TOXOPLASMOSIS IN PREGNANCY

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**TOXOPLASMA GONDII**

a ubiquitous protozoan parasite

usually acquired during childhood and adolescence

toxoplasmic infection is acquired for the first time during pregnancy, the parasites can be transmitted from the mother to the fetus, resulting in congenital toxoplasmosis

The frequency of congenital toxoplasmosis increases with increasing gestational age at maternal infection

frequency of severe sequelae in offspring is greater when infection occurs early in pregnancy
MATERNAL INFECTION

SOURCES OF INFECTION

• an obligate intracellular parasite that exists in three forms:
  • sporozoite
  • tachyzoite
  • bradyzoite

• **main source**: meat products, soil or water or soil-contaminated fruit or vegetables

• drinking unpasteurized goat’s milk
SEROPREVALENCE AMONG WOMEN OF CHILDBEARING AGE

- In industrially developed, temperate-climate countries, 10 to 50 percent of adults aged 15 to 45 years have serologic evidence of past *T. gondii* infection
- which represents a decline in seroprevalence over recent decades
INCIDENCE OF ACUTE PRIMARY INFECTION IN PREGNANCY

• maternal infection during pregnancy ranged from 0.5 to 8.0 per 1000 susceptible pregnancies in a study conducted in six European countries in the 1990s
CLINICAL MANIFESTATIONS

• Acute maternal infection is usually **asymptomatic** (≥80 percent of cases)
• symptoms of infection: they are typically **nonspecific and mild**: fever, chills, sweats, headaches, myalgias, pharyngitis, hepatosplenomegaly, and/or a diffuse nonpruritic maculopapular rash.
• The febrile episodes usually last two to three days.
• **Lymphadenopathy** is the most common symptom.
  • It is typically bilateral, symmetrical, nontender, and cervical
  • The lymph nodes are usually smaller than 3 cm in size and nonfluctuant. lymphadenopathy can persist for weeks.
• **Ocular disease** (chorioretinitis [posterior uveitis]) may occur with acute disease but is more common with reactivation. It presents with visual loss or floaters.
**PREGNANCY OUTCOME**

- The overall risk for miscarriage is approximately **0.5 percent** among women who seroconvert.
- Risk of fetal demise is estimated to be **1.3 to 1.6 percent**.
INDICATIONS FOR MATERNAL DIAGNOSTIC TESTING

• A high clinical suspicion of acute infection in the mother based on symptoms (e.g., fever and adenopathy, particularly cervical).

• Ultrasonographic abnormalities in the fetus that suggest congenital toxoplasmosis (e.g., intracranial hyperechogenic foci or calcifications and/or cerebral ventricular dilation).
INTERPRETATION OF SCREENING RESULTS

• If the IgM is positive or equivocal (regardless of the IgG), the diagnosis should be confirmed by an experienced reference laboratory.

• If screening is performed early in pregnancy, particularly in the first trimester, negative IgM and positive IgG antibodies indicate prior immunity; confirmatory testing is not recommended.

• If screening is performed later in pregnancy, particularly after approximately 20 weeks, and the IgM is negative and the IgG is positive, the timing of infection is less clear, and confirmatory testing by an experienced reference laboratory is recommended.
INTERPRETATION OF SCREENING RESULTS

- IgM antibodies appear as early as two weeks after infection and may persist for years.
- IgG antibodies peak six to eight weeks after infection and then decline over the next two years but remain positive.
- For women who are initially screened at the end of the first trimester and have positive IgM and IgG, the probability that infection occurred after conception is 1 to 3 percent.
- To establish whether the positive IgM and IgG antibodies reflect recent or chronic infection or a false-positive result, confirmatory testing must be obtained with avidity testing. High IgG avidity is a hallmark of chronic infection (>4 months old).
- A rising IgG titer is another factor to consider in establishing a diagnosis of probable recent versus chronic infection. A twofold or greater increase in IgG titer over two sequential samples obtained three weeks apart and tested simultaneously in the same laboratory with the same technique can also suggest recent infection.
FETAL INFECTION

• Fetal infection results from transplacental transmission of tachyzoites following primary maternal infection

• **Consequences of fetal infection**: In France, approximately 90 percent of live born children with congenital toxoplasmosis are asymptomatic at birth;

• two-thirds of symptomatic newborns have moderate disease (intracranial calcifications, peripheral retinochoroiditis)

• one-third have severe disease (disseminated form, hydrocephalus, or macular retinochoroiditis)
RISK FACTORS FOR MATERNAL-TO-FETAL TRANSMISSION

- Maternal infection at an advanced gestational age.
- High parasite load.
- Maternal parasite source (risk of fetal infection is higher when the source is sporozoites in oocysts [cat feces] than bradyzoites in tissue cysts [meat]).
- High-virulence *T. gondii* strain.
- Maternal immunocompromise.
IMPACT OF GESTATIONAL AGE

• The frequency of fetal infection increases steeply with advancing gestational age at the time of maternal seroconversion
  • ● At 13 weeks – 15 percent
  • ● At 26 weeks – 44 percent
  • ● At 36 weeks – 71 percent
• Although the frequency of fetal infection increases with gestational age at seroconversion, the overall frequency of clinical manifestations during infancy decreases with older gestational age at seroconversion, with a marked reduction in intracranial lesions with older gestational age at seroconversion, and a less marked reduction in ocular lesions
RISK OF FETAL INFECTION FROM REACTIVATION OR REINFECTION

• Congenital toxoplasmosis secondary to maternal reinfection with a different *T. gondii* strain is a very rare event.

• Theoretically, reactivation of latent toxoplasmosis during pregnancy leading to congenital infection could occur in pregnant women with HIV who are severely immunocompromised, but the risk appears to be absent or very low.
ULTRASOUND FINDINGS IN CONGENITAL TOXOPLASMOSIS

- Intracranial hyperechogenic foci (calcifications/densities)
- Ventricular dilation/hydrocephalus
- Echogenic bowel
- Hepatosplenomegaly
- Intrahepatic calcifications/densities
- Growth restriction
- Ascites
- Pericardial and/or pleural effusions
- Hydrops fetalis
- Fetal demise
- Placental densities and/or increased thickness
DIAGNOSTIC SIGNIFICANCE IN THE ABSENCE OF PRENATAL SCREENING

• In the absence of maternal serologic screening, one or more of the ultrasound findings described above may lead to suspicion of congenital toxoplasmosis.

• The sonographic signs are nonspecific, so prenatal ultrasound cannot reliably distinguish between congenital toxoplasmosis and other congenital infections or various genetic diseases.

• When toxoplasmosis is suspected because of ultrasound findings rather than a prenatal screening protocol, maternal serology for toxoplasmosis and cytomegalovirus, at a minimum, should be performed as these are the two most common infectious causes for these findings.

• If maternal IgG and IgM are negative for toxoplasmosis, fetal toxoplasmosis infection is ruled out.
PROGNOSTIC SIGNIFICANCE IN INFECTED FETUSES

• depends on the severity of the cerebral damage, and not all abnormal fetal findings lead to serious disabling sequelae, particularly in the presence of early therapy
• the sonographic signs clearly associated with poor prognosis are:
  • Ventricular dilation
  • Large brain abscesses
  • Brain necrosis
  • Gyration disorders
  • Microcephaly
• Cerebral calcifications, are a risk factor for the development of retinochoroiditis during childhood
TIMING OF AMNIIOCENTESIS

- to obtain PCR for *T. gondii* DNA in amniotic fluid is offered to women at ≥18 weeks of gestation with serologically confirmed or strongly suspected recent infection for prenatal diagnosis of fetal infection.
- When possible, amniocentesis is delayed until two weeks after documentation of seroconversion (or four weeks after the estimated date of maternal primary infection) to improve diagnostic performance.
- If the mother begins treatment (especially pyrimethamine-sulfadiazine) before undergoing amniocentesis, the PCR test may become negative due to low parasite load from maternal treatment.
• Antimicrobial therapy directed against *T. gondii* is offered to symptomatic and asymptomatic pregnant women diagnosed with recent *T. gondii* infection (acquired during pregnancy) to reduce the risk of congenital toxoplasmosis
• There are no direct maternal benefits from treatment
TIMING AND CHOICE OF INITIAL DRUG REGIMEN

• The initial antimicrobial regimen is begun as soon as possible upon documentation of probable maternal infection. We start therapy before amniocentesis, even in patients near 18 weeks of gestation.

• This time (ideally <3 weeks from seroconversion) is considered the therapeutic "window of opportunity" when maternal administration of antibiotics may prevent or reduce fetal neurologic damage.

• General consensus to use spiramycin when therapy is begun in the first trimester (<14 weeks) and pyrimethamine-sulfadiazine when therapy is begun thereafter (≥14 weeks).

• Available evidence supports the superiority of pyrimethamine-sulfadiazine over spiramycin for therapy.

• Patients who begin spiramycin before 14 weeks can continue this drug until polymerase chain reaction (PCR) results from amniocentesis at 18 weeks are available, or they may switch to pyrimethamine-sulfadiazine at 14 weeks and continue pyrimethamine-sulfadiazine until PCR results from amniocentesis at 18 weeks are available.
MODIFICATION OF THE DRUG REGIMEN AFTER FETAL DIAGNOSIS

• **Positive PCR:** If amniotic fluid PCR for *T. gondii* is positive and the patient plans to continue the pregnancy, we treat with pyrimethamine-sulfadiazine until delivery.

• After birth, the child will be treated with the same regimen.

• **Negative PCR**

• **Patients with a normal fetal ultrasound examination undergoing fetal diagnosis because of seroconversion during routine prenatal screening**

• some authorities would not continue treatment whereas others would continue treatment because of concerns about placental transmission occurring after the amniocentesis. The risk of this happening is rare when maternal infection occurs early in pregnancy but increases when the infection occurs in the late second to third trimesters.
In cases of periconceptional or first-trimester seroconversion, spiramycin is preferred for continuing therapy after the negative amniotic fluid PCR because the likelihood of fetal infection is very low, it has been used safely for decades in pregnancy, and it has fewer tolerance issues than pyrimethamine-sulfadiazine.

- In cases of second- or third-trimester seroconversion, patients on pyrimethamine-sulfadiazine are switched to spiramycin when the amniotic fluid PCR is negative, but after a total of at least four weeks of pyrimethamine-sulfadiazine prophylaxis, and then spiramycin is continued until delivery.

Other approaches after a negative amniotic fluid PCR include:

- If seroconversion occurred after 33 weeks, some clinicians continue pyrimethamine-sulfadiazine until delivery unless side effects are bothersome, given the high false-negative amniotic fluid PCR rate in the third trimester.

- Some clinicians use pyrimethamine-sulfadiazine in all patients who choose to continue therapy after a negative amniotic fluid PCR because it appeared to be more effective than spiramycin prophylaxis.
SCREENED PATIENTS WHO SEROCONVERT, HAVE A NORMAL ULTRASOUND, AND DECLINE AMNIOCENTESIS FOR PCR

- Some patients who undergo routine screening may decline to undergo amniocentesis for PCR, particularly when the fetal ultrasound examination is normal. If a patient in a screening program declines amniocentesis, we suggest treatment with pyrimethamine-sulfadiazine from diagnosis of maternal infection ≥14 weeks until delivery since fetal infection cannot be excluded and treatment may improve outcome.

- If the patient does not want prolonged treatment, we suggest treatment for at least 8 weeks and until results from a fetal ultrasound after 22 weeks are available and negative for anomalies, with the understanding that the risk is not eliminated because a normal ultrasound does not exclude the possibility of congenital toxoplasmosis. In such cases, attempts should be made to diagnose congenital toxoplasmosis at delivery by collecting amniotic fluid for PCR and cord blood for antitoxoplasmosis IgM and IgA testing in a reference laboratory.
UNSCREENED PATIENTS UNDERGOING FETAL DIAGNOSIS BECAUSE OF ABNORMAL FINDINGS ON FETAL SONOGRAPHY

• The timing of maternal seroconversion in such cases usually cannot be determined with certainty. When the amniocentesis is performed because of fetal ultrasound anomalies suspicious for congenital toxoplasmosis in a patient who is IgG positive, we consider a negative amniotic fluid PCR result from a reference laboratory reliable evidence to exclude congenital toxoplasmosis as the cause of the anomalies. In this situation, the clinician should evaluate for other diagnoses with similar fetal findings. Antiparasitic therapy is not indicated
SPIRAMYCIN

• **Dose** – The dose of spiramycin is 1 g (1 million international units) orally three times daily, without food.

• **Contraindications** – Long QT syndrome is a contraindication as polymorphic ventricular tachycardia can occur in patients with a long QT interval.

• **Side effects** – Side effects include nausea, vomiting, diarrhea, skin reactions (pruritus, rash, urticaria)

• **Monitoring** – No laboratory monitoring is required.
**PYRIMETHAMINE-SULFADIAZINE**

- **Dose** – Pyrimethamine 100 mg/day orally divided into two doses for two days followed by 50 mg orally daily plus Sulfadiazine 75 mg/kg per dose orally for one dose, followed by 100 mg/kg per day orally divided into two doses (maximum sulfadiazine 4 g/day) plus Folinic acid (leucovorin) 10 to 20 mg/day orally during and one week after pyrimethamine therapy
  
  - In France: Pyrimethamine 50 mg once per day orally plus Sulfadiazine 3 g/day orally divided into three doses plus Folinic acid (leucovorin) 50 mg weekly orally

- **Contraindications** – Sulfadiazine can precipitate serious hemolysis in individuals with (G6PD)

- **Side effects** – Pyrimethamine is a folic acid antagonist, which can cause dose-related bone marrow suppression with resultant anemia, leukopenia, and thrombocytopenia
  
  - 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.

- Crystalluria can occur during treatment with sulfonamides, so patients should be instructed to drink at least 2 liters per 24 hours and to alkalinize the urine

- **Monitoring** – CBC and plt counts should be performed weekly. If a significantly abnormal result is reported, the therapy should be stopped and/or the dose of leucovorin increased and the blood count repeated after a week.
EFFICACY
PYRIMETHAMINE-SULFADIAZINE VERSUS SPIRAMYCIN
FOR REDUCING MATERNAL-TO-FETAL TRANSMISSION

• Experimental evidence supports the superiority of pyrimethamine-sulfadiazine over spiramycin for preventing maternal-to-fetal transmission.

• Suggest overall that prompt prophylactic therapy with pyrimethamine-sulfadiazine following maternal seroconversion reduces the risk of congenital toxoplasmosis.

• Treatment started within three weeks of seroconversion reduced mother-to-child transmission compared with treatment started after eight or more weeks.
EFFICACY
PYRIMETHAMINE-SULFADIAZINE VERSUS SPIRAMYCIN
FOR REDUCING MATERNAL-TO-FETAL TRANSMISSION

• Treatment initiated more than three but within eight weeks of seroconversion showed a trend toward reduced mother-to-child transmission.
• In pharmacokinetic studies, spiramycin levels in fetal blood samples are approximately one-half those found in maternal serum; thus, it may be effective for preventing placental infection after a recent maternal infection but may be insufficient for treating fetal infection after placental transmission has occurred. Pyrimethamine-sulfadiazine is able to pass the blood-brain barrier whereas spiramycin does not reach the brain.
EFFICACY OF MATERNAL TREATMENT FOR REDUCING SERIOUS CLINICAL SEQUELAE IN OFFSPRING

• Even if it is not possible to prevent maternal-to-fetal transmission, transplacental fetal therapy that reduces the risk of serious neurologic sequelae or postnatal death in children with congenital toxoplasmosis would be a benefit of maternal therapy.
EFFICACY OF MATERNAL TREATMENT FOR REDUCING NONSERIOUS CLINICAL SEQUELAE IN OFFSPRING

• SYROCOT (individual patient data meta-analysis of 20 European cohort studies described above) found no reduction in retinochoroiditis in pregnancies in which maternal treatment was initiated after seroconversion.

• A subsequent study of 281 children with congenital toxoplasmosis in whom 50 developed ocular disease also found that prenatal treatment had no significant effect on the age at first or subsequent lesions.

• Multivariate analysis suggested that a delay of >8 weeks between maternal seroconversion and the beginning of treatment, female sex, and cerebral calcifications were risk factors for retinochoroiditis during the first two years of life in infants treated for congenital toxoplasmosis.
Prenatal care is routine, exclusive of the diagnostic and treatment issues described above. Congenital toxoplasmosis does not affect the timing or route of delivery.

**Ultrasound follow-up** — fetal ultrasound follow-up is recommended at least **monthly**. Sonographic abnormalities may appear or worsen several weeks after fetal infection.

The appearance of fetal lesions suggestive of infection on ultrasound following a **negative PCR** is exceptional, ultrasound follow-up is suggested every **four to six weeks**.

**Placental histology** — Placental findings of toxoplasmosis include 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.

**placental histology or parasitology is not recommended** for postnatal diagnosis because sensitivity and specificity are insufficient to make a reliable diagnosis of congenital toxoplasmosis.
PREVENTION

• Avoid drinking unfiltered water in any setting.
• Avoid ingesting soil by observing strict hand hygiene after touching soil (e.g., gardening). Fruit and vegetables should be washed before eating. Hand washing is the single most important measure to reduce transmission of microorganisms from one site to another.
• 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.
• Meat should be cooked to 152°F (66°C) or higher or frozen for 24 hours in a household freezer (at less than 10°F [-12°C]), both of which are lethal to tachyzoites and bradyzoites. Freezing meat before consumption appears to be the most effective intervention in preventing toxoplasmosis transmitted by meat.
• Meat farmed in strict indoor conditions is less likely to be contaminated than outdoor-reared meat. 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.
• Avoid eating raw shellfish since seawater can be contaminated by *T. gondii* oocysts that survive or bypass sewage treatment.
• 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 outdoors 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).
• 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, 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 one to three months after an acute infection are extremely unlikely to transmit the infection to the fetus.
Thank you