Toxoplasmosis and pregnancy

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INTRODUCTION — *Toxoplasma gondii* is a ubiquitous protozoan parasite that infects humans in various settings. The parasite is mainly acquired during childhood and adolescence [1]. In industrially developed, temperate climate countries, the prevalence of infection has declined over the last 30 years [1], with 10 to 50 percent of adults aged 15 to 45 years displaying serological evidence of past infection [2]. Much higher rates of infection (up to 80 percent) are found in the tropics in communities exposed to contaminated soil, undercooked meat, or unfiltered water [3-5].

Once a person is infected, the parasite lies dormant in neural and muscle tissue and will never be eliminated. Studies based in Europe and North America suggest that the large majority of immunocompetent humans are able to limit the spread of the parasite and the associated tissue damage, ensuring that it remains in its dormant form [3]. Inflammation of the retina and choroid (retinochoroiditis) is the most frequent, permanent manifestation of toxoplasmic infection. In Europe and North America, up to 1 percent of infected individuals eventually develop such lesions [6-9].

Evidence has been accumulating over the last 15 years that these findings are not applicable to parts of Latin America, where clinical manifestations of infection are much more common and more severe, probably because of the predominance of more diverse and more virulent parasite genotypes [10-12]. *Toxoplasma gondii* strains in Europe and North America belong to three distinct clonal lineages, type I, type II, and type III [13]. A comparison of European and Brazilian cohort studies of newborns identified by universal screening showed that eye lesions were larger and more numerous and more likely to impair vision in Brazilian cohorts [14].

In contrast to Europe and North America, acquisition of toxoplasmosis during childhood or adulthood in Brazil accounts for high levels of eye disease. In parts of Brazil, up to 20 percent of the population has toxoplasmic retinochoroiditis, resulting in high levels of visual impairment [15-18]. Toxoplasmosis is a leading cause of blindness in South America [19], but not in Europe or North America [20,21].

When toxoplasmic infection is acquired for the first time during pregnancy, infection can be transmitted to the fetus, resulting in congenital toxoplasmosis and associated neurological and ocular manifestations. Continued parasite proliferation and tissue destruction can occur within the fetal brain even after a marked maternal immune response, including maternal IgG production [22].

This topic will focus on maternal infection and its effect on the fetus. Other aspects of toxoplasmosis infection are reviewed separately.

- (See "Diagnostic testing for toxoplasmosis infection".)
- (See "Toxoplasmosis in immunocompetent hosts".)
- (See "Toxoplasmosis in HIV-infected patients".)
- (See "Congenital toxoplasmosis: Clinical features and diagnosis".)
- (See "Congenital toxoplasmosis: Treatment, outcome, and prevention".)

SOURCES OF INFECTION — *Toxoplasma gondii* is an obligate intracellular parasite that exists in three forms: the oocyst, which is shed only in cat feces; the tachyzoite (a rapidly dividing form observed in the acute phase of infection); and the bradyzoite (a slow growing form observed within tissue cysts) [3]. During a primary infection, a cat can shed millions of oocysts daily from its alimentary canal for a period of one to three weeks. These oocysts become infective one to five days later and may remain infectious for over a year, especially in warm, humid environments. Cats typically develop immunity after a primary infection; therefore, recurrent infection with passage of oocysts is unlikely.

In developed temperate climate countries, the main source of maternal infection is thought to be ingestion of bradyzoites contained in undercooked or cured meat or meat products. Maternal ingestion of oocysts from consumption of contaminated soil or water or soil-contaminated fruit or vegetables is also a major source of infection [3-5,23-27]. Food animals (pigs, chickens, lambs, goats) become infected by the same routes, resulting in meat containing tissue cysts [28].

In a study from the United States, household members of a patient with acute toxoplasmosis were at higher risk of infection, which suggest a common environmental or food source [29].

MATERNAL INFECTION

Incidence — The incidence of maternal infection during pregnancy ranges from 1 to 8 per 1000 susceptible pregnancies, with the highest reported rates in France [30]. However, the rate in France has significantly decreased in the past decade; the incidence of *Toxoplasma* infection diagnosed by seroconversion in French women was 2.1 per 1000 in 2010 [31].

Clinical manifestations — Acute infection in the mother is usually asymptomatic. When symptoms of infection occur, they are nonspecific, such as fatigue, fever, headache, malaise, and myalgia. Lymphadenopathy is a more specific sign of the disease. In a prospective European cohort study, lymphadenopathy was noted in 7 percent of 1144 infected pregnant women before diagnosis of infection [32]. Pregnant women who experience a mononucleosis-like illness, but who have a negative heterophile test, should be tested for toxoplasmosis as part of their diagnostic evaluation. (See "Infectious mononucleosis in adults and adolescents" and "Toxoplasmosis in immunocompetent hosts", section on 'Acute systemic infection'.)

Clinical differential — Differential diagnosis of the clinical features of toxoplasmosis includes acute Epstein-Barr virus infection, cytomegalovirus infection, HIV infection, syphilis, sarcoidosis, Hodgkin's disease, and lymphoma. (See "Toxoplasmosis in immunocompetent hosts", section on 'Differential diagnosis of acute systemic infection'.)

Diagnosis — Maternal infection during pregnancy is most accurately diagnosed when based on a minimum of two blood samples at least two weeks apart showing seroconversion from negative to positive *Toxoplasma*-specific IgM or IgG. It is important to note that detection of

Toxoplasma-specific IgM antibodies alone is not diagnostic of acute infection because IgM antibodies may persist for years. In a study from the United States, only 20 percent of women with *Toxoplasma*-specific IgM antibodies had acute infection [33].

Diagnosis of maternal toxoplasmosis, including interpretation and follow-up of serological studies, is reviewed in detail separately. (See "Toxoplasmosis in immunocompetent hosts", section on 'Approach to diagnosis' and "Diagnostic testing for toxoplasmosis infection", section on 'Serologic testing'.)

Screening — We agree with recommendations of national societies in the United States, Canada and the United Kingdom against routine universal screening for toxoplasmosis in pregnancy [30,34,35]. In North America and the United Kingdom, routine screening is not recommended because the prevalence of the disease is relatively low, lack of standardized serologic assays except in research laboratories, lack of highly effective treatment, and cost. Issues related to immunosuppressed or human immunodeficiency virus (HIV)-positive are discussed separately. (See "Toxoplasmosis in HIV-infected patients".)

Serial testing of susceptible asymptomatic women is usually feasible only as part of a prenatal screening program. Monthly or every three months retesting schedules operate in parts of Europe [32,36]. The more frequently a woman is retested, the greater the chance of detecting infection early, when treatment is more likely to be effective. However, the costs of frequent testing and the chances of false positive results increase as the frequency of retesting increases [30,37]. Thus, women may undergo invasive prenatal investigations and be treated unnecessarily. These potential harms have to be weighed against potential benefits of treatment, which have been found only for rare, serious neurological sequelae of congenital toxoplasmosis [38,39]. Randomized controlled trials are needed to determine if these benefits outweigh the harms of screening.

In acute infection, IgM antibodies appear within the first week of infection. The diagnosis of recent toxoplasmosis can be made with greater confidence when initial serologic testing demonstrates a positive IgM antibody and a negative IgG result with both tests becoming positive two weeks later. This pairing of results is consistent with acute infection occurring about two weeks before the first positive IgM and eliminates the possibility of a "non-specific" IgM response [40,41]. If follow-up IgG remains negative two to four weeks later, but IgM is still positive, then the IgM is likely a false positive result. A negative IgG antibody essentially rules out prior or recent infection in an immunocompetent host since IgG antibodies remain detectable for life.

However, paired serologies showing this type of response are uncommon. Instead, serologic assays often demonstrate both IgM and IgG antibodies at the first prenatal visit. For women who are initially screened at the end of the first trimester and have positive IgM and IgG antibodies, the probability that infection occurred after conception is 1 to 3 percent, depending on the test used [42]. The timing of infection in these cases is difficult to determine since IgM antibodies appear as early as two weeks after infection and may persist for years, while IgG antibodies peak six to eight weeks after infection and then decline over the next two years, but remain positive [42]. Thus, to establish whether positive IgM and IgG antibodies reflect recent or chronic infection or a false positive result, confirmatory testing must be obtained with additional testing (eg, IgG avidity assay, serial titers) [43]. High IgG avidity is a hallmark of latent infection, but low avidity is not diagnostic of acute infection as low IgG avidity can persist for years in some women [44-46]. The usefulness of a rising IgG titer for diagnosis of acute infection has never been adequately evaluated and is subject to error because of lack of reproducibility in many laboratories. A reference laboratory should be consulted in these cases (eg, the Palo Alto Medical Foundation Toxoplasma Serology

Laboratory, which is the reference laboratory of the Centers for Disease Control and Prevention, at http://www.pamf.org/serology).

FETAL INFECTION

Risk factors — The risk of fetal infection increases steeply with advancing gestational age at the time of maternal seroconversion [47]. A meta-analysis of all available cohorts estimated the risk of transmission to be 15 percent when the mother seroconverted at 13 weeks, 44 percent at 26 weeks, and 71 percent at 36 weeks [47]. Although these figures are based on women who were mostly treated during pregnancy, they are likely to be generalizable to untreated women, as there is no clear evidence that prenatal treatment administered in screening programs reduces the risk of mother to child transmission of toxoplasmosis (see 'Rationale for prenatal treatment' below).

Immunocompetent women infected prior to conception virtually never transmit toxoplasmosis to the fetus, although rare exceptions have been reported [48-54]. Immunocompromised women (eg, women with acquired immunodeficiency syndromes [AIDS] or taking immunosuppressive medications) may have parasitemia during pregnancy despite preconceptional infection; their infants are at risk of congenital infection [55].

Congenital toxoplasmosis secondary to reinfection is a rare event; this phenomenon has been reported in approximately six women over the past three decades [56]. One well-documented case demonstrated that prior immunity to *Toxoplasma* did not protect against reinfection with an atypical strain [56]. (See "Toxoplasmosis in HIV-infected patients".)

Pathogenesis of fetal infection — Maternal toxoplasmosis infection is acquired orally. Fetal infection results from transmission of parasites via the placenta following primary maternal infection [3]. It is likely that transmission occurs in most cases during the parasitemic phase in the days after infection and before the development of a serologic response. The risk of transmitting infection to the fetus increases steeply with the gestational age at seroconversion [47].

To survive and multiply, the tachyzoite invades host cells, especially in the brain and muscle, where it forms tissue cysts which can remain dormant for years. In immunocompetent animal models, tissue cysts can be formed within a week of infection [57,58]. It is not known how long this process takes in the relatively immunologically immature fetus. The transition from acute infective tachyzoite form, which is responsible for cell damage, to the dormant bradyzoite form contained in tissue cysts impenetrable to antibiotics has important implications for the therapeutic "window of opportunity."

Fetal sequelae — Fetal ultrasound can be useful to provide diagnostic information, although findings are nonspecific. The most common intracranial sonographic findings in fetal toxoplasmosis are intracranial hyperechogenic foci or calcifications and ventricular dilatation, which are poor prognostic signs [38,59-61]. Cerebral ventricular dilatation is generally bilateral and symmetrical. In one series of 32 proven infected cases, evolution was always very rapid over a period of a few days [59]. In a European prospective cohort study [38], abnormal sonographic cranial findings (intracranial calcification or ventricular dilatation) were found in 6 percent (14/218) of infected fetuses. As reported in this and other studies, abnormal cranial findings appear only after 21 weeks of gestation [38,59].

Abnormal findings involving areas other than the brain (eg, ascites) are less specific for toxoplasmosis. Intrahepatic densities, increased thickness and hyperdensity of the placenta,

ascites, and, rarely, pericardial and pleural effusions have also been observed [59]. Serial ultrasound is useful if late termination is being actively considered.

Not all abnormal fetal findings lead to serious disabling sequelae. The European prospective study estimated the probability of serious neurologic sequelae or death for fetuses with abnormal intracranial ultrasound findings was 43 percent (95% CI 6-90 percent) [38]. Serious neurologic sequelae included a diagnosis of cerebral palsy, microcephaly, or bilateral blindness, or hydrocephalus or epilepsy requiring treatment. Death included both postnatal death before age two years and terminations of pregnancy for congenital toxoplasmosis. For infants with abnormal findings detected in the first six months of postnatal life (abnormal cranial ultrasound, retinochoroiditis, or lymphadenopathy or hepatosplenomegaly), the estimated probability of serious neurologic disease or death was 30 percent (Bayesian credible interval 14 to 47 percent) versus 1 percent (Bayesian credible interval 0-2.3 percent) in infants with none of these findings. These estimated probabilities were much higher in women infected early in pregnancy and in untreated women.

Intrauterine growth restriction and microcephaly are not characteristic of congenital toxoplasmosis [59,62]. Stillbirth appears to be a rare complication; a prospective European cohort study of 1208 infected women found the risk of stillbirth among 448 women infected during the first trimester was no higher than that in the general obstetrical population matched for age [62]. An observed association between early maternal infection and preterm delivery may be due to obstetric intervention, rather than the disease itself [62].

Prenatal diagnosis — The main purpose of prenatal diagnosis of fetal infection is to help decide whether to change prenatal treatment from spiramycin to a pyrimethamine-sulfonamide combination (see 'Rationale for prenatal treatment' below). As prenatal diagnosis requires amniocentesis, which is an invasive test with a small but well-established risk of miscarriage, clinicians need to ensure that women are sufficiently informed to enable them to weigh the potential benefits and risks when deciding whether to undergo prenatal diagnosis. (See "Diagnostic amniocentesis".) Although there have been no randomized controlled trials comparing types of treatment, none of the comparative cohort studies have provided any evidence that a pyrimethamine-sulfonamide combination is more effective than spiramycin for any outcomes related to congenital toxoplasmosis in humans [4,47].

In some women, prenatal diagnosis is important to aid in their decision as to whether to terminate the pregnancy. Exclusion of fetal infection by prenatal diagnosis can also prevent unnecessary postnatal treatment in children without clinical signs of toxoplasmosis and at low risk of congenital infection [38,63].

Polymerase chain reaction (PCR) for *T. gondii* DNA in amniotic fluid is the best method for diagnosing fetal infection [64], but accuracy varies among laboratories and techniques and sensitivity is lower in early (<18 weeks of gestation) than in late pregnancy [63,65,66]. The B1 nuclear target initially used for PCR diagnosis of *T. gondii* has been replaced by the REP-529 target, which has superior sensitivity [67,68].

In a 2016 systematic review and meta-analysis of the performance of PCR of amniotic fluid for diagnosis of congenital toxoplasmosis, pooled sensitivity was 67 percent and increased with later gestational age at maternal infection [64]. The relationship between timing of PCR testing after maternal infection was uncertain, but diagnostic performance appeared to be better when the test was performed ≥5 weeks after maternal diagnosis: pooled sensitivity 87 percent and specificity 99 percent. At least one study has reported no association between a positive amniocentesis and

time since seroconversion, thereby challenging the rationale for delaying amniocentesis until four weeks after seroconversion [63].

Mouse inoculation of amniotic fluid, used in some European centers to diagnose fetal infection, is hard to justify, given the high cost, limited sensitivity, and the fact that results take four to six weeks [63]. Cordocentesis has not been widely used for more than a decade because of the risk of fetal loss [47].

Some clinicians recommend fetal ultrasound to detect fetal abnormalities suggestive of infection in women with negative amniotic fluid testing, in case of a false negative PCR result [69]. However, this strategy subjects a very large number of uninfected fetuses to unnecessary repeated ultrasounds.

After delivery, placental findings of toxoplasmosis include (picture 1): granulomatous villitis, cysts, plasma cell deciduitis, villous sclerosis, and chorionic vascular thromboses. Free trophozoites may be observed in villous stroma, amniotic epithelium, chorion, and Wharton's jelly.

RATIONALE FOR PRENATAL TREATMENT — The approach to management of toxoplasmosis during pregnancy was largely based upon the experience of Desmonts and Couvreur, who reported more than 40 years ago that prenatal treatment with spiramycin was associated with a reduced risk of congenital infection [70]. Their findings were flawed because they did not take into account the fact that the treated women in their study seroconverted in early pregnancy, and, therefore, were at low risk of fetal infection, whereas the untreated women mostly seroconverted in late pregnancy and were at high risk of fetal infection [71]. Their findings have since been refuted by a series of cohort studies [32,47,72,73].

Whether any treatment reduces the risk of mother to child transmission remains controversial, as no randomized trials evaluating this issue have been performed. The most robust evidence comes from a 2007 systematic review and individual patient data meta-analysis at single patient level of 20 European cohort studies (1438 women) in which universal screening for toxoplasmosis in pregnancy was performed [47]. The analysis assessed the effect of timing and type of prenatal treatment on mother-to-child transmission of infection and clinical manifestations before age one year. Prenatal regimens included spiramycin alone, spiramycin followed by pyrimethamine-sulfonamides, and pyrimethamine-sulfonamides alone.

The authors found weak evidence that treatment started within three weeks of seroconversion reduced mother-to-child transmission compared with treatment started after eight or more weeks (OR 0.48, 95% CI 0.28-0.80; p = 0.05), but they could not distinguish whether this was a real benefit of treatment or a bias due to late detection and inclusion in the cohort of women at increased risk of fetal infection. Only one in five women were treated within three weeks of seroconversion, despite the fact that most (76 percent) were identified in France, where a regimen of monthly retesting is mandated by law. Thus, even if early treatment is effective, it will be difficult to identify and treat women so quickly after seroconversion.

In addition, the authors found no statistically significant evidence that early treatment reduced the risk of intracranial lesions detected after birth, or of retinochoroiditis detected during infancy [47]. Two other large cohort studies also found no evidence that prenatal treatment reduced the risk of retinochoroiditis up to school age [74,75]. However, there is evidence of a reduction in serious neurological sequelae or postnatal death in children with congenital toxoplasmosis whose mothers were treated during pregnancy.

In a European study involving 293 infected fetuses, 8 percent had serious neurological sequelae [38]. The authors estimated that prenatal treatment reduced the risk of serious neurological sequelae or death by three-quarters. They also estimated that, to prevent one case of serious neurological sequelae or death after maternal infection at 10 weeks of pregnancy, it would be necessary to treat three fetuses with confirmed infection. To prevent one case of serious neurological sequelae or death after maternal infection at 30 weeks of pregnancy, 18 fetuses would need to be treated. However, they also urged caution in interpretation of these findings because of the small number of cases of serious neurological sequelae, uncertainty about the timing of maternal seroconversion, and consideration that the findings only relate to the more benign strain of *T. gondii* that predominates in Europe and North America, not the more virulent strains that occur in South America.

There is fairly strong evidence, again from cohort studies, that treatment with a pyrimethamine-sulfonamide combination is no more effective than spiramycin alone for reducing the risk of clinical manifestations in the infected infant. In a 2016 systematic review and meta-analysis of the efficacy of anti-toxoplasma gondii medicines in humans, there was no difference between spiramycin, azithromycin, or traditional Chinese medicine (which has anti-T*oxoplasma* properties) for rates of seroconversion in nonpregnant, asymptomatic individuals exposed to infection [76]. There was also no evidence that the risk of vertical transmission differed according to the type of maternal drug treatment, including pyrimethamine combinations. The authors added to calls for randomized trials of treatment in pregnancy.

Despite this lack of evidence, pyrimethamine-sulfonamide or pyrimethamine-clindamycin combinations are widely recommended, based on evidence that levels of spiramycin in fetal blood samples are about half those found in maternal serum, and may be insufficient for treating fetal infection [3,34,77]. However, this issue remains controversial, given the difficulty in measuring blood levels of spiramycin and the extent of variation in blood levels between women [78].

The lack of evidence that pyrimethamine-sulfonamide combinations are more effective than other drugs is important and undermines the rationale for prenatal diagnosis. Clinicians and women need to be aware that we simply do not know whether changing treatment from spiramycin to a pyrimethamine-sulfonamide combination if the fetus is infected is beneficial.

Adverse drug effects are more common with pyrimethamine-sulfonamide combinations than with spiramycin. A European multicenter cohort study found adverse effects requiring treatment cessation in 3.4 percent (11/322) of women prescribed pyrimethamine-sulfonamide compared with 1.7 percent (13/780) of women prescribed spiramycin alone [32]. A prospective study of 48 children with congenital toxoplasmosis identified by neonatal screening found that 7 experienced adverse reactions leading to treatment cessation; 6 of the 7 patients with adverse reactions had neutropenia [79].

In summary, there is evidence that prenatal treatment reduces serious neurological sequelae of congenital toxoplasmosis, but no evidence of any effect on ocular disease, vision, or mother-to-child transmission of infection. Randomized controlled trials are required to determine whether the benefits of prenatal treatment justify the potential harms and costs of prenatal screening. However, if toxoplasmosis is identified through testing because of maternal symptoms or a high risk of exposure to infection, then treatment is justified, though uncertainty remains about the type of treatment and duration.

TREATMENT REGIMENS — Despite the lack of evidence of treatment efficacy, prenatal treatment is usually offered to pregnant women who are diagnosed with toxoplasmosis. The

uncertainty about treatment effectiveness, risk of adverse effects, and the high probability that the child will not be impaired should be discussed with women when deciding whether or not to treat.

Spiramycin — Pregnant women who become infected during pregnancy are generally treated immediately with spiramycin (1 g orally every eight hours without food), which is a macrolide antibiotic similar to erythromycin. It is concentrated in the placenta, where it is thought to treat placental infection and thus helps to prevent transmission to the fetus, at least theoretically [3,80]. The drug is licensed in Europe and Canada, and is available in the United States for use in pregnancy from Rhone-Poulenc (Montreal, Quebec) if an Investigational New Drug (IND) number is obtained from the US Food and Drug Administration (FDA) ("compassionate use" pathway).

Pyrimethamine and sulfadiazine — Pyrimethamine is a folic acid antagonist which can cause dose-related bone marrow suppression with resultant anemia, leukopenia, and thrombocytopenia. It is teratogenic in animals when given in large doses [3]. Sulfadiazine, another folic acid antagonist, works synergistically with pyrimethamine against *T. gondii* tachyzoites, and can also cause bone marrow suppression and reversible acute renal failure. Due to the potential toxicity of these drugs, their use during pregnancy should only be considered if fetal infection has been documented, although there is no clinical evidence that these drugs are more effective than spiramycin [3,47,72,74,81]. There are no direct maternal benefits from these drugs.

Various dosing regimens have been proposed but, even in France, where prenatal screening has operated for 30 years, treatment regimens vary [3,32,82]:

- A three-week course of pyrimethamine (50 mg once per day orally or 25 mg twice per day) and sulfadiazine (3 g/day orally divided into two to three doses), alternating with a three-week course of spiramycin (1 g orally three times per day) until delivery.

- Pyrimethamine (25 mg once per day orally) and sulfadiazine (4 g/day orally divided into two to four doses) administered continuously until term.

Leucovorin calcium (folinic acid, 10 to 25 mg/day orally) is added during pyrimethamine and sulfadiazine administration to prevent bone marrow suppression. Monitoring of complete blood counts and platelet counts should be performed weekly, and treatment discontinued, if a significantly abnormal result is reported.

Other — Azithromycin has been used successfully to treat *T. gondii* in both an animal model and in humans with acquired immunodeficiency syndromes (AIDS) [3,83-85]. (See "Toxoplasmosis in HIV-infected patients".) It is a Category B drug that has been used safely for treatment of Chlamydia trachomatis infections in pregnancy. Large clinical trials are necessary to determine whether this agent, or perhaps clarithromycin, is an effective alternative to spiramycin to prevent in utero infection with *T. gondii* [3]. Pyrimethamine (100 mg loading dose orally followed by 25 to 50 mg/day) combined with azithromycin (500 mg per day) has been found to have equivalent effects to the combination with sulfonamide in a randomized controlled trial of adult patients with toxoplasmic retinochoroiditis [86]. Women intolerant of pyrimethamine may consider trimethoprim-sulfamethoxazole [87] or clindamycin [88,89]. However, the safety and efficacy of these drugs for treating in-utero toxoplasmosis infection are unknown.

TERMINATION OF PREGNANCY — A small proportion of women have their pregnancies terminated because of toxoplasmosis. Within the prenatal screening program in France, termination is discouraged unless there is definite evidence of fetal infection based on polymerase chain reaction (PCR) performed in a reference laboratory and evidence of intracranial

abnormalities on fetal ultrasound. The rationale for this approach is that most infected babies have a good prognosis and, on average, do not differ in their development at three to four years from uninfected children [82,90,91]. However, fetuses with ultrasound evidence of intracranial lesions are thought to be at high risk of serious neurological sequelae or postnatal death. It is not clear whether prenatal treatment reduces these risks once intracranial lesions are apparent [38]. In France, approximately 1.4 percent (17/1208) of infected women undergo termination and just over half of these pregnancies have proven fetal infection [32,63].

NEONATAL MANAGEMENT AND OUTCOME — *Toxoplasma* infection in the newborn is discussed in detail separately. (See "Congenital toxoplasmosis: Clinical features and diagnosis" and "Congenital toxoplasmosis: Treatment, outcome, and prevention".)

PREVENTION — Prevention of primary infection is based upon avoidance of sources of infection. While access to reliable information on sources of infection is undoubtedly important, systematic reviews have found no high quality evidence that such information changes women's behavior during pregnancy [92,93]. Evidence from case control studies of risk factors in Europe has identified the following principal sources of infection:

- Travel to less developed countries is a major risk factor, especially to South America, where more virulent parasite genotypes predominate [5,23].
- Women should avoid drinking unfiltered water in any setting [4,5,94].
- Avoid ingesting soil by observing strict hand hygiene after touching soil. Fruit and vegetables should be washed before eating [23,25].
- Raw or undercooked meat is an important source of infection. Cutting boards, knives, counters and the sink should be washed after food preparation. Avoid mucous membrane contact when handling uncooked meat. Women should also avoid tasting meat while cooking [4,5,23,25].
- Meat should be cooked to 152ºF (66ºC) or higher, or frozen for 24 hours in a household freezer (at less than -12ºC), both of which are lethal to tachyzoites and bradyzoites [95]. Freezing meat before consumption appears to be the most effective intervention in preventing toxoplasmosis transmitted by meat [96].

  Meat farmed in strict indoor conditions is less likely to be contaminated than outdoor reared meat [5]. There is weak evidence that meat that has been smoked or cured in brine is not safe. The risk of infection is likely to be increased when cured products involve meat from more than one animal and limited drying and curing, as in some local production methods [5,24,97].
- There is some evidence that shellfish can be infected with *Toxoplasma* cysts [98].
- Owning a cat is only weakly associated with acute infection. This is probably because cats only excrete oocysts for three weeks of their life, and people are just as likely to be exposed to oocysts excreted by someone else's cat. Nevertheless, it seems sensible for pregnant women with cats to ask someone else to change the litter box daily (fresh cat feces are not infectious) [5,23,25].

Hand washing is the single most important measure to reduce transmission of microorganisms from one site to another on the same patient. Thus, handwashing is important after activities such as preparing food or gardening.

Timing pregnancy after maternal infection — There are limited data on which to base a recommendation for how long to delay pregnancy after an acute toxoplasmosis infection. Although a delay of six months has been suggested [34], parasitemia is very short lived and it is likely that encystment occurs rapidly in women with adequate immune function, thus immunocompetent women who become pregnant at least three months after an acute infection are unlikely to transmit the infection to the fetus. In a study of parasitemia after acute infection, none of the 54 patients had positive blood polymerase chain reaction (PCR) results by 21 to 25 weeks from onset of lymphadenopathy [99] and data from the Systematic Review on Congenital Toxoplasmosis (SYROCOT) study suggested congenital infection occurs within three weeks of maternal infection [47].

Reactivation of latent toxoplasmosis during pregnancy could occur in human immunodeficiency virus (HIV)-infected pregnant women, particularly in those who are severely immunocompromised. In the European Collaborative Study, a large prospective study of children born to HIV-infected women, 451 children recruited to the study were born to mothers with anti-*Toxoplasma* IgG antibody and none of these children had clinical evidence of congenital toxoplasmosis [100]. Congenital infection was excluded serologically in a subgroup of 71 children. These findings indicate a very low risk of maternal-fetal transmission of the parasite, with a statistical upper limit of approximately 4 percent [101]. However, most of the women in the study were asymptomatic, and the risk of transmission may be higher in severely immunocompromised HIV-infected women. Management of HIV infected women is discussed separately. (See "Toxoplasmosis in HIV-infected patients" and "Prenatal evaluation of the HIV-infected woman in resource-rich settings".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Avoiding infections in pregnancy (The Basics)")
- Beyond the Basics topics (see "Patient education: Avoiding infections in pregnancy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

General principles

- The main sources of maternal toxoplasmosis infection are ingestion of contaminated undercooked or cured meat or meat products, soil-contaminated fruit or vegetables, or contaminated unfiltered water. (See 'Sources of infection' above.)

- Serological diagnosis of acute maternal infection should be confirmed by a reference laboratory. (See 'Diagnosis' above.)

- For women planning pregnancy or who are pregnant, we recommend avoidance of risky behaviors, such as eating raw or undercooked meat or drinking unfiltered water. Public health interventions include provision of clean filtered water and promoting greater awareness of the sources of infection. (See 'Prevention' above.)

- Despite the lack of evidence of cost effectiveness, prenatal treatment is usually offered to pregnant women with toxoplasmosis. Pregnant women who become infected during pregnancy are generally treated immediately with spiramycin to prevent maternal-fetal transmission. For women with proven fetal infection who choose to be treated, pyrimethamine plus sulfadiazine is more widely used than spiramycin or azithromycin, but there is no evidence of improved effectiveness and it is associated with more serious adverse effects. The major benefit of prenatal treatment is a possible substantial reduction in serious neurological sequelae or postnatal death. (See 'Rationale for prenatal treatment' above and 'Treatment regimens' above.)

For toxoplasmosis strains circulating outside of South America

- Maternal toxoplasmosis infection is usually asymptomatic, but may be manifested by nonspecific symptoms. In most cases, the most serious consequence of maternal infection is transmission to the fetus. (See 'Clinical manifestations' above and 'Fetal sequelae' above.)

- The risk of vertical transmission increases with increasing gestational age at maternal infection. Conversely, the risks of intracranial lesions and serious neurodevelopmental sequelae decrease with increasing gestational age at maternal infection. Rarely, fetal infection leads to stillbirth or neonatal death. (See 'Fetal sequelae' above.)

- Maternal infection during pregnancy is most accurately diagnosed when based on a minimum of two blood samples at least two weeks apart showing seroconversion from negative to positive toxoplasma-specific IgM or IgG. Polymerase chain reaction (PCR) for *T. gondii* DNA in amniotic fluid is the best method for diagnosing fetal infection, but is not sensitive when women seroconvert in the first trimester. Sonography of an infected fetus may show intracranial calcification or ventricular dilatation after 21 weeks of gestation. (See 'Screening' above and 'Diagnosis' above.)

- We suggest not performing routine universal prenatal screening for toxoplasmosis in women at low risk of infection, given there is insufficient evidence that the benefits of prenatal treatment outweigh the potential harms and costs (**Grade 2C**). However, serological testing is clinically indicated to diagnose infection in women with symptoms of toxoplasmosis or at high risk of recent exposure. In such cases, prenatal treatment is justified to reduce the risk of serious neurological sequelae or postnatal death, although information on the low risk of serious adverse outcome and the risk of adverse drug effects should be shared with women when deciding whether or not to treat. (See 'Screening' above and 'Prenatal diagnosis' above and 'Rationale for prenatal treatment' above.)

For toxoplasmosis strains circulating in South America

- Infection acquired during pregnancy in South America carries a much higher risk of serious sequelae for the fetus than does infection acquired in Europe or North America. (See 'Prevention' above.)

- Although evidence is lacking for the effectiveness of treatment for these more virulent strains, we suggest treating women who are tested for clinical indications and acquired infection in South America (**Grade 2C**). (See 'Rationale for prenatal treatment' above.)

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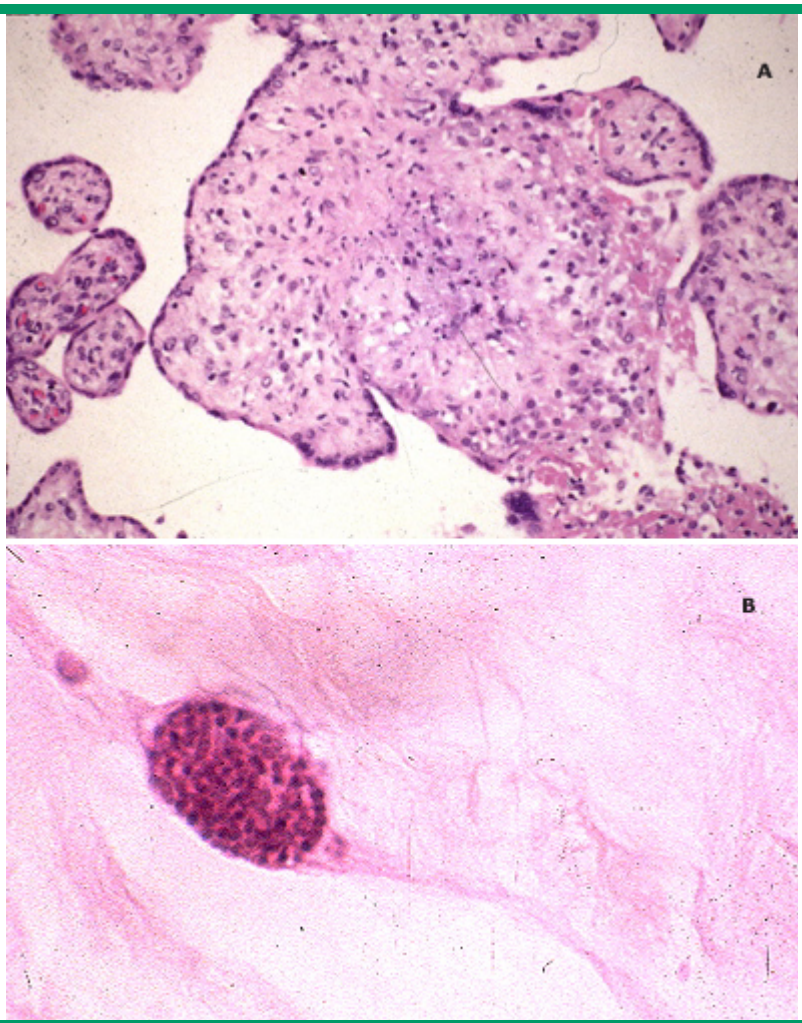
GRAPHICS

Toxoplasmosis of the placenta



(A) Granulomatous villitis (B) Trophozoites.

Courtesy of Drucilla J Roberts, MD.

Graphic 52889 Version 2.0

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Ruth Gilbert, MD Nothing to disclose **Eskild Petersen, MD, DMSc, DTM&H** Nothing to disclose **Charles J Lockwood, MD, MHCM** Consultant/Advisory Boards: Celula [Aneuploidy screening (No current products or drugs in the US)]. **Peter F Weller, MD, MACP** Grant/Research/Clinical Trial Support: GlaxoSmithKline [Anti-IL5 mAb for EGPA (Mepolizumab)]. **Vanessa A Barss, MD, FACOG** Nothing to disclose

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