

Toxoplasma gondii infection in pregnancy

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ABSTRACT

Toxoplasmosis is a worldwide spread infection, caused by the parasite *Toxoplasma gondii*, acquired through ingestion of contaminated food or water, or consuming infected undercooked meat. Despite the fact that in healthy, non-pregnant population, this infection is predominantly asymptomatic and self-limited, in pregnancy it requires special care to minimize the risks to the fetus by vertical transmission. Congenital toxoplasmosis can result in permanent neurological impairment and even blindness. Once diagnosed in pregnancy, this infection needs prompt medical therapy to prevent fetal complications. Primary prevention of the toxoplasmosis consists of dietary and lifestyle changes with the purpose to limit the contact with the parasite. Secondary prevention includes the screening of the pregnant women. Screening programs are implemented in various countries depending on the prevalence of the parasite in the respective areas. The purpose of this article is to make a review of the medical literature concerning the management of *Toxoplasma gondii* infection in pregnancy. For this purpose, scientific research in databases and online medical publications such as Medline, PubMed, Elsevier and The Lancet was conducted.

Keywords: *Toxoplasma gondii*, pregnancy, congenital toxoplasmosis, transmission, diagnosis, treatment

INTRODUCTION

Toxoplasmosis is a worldwide spread infection caused by the protozoan *Toxoplasma gondii* (*T. gondii*), an obligate intracellular parasite belonging to the phylum Apicomplexa. It is one of the most prevalent chronic infections, affecting a third of the global population (1,2).

In immunocompetent people, toxoplasmosis is generally an asymptomatic and self-limited infection. However, if the infected person becomes immunosuppressed, the infection can get reactivated and cause severe disease with predominant neurological manifestation. Special consideration needs to be given to women of reproductive age, because, if the infection is acquired during pregnancy, the parasite can cross the placenta and infect the fetus, in the absence of a treatment. Significant long-term

manifestation may become obvious only months or years later, although the majority of newborns appear to be healthy at birth.

EPIDEMIOLOGY

The prevalence of this infection varies among the different geographical regions. The seroprevalence range from 10-50% among women of reproductive age from industrialized countries with temperate climate (2,3), up to 80% in tropical areas with exposure to unfiltered water, contaminated soil, or infected undercooked meat (4).

Approximately 500 to 5,000 cases of congenital toxoplasmosis occur each year in the United States (1,2). The incidence of congenital toxoplasmosis was 3.4 per 100,000 live births in 2002-2004 in England and Wales, (2,5), 1/1000 in France, less than

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1/10,000 live births in Sweden, Norway and Austria, 2–3/10 000 live births in Brazil and Poland (2,6,7).

The life cycle of *Toxoplasma gondii* is based on intermediate and definitive hosts. Felines and especially cats, are the definitive hosts. They make possible the reproduction of the parasite resulting oocytes, which eliminated in the feces and contaminate the soil and water and thus, fruits, vegetables, and food. Animals like pigs, cows, lambs, and also humans, incidentally, ingest these oocytes and become the intermediate hosts. Here the parasite multiplies in the digestive system and cause parasitemia. In this phase, by blood dissemination, the parasites can affect any other organ and also can cross the placenta and infect the unborn child.

The maternal-fetal transfer is facilitated with increasing maturity of the placenta and the risk of fetal infection increases with the gestational age (2,9,10,11). There is no evidence to prove that *T. gondii* is transmitted via breastfeeding or by direct human-to-human contact (5). In an immunocompetent intermediate host, the parasites can be found in the cysts that persists in tissues like the striated muscle or brain, for long periods of time, even lifelong (2,8).

TOXOPLASMOSIS IN PREGNANCY

The maternal-fetal transfer occurs predominantly in women who acquire their primary infection during pregnancy or shortly before conception (even 3 months before conception) (13-17). In very rare cases, congenital toxoplasmosis has been caused by the reactivation of the chronic infection in women with a immunocompromised state (e.g., HIV or treatment with immunosuppressive medications such as corticosteroids, for underlying disease), or by reinfection with a new higher virulence strain after international travel (13-17).

Most frequent sources of *Toxoplasma* infection in pregnancy are (2,12): contaminated soil or water with *T. gondii* from cat feces (drinking untreated water or unpasteurized raw milk; not wearing gloves when gardening; cleaning a cat's litter box; eating unwashed fruit or vegetables contaminated with infected soil); contact with contaminated meat (eating undercooked contaminated meat, especially pork, lamb, or venison or shellfish like oysters, clams, and mussels; touching face or mouth after handling raw contaminated meat); other (receiving an infected organ transplant or blood transfusion; workers who handle infected blood by accidental inoculation).

In the absence of treatment, the overall risk of maternal-to-child transmission from acute toxoplasmosis in pregnancy ranges from 20 to 50% (2,14).

On one hand, if the maternal infection is acquired early in pregnancy, the risk of transmission is lower, but the outcome can be severe or life-threatening to the fetus (2,18). On the other hand, maternal infection acquired later in pregnancy, has a higher risk of transmission to the fetus, but the clinical outcome is less severe, or the child may even be born asymptomatic (2,18). Infection acquired in the 2-3 months before conception can very rarely present a risk to the fetus (2,18), but a delay of 6 months has been suggested in planning a pregnancy after acute *Toxoplasma* infection (Grade III-B recommendation, SOGC) (2,14).

TABLE 1. Risk of transmission and frequency of fetal abnormalities with gestational age (2,19)

Weeks of gestation anomalies	Vertical transmission	Fetal morphological
6-20 wks	21%	11%
21-30 wks.	63%	4%
≥ 30 wks.	89%	0%

SYMPTOMS AND CLINICAL MANIFESTATIONS IN PREGNANCY

Approximately 80% of cases of *T. gondii* infection in pregnant women are asymptomatic (2). In symptomatic patients, most of the symptoms are mild or moderate and non-specific e.g., fever (lasts 2 to 3 days), headaches, sweats, chills, pharyngitis, myalgia, discrete not tender cervical or occipital lymphadenopathy (the most typical clinical manifestation and can persist for several weeks), hepatomegaly, splenomegaly, maculopapular rash. In severe cases, pregnant women could present visual disturbances, such as “headlight in the fog”, due to toxoplasmic chorioretinitis, especially in those cases that are due to reactivation of infection (20).

ANTENATAL TOXOPLASMOSIS

Occasionally, the diagnosis of *T. gondii* infection in a pregnant woman is first considered when ultrasonographic exam reveals the presence of fetal abnormalities (21,22). The most common ultrasonographic findings suggestive of congenital disease are intracranial calcifications and ventricular dilatation/hydrocephalus (2,5) with an incidence of 6 % estimated by a European cohort study (23).

Other ultrasound findings include (24) microcephaly, echogenic bowel, hepatomegaly, splenomegaly, intrahepatic calcifications, ascites; pericardial and/or pleural effusions, hydrops fetalis, growth restriction, fetal demise, placental densities and/or increased thickness.

These ultrasound anomalies of the fetus are not specific and can be found in other genetic diseases

or congenital infections and need be followed up with laboratory investigations to confirm the diagnosis (2). The prognosis of the infected fetus depends on the severity of cerebral damage. If the infection is early treated, not all the fetal ultrasound findings are linked with serious sequelae (25), excepting severe ventricular dilatation, brain necrosis, gyration disorders, and microcephaly, that have been associated with poor prognosis (23).

A European prospective cohort study conducted in 2010, found that the fetuses with abnormal ultrasound findings have a risk of serious neurological sequelae such as epilepsy, cerebral palsy, blindness, or death, around 43% (23).

NEONATAL TOXOPLASMOSIS

It has been estimated that about 80% of the babies born with congenital toxoplasmosis are asymptomatic at birth (2,26). From the symptomatic newborns, two-thirds have moderate disease with peripheral retinochoroiditis and intracranial calcifications, and about one-third have a severe form of the disease that is a disseminated form with hydrocephalus or macular retinochoroiditis (2,26).

In a French study, it was shown that the maximum risk of delivering a symptomatic infant was 8-14%, which occurred at approximately 24-30 gestational weeks (27).

DIAGNOSIS OF TOXOPLASMOSIS

T. gondii infection can be diagnosed directly by PCR, hybridization, isolation, and histology, and indirectly with serological methods. In countries with high disease prevalence, such as France, secondary prevention programs with maternal serological screening have been instituted (e.g., in France, screening for toxoplasma immunoglobulins IgM and IgG, is mandatory during preconception care and, as early as possible in the first trimester of pregnancy) (2,28). Contrary, countries with low prevalence rates, such as Canada or the United States, do not recommend universal screening (2), but instead, current practice suggests maternal screening when abnormal fetal ultrasound findings indicate possible infection (2,14,29).

The presence or the absence of IgG antibodies before or early in pregnancy, helps to identify women at risk of acquiring the infection (5). IgG antibodies arise within 1–2 weeks after infection and persist for the individual's lifetime (5). If the serological screening indicates the presence of IgG antibodies, the next step is to find if the infection is recent or not. The presence of IgM antibodies indicates a recent infection. In order to find when did the infection occurred in relation to conception, the IgG avidity assay must be done (2).

High IgG avidity is a mark of chronic infection (>4 months old) and a high avidity in the early gestation practically rules out fetal risk (2), but in the later gestation, after 16 weeks, a high avidity result can help only to ascertain the timing of infection to determine the extent of severity (2). On the other hand, low IgG avidity can persist for years in some women, and this is not diagnostic of recent infection (2). If both IgM and IgG are positive, a second blood sample should be sent to the reference laboratory for confirmation (30).

Not every maternal toxoplasmosis will result in fetal infection, and the diagnosis is based upon the detection of the parasite or specific antibody responses in the fetus (2). The polymerase chain reaction or PCR amplification of toxoplasmosis DNA from amniotic fluid is the most reliable and safe method of prenatal diagnosis and has replaced the direct sampling of fetal blood (2,31).

Amniocentesis for identification of *T. gondii* in the amniotic fluid by PCR should be offered in case of maternal primary infection diagnosis, if serologic testing cannot confirm or exclude acute infection, or in the presence of abnormal ultrasound findings (2) and should not be done before 18 weeks of pregnancy and not less than 4 weeks after suspected acute maternal infection to avoid false-negative results (2,14). PCR with amniotic fluid had a 100% positive predictive value, a sensitivity of 64%, a specificity of 100% and a negative predictive value of 88% (2).

A recent multicenter study published in 2021 showed that anti-Toxoplasma therapy during pregnancy may set back biological evidence of neonatal infection at birth and underline the need for a careful serological follow-up of infants with normal results (32).

Newborn infants with suspected congenital toxoplasmosis should be evaluated by specialists including neurologists, experienced neonatologists, retina specialists and pediatric infectious disease specialists (2).

MANAGEMENT OF TOXOPLASMOSIS

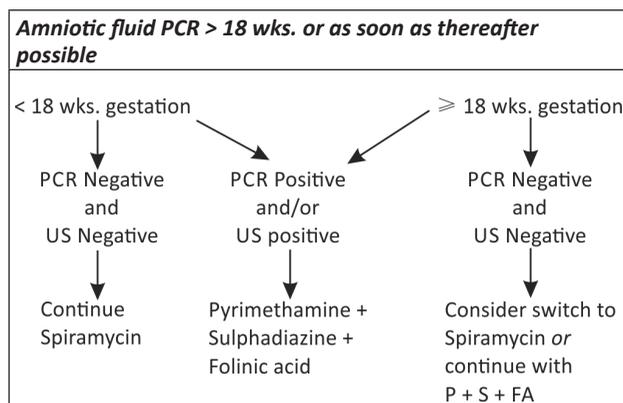
Once the serological test results are consistent with a recently acquired infection, before conception or before 18 weeks of gestation, an attempt to prevent vertical transmission of the parasite through treatment with spiramycin is recommended by many investigators in the United States and Europe (13,33). If fetal infection is confirmed at 18 weeks of gestation or later, by a positive result of PCR of amniotic fluid, treatment with pyrimethamine, sulfadiazine, and folinic acid is recommended (if the patient is already receiving spiramycin, the recommendation is to switch to this combination) (13,33).

TABLE 2. Medical treatment of toxoplasmosis in pregnancy (2,30)

Pregnant woman suspected/confirmed toxoplasmosis during pregnancy	
< 18 wks. gestation	≥ 18 wks. gestation
Spiramycin * 1g x 3/day	Pyrimethamine** 50 mg/day Plus Sulfadiazine 500 mg x 3/day Plus Folinic acid 25 mg x 2/day Water intake: 2 l/day to alkalinize urine
Treatment should be continued till delivery	

*Side effects: nausea, vomiting, diarrhea, skin reactions.
Monitoring: none. **CI:** long QT syndrome.
 Side effects: bone marrow suppression, reversible acute renal failure, skin rash. **Monitoring: complete blood count weekly. **CI:** G-6PD deficiency.

TABLE 3. Monitoring a pregnant woman with toxoplasmosis (2,30)



US: ultrasound; P: pyrimethamine; S: Sulphadiazine; FA: folinic acid

PREVENTION

Primary prevention of congenital toxoplasmosis focuses on effective avoidance of infection during

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pregnancy according to the recommendations of the Centers for Disease Control and Prevention (CDC) (2).

Secondary prevention involves systematic screening of pregnant women for *Toxoplasma* infection. The balance of benefits and risks of prenatal screening needs to be individualized by each country depending on the disease prevalence (2). United States, United Kingdom, Canada, and some countries of Europe recommend against routine universal screening for toxoplasmosis in pregnancy because of the low disease prevalence and incidence of maternal infection making screening costly (2,14). In other countries such as France, screening is performed at regular intervals as part of routine prenatal care (2,20).

CONCLUSIONS

Toxoplasma gondii infection, although is a benign condition in non-pregnant women, can cause severe impairment to the fetus during pregnancy. The most simple and important thing to avoid complications in pregnancy is primary prevention and preconceptional screening. Once the diagnosis has been established, the patient should be counseled regarding all the implications of congenital toxoplasmosis and the need for invasive tests, such as amniocentesis, and antibiotic therapy. Toxoplasmosis in pregnancy should be managed by a multidisciplinary team including maternal-fetal medicine, infectious disease, and neonatology specialists to minimize the risks of the fetus and help the mother make an informed decision.

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