gloves while, and wash hands immediately after, changing cat litter.

Knowledge of risk factors

While the risk factors for toxoplasmosis infection are well established, it is less clear if pregnant women are being advised appropriately. In a 1999 survey of 364 U.S. obstetricians, 100% of responders counseled pregnant women on the appropriate handling of cat litter, while only 83% and 77% counseled on the consumption of undercooked foods and handling of raw foods. Even less (68%) gave advice on the risk of gardening.¹⁶ Gardening and the consumption of undercooked meat, the most direct risk factors for primary toxoplasmosis infection, need to be addressed.

Another survey designed to assess knowledge of toxoplasmosis among 403 pregnant women in the United States revealed that 60% of respondents cited cat litter as a risk factor, but only 30% were aware of the risk of undercooked or raw meat and 29% believed that toxoplasmosis could be transmitted by gardening without gloves.¹⁵ Pregnant women need further reinforcement of the risk of undercooked meat and soil contact to lower the risk of congenital toxoplasmosis. Education of women has been shown to be effective in increasing general knowledge of toxoplasmosis and potentially decreasing the incidence of congenital toxoplasmosis.^{17,18}

Prenatal and neonatal diagnosis of toxoplasmosis

Since more than 90% of primary toxoplasmosis infections in immunocompetent persons are asymptomatic, the diagnosis of maternal infection is difficult. In asymptomatic women, the only sign of primary infection during pregnancy is seroconversion via detection of IgG or IgM by the immunofluorescence antibody test, the enzyme-linked immune filtration assay, the immunosorbent agglutination assay (ISAGA), or other similar assays.¹⁰ IgG antibody levels become detectable 1 to 2 weeks after infection and remain elevated indefinitely, while IgM antibody levels increase

within days and usually remain elevated for 2 to 3 months.⁶ However, IgM antibody levels can remain positive for more than 2 years in up to 27% of women when using ISAGA, making it difficult to pinpoint the timing of infection.¹⁹ Thus, the detection of IgG in a woman at the beginning of pregnancy indicates prior infection and thus eliminates the risk of congenital transfer of tachyzoites. Only new seroconversions (IgM or IgG) place a developing fetus at risk of congenital toxoplasmosis.

Whether or not pregnant women should be screened for primary *T. gondii* infection through serological testing remains controversial for several reasons. First, the false-positive rate of IgM antibody detection during pregnancy has been estimated to be as high as 1.3%.²⁰ Up to 20% of pregnant women who are informed about a positive IgM antibody test result and the risk of congenital toxoplasmosis infection will request early termination of pregnancy.²¹ If these decisions are made based on false-positive results, many uninfected fetuses would be aborted.

Second, the incidence of maternal primary infection is relatively low, with seroconversion rates ranging from 0.15% in Norway to 0.5% in Hungary.^{20,22} If the rate of false-positive IgM test results exceeds the rate of true-positive IgM results, the screening test would be ineffective. However, in certain high-risk populations, maternal infection rates of up to 3.5% have been detected, making screening a more viable option.²³ Screening of pregnant women is practiced in France and Austria, but not routinely in the United States and the United Kingdom, due to differences in prevalence. However, certain groups of women should be screened for acute infection in the United States if deemed to be at high risk by their obstetricians on the basis of exposure to risk factors (e.g., raw meat, soil contact).

Finally, if maternal infection is diagnosed, it is not known if antenatal treatment is effective. Unfortunately, there are no randomized controlled trials to assess the effect of prenatal antimicrobial therapy with either spiramycin or pyrimethamine-sulfadiazine. A large prospective cohort trial of 1208 pregnant women in Europe with primary *T. gondii* infection failed to reveal any difference in the risk of congenital infection with treatment (with spiramycin or pyrimethamine-sulfadiazine) or no treatment.²⁴ However, other uncontrolled studies have demonstrated the benefits of prenatal treatment with spiramycin or pyrimethamine-sulfadiazine. One study of 5288 susceptible pregnancies showed the risk of congenital toxoplasmosis to be four times greater in neonates born to untreated mothers when compared with treated mothers.²³ Another study of 88 pregnant women with primary toxoplasmosis infection who were treated with spiramycin alone showed a 0% rate of congenital toxoplasmosis at 2 years.²² A systematic review of nonrandomized studies found therapy to be effective in five trials but ineffective in four studies.²⁵ Of the four trials without statistical benefit, two demonstrated a nonstatistically significant reduction in congenital toxoplasmosis with antiparasitic therapy. Thus, while there are no randomized

studies yet, it is still recommended that all pregnant women who have been diagnosed with primary toxoplasmosis infection be treated with spiramycin with or without pyrimethamine-sulfadiazine. Pyrimethamine is teratogenic and contraindicated in the first trimester.⁷

Once an infant is born to a mother with primary toxoplasmosis, the diagnosis of congenital toxoplasmosis can be made by either indirect or direct methods. The detection of IgM or IgA antibodies to *T. gondii* in an infant is highly sensitive for the diagnosis of congenital toxoplasmosis. Amplification of *T. gondii* DNA by polymerase chain reaction (PCR) is almost 100% sensitive and specific and can be detected in most body fluids of a congenitally infected neonate.¹⁰ PCR amplification of amniotic fluid or fetal blood samples obtained via cordocentesis can identify congenitally infected fetuses while still in utero, but is associated with certain inherent procedure-related risks.³ If an infant is diagnosed with congenital toxoplasmosis, recommendations include treatment with pyrimethamine, sulfadiazine, and leucovorin for up to 1 year.¹⁰

Conclusion

Although uncommon in the United States, congenital toxoplasmosis can have serious effects on the developing fetus. Since most primary infections during pregnancy are asymptomatic and screening for primary infection is problematic, primary prevention is the most logical method to lower the risk of congenital infection. Both women of childbearing age and physicians need to be informed of the risks associated with undercooked meat and soil contact. There is also a need to educate women on the safe handling of cat litter during pregnancy.

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