Review Article

Toxoplasma Gondii Infection in Pregnancy and Neonatal period

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Summary

Toxoplasma Gondii is the causative agents of Toxoplasmosis and can infect growing embryo or fetus, and cause abortion, abnormal fetal development, severe congenital anomalies, mental retardation and fetal or neonatal death. Congenital toxoplasmosis is common in sub-Saharan Africa including Nigeria. Only primary T. gondii infection during pregnancy is associated with mother to child transmission. The challenge to health personnel caring for pregnant women is two folds. First is to confirm an infection since it is mainly asymptomatic and secondly to differentiate between primary or a non-primary infection. The combination of maternal serum IgM and IgG antibodies results with IgG avidity test result helps to differentiate the type of infection. A positive IgM antibody with a low IgG avidity test results confirms primary infection. It is recommended that all pregnant women diagnosed with primary toxoplasmosis be treated with spiromycin with or without pyrimethamine-sulfadiazine. Pyramethamine is teratogenic and contraindicated in the first trimester. Prevention of transmission from mother to fetus by treating mothers with acute infection is a second way to prevent fetal infection.

Keywords: Toxoplasmosis, maternal, newborn, congenital abnormality, IgG avidity test

Introduction

Toxoplasma gondii (T. gondii) infection poses an important public health challenge as it may cause serious morbidity and mortality in congenitally infected newborns and immune compromised patients¹. T. gondii is an intracellular protozoan of paradoxes, as it can either be a potential killer or a silent lifelong companion characterized by a self-limiting infection in healthy individuals².

T. gondii is the causative agents of Toxoplasmosis, one of the TORCH groups of infections. TORCH is an acronym originally coined from the first two letters of Toxoplasmosis and first letters Rubella, Cytomegalovirus, and Herpes virus type 2 infections. However, contemporary revision describes the O as standing for other transplacental infections like human immunodeficiency virus, Hepatitis B, Human parvovirus and Syphilis.
Globally the seroprevalence of T. gondii antibodies in pregnant women is high and its infection during the period of organogenesis has been associated with abnormal neurological development\(^3,4\). A fetus can become infected and develop congenital toxoplasmosis if the mother contracts toxoplasmosis during pregnancy. Congenital toxoplasmosis, transmitted transplacentally from mother to fetus, can have serious and potentially devastating effects in virtually all infected and untreated children at varying times in their lives\(^5\). T. Gondii infection causes abortion, abnormal fetal development, severe congenital anomalies, mental retardation and fetal or neonatal death \(^5\). The challenge to health personnel caring for pregnant women is to have clinical or serologic evidence of toxoplasma gondii infection and also to determine if the infection is primary or a non-primary infection by estimation of maternal serum IgM and IgG antibodies\(^6\). The presence of IgM antibodies in the serum of pregnant women may represent either a primary infection or a recurrent infection. Primary infections are associated with increased risk of congenital malformation in the fetus especially if it occurs during the period of organogenesis. Recurrent infections have been linked with less risk of congenital malformation compared with primary infections. High titres of IgG antibodies may represent a pre-conceptual immunity to T. Gondii infections following a primary infection and has been associated with reduced risk of transplacental transmission of T. gondii infections. The knowledge of the serological status of women during pregnancy assists health personnel to identify women at high risk of having fetuses with congenital malformation and institute appropriate measures\(^6-13\).

**Epidemiology and risk factors**

Over one third of world’s population is estimated to have evidenced of previous infection with toxoplasma. The previous infection is usually without recognized symptoms\(^11\). T. gondii is found universally throughout all geographic locations, socio economic groups, races and age groups. Although T. gondii infection has a global distribution, it is more common in low income countries and prevalence varies greatly with a variety of epidemiological factors\(^12\).

The overall age-adjusted seroprevalence of T. gondii ranged from 3% to 42 % and 15% among women of child bearing age\(^1,2,12\). In Turkey, it is reported that about quarter of million cases of T. gondii infection occur per year, resulting in 5000 hospitalizations and 750 deaths, making T. gondii the third most common cause of foetal food borne illness in that country\(^13\). In southern Turkey T. gondii IgG and IgM antibodies were found to be 52.1% and 0.54% respectively\(^14\). Nissapatron and colleagues\(^15\) found significant differences in T. gondii seroprevalence rates among the different races in Malaysia. The T. gondii seroprevalence was highest among the Malaya populations (55.7%), followed by the Indian (55.3%) and the Chinese (19.4%) populations.
In sub-Saharan Africa the prevalence ranges from 4 to 92.5%\textsuperscript{1, 2, 12, 16}. Bowery and colleague in a study of T. gondii antibodies among preschool and young school children in Nairobi, Kenya reported a seroprevalence of 35% and 60% respectively. Among pregnant women the seroprevalence also varied from region to country. Seroprevalence rates of 34.1% and 40.2% were reported among pregnant women in Sudan and Senegal\textsuperscript{2} respectively. Ertug and associates\textsuperscript{17} reported a lower seroprevalence of 30.1% from Aydin province in Turkey. A significantly lower rate of 25% was reported from Canada among women intending to get pregnant\textsuperscript{18}.

The seroprevalence of T. gondii infection is influenced by a number of factors ranging from climate, age, socioeconomic situations, food practices and pet keeping status. The seroprevalence of T. gondii infection has been found to be high in countries such as France (71%) where the consumption of undercooked meat is common\textsuperscript{19, 20} and in sub-Saharan Africa (44-83%)\textsuperscript{18-24}, where cats are abundant and the climate favour survival of oocysts\textsuperscript{17-23}. Studies conducted in Scandinavian countries and in England showed lower seroprevalence\textsuperscript{24, 25}.

In Nigeria, the reported seroprevalence rates of T. gondii ranged from 7% to 78% in normal pregnant women, with variations depending on the type of kit and testing algorithm used to confirm T. gondii infection.\textsuperscript{7, 9, 10, 26, 27} Onadeko and colleagues in a study in Ibadan, south west Nigeria among pregnant women found a prevalence of 78%, using Sabin Felman dye test\textsuperscript{25}. In Zaria, northern Nigeria, Alayande et al\textsuperscript{10} using Toxo-latx kit by Linear chemicals, reported seroprevalence of 30.5%, 22.5% and 30.7% for each of the trimesters respectively. Deji-Agboola and colleagues\textsuperscript{7} in their study among pregnant women in Lagos Nigeria using enzyme immunoassay reported a rate of 32.6%. Ishaku and colleagues\textsuperscript{9} found a sero-prevalence rate of 29.9% among pregnant. The prevalence was found to be higher in women who drink well water compared to those that drink packed water. A recent study among women of childbearing age in the Benue River basin by Olise and colleagues showed a high prevalence of 43.7%, confirming T. Gondii infection is still very common\textsuperscript{8}.

A number of studies both in low and high income settings have identified a number of habits that predisposes individuals to T. gondii infection, with majority involving contact with undercooked meat\textsuperscript{18, 28-31}. The risk factors for t. gondii infection include eating raw or undercooked meat, ownership of cat, eating unwashed raw vegetables or fruits. While eating undercooked meat allows direct ingestion of tissue cysts, ownership of cat and eating unwashed raw vegetables allows fecal-oral transmission of oocysts.

Based on these established risk factors for primary toxoplasmosis, pregnant women or those trying to become pregnant should be appropriately advised by their obstetricians on how to lower the risk of congenital toxoplasmosis.
Biology

T. gondii is an obligate intracellular protozoan that can infect all mammals, who serve as intermediate hosts. T. gondii is a coccidian protozoa of global distribution that infects a wide range of birds and animals but does not appear to cause disease in them. The normal final hosts are strictly animals belonging to the cat family – Felidae. This is because they are the only hosts in which the oocysts producing sexual stage of toxoplasma can develop.32 The trophozoites are boat-shaped, thin-walled cells that are 4-7 x 2-4 µm within tissue cells and somewhat larger outside them. The trophozoites stain lightly with Giemsa’s stain and often appear crescentic. Occasionally packed intracellular aggregates are seen. T. gondii cysts are found in the brain or certain other tissues. Ingestion of tissue containing these true cysts which contain thousands of spore-like bradyzoites, can initiate a new infection in a mammal ingesting the cyst-bearing tissue.14,33 T. gondii may be cultured only in cells culture, eggs or in the presence of living cells. Intracellular and extracellular organisms may be typically seen. Optimal growth occurs in livings cell between 37-39 °C temperatures. Considerable variation occurs in strain infectivity and virulence and may be due to the degree of adaptation to a particular host. However all of these T. gondii forms are thought to comprise a single species, T. Gondii.

Pathogenesis.

During the life cycle there are three forms of T. Gondii, the oocysts, Tachyzoites and bradyzoites. The oocysts are product of sexual reproduction, which occurs in the cat small intestine. Cat infection results from ingestion of tissue containing cysts in the uncooked or partially cooked meat. Approximately 14 days after cat infection, oocysts containing infective sporozoites are produced. They become infective 1 to 5 days later.34,35 Tachyzoites are the rapidly dividing products of asexual reproduction. The division of tachyzoites occurs in macrophages following invasion of the host intestinal wall by either sporozoites (from oocysts) or bradyzoites (from tissue cysts). Macrophages are the vehicle for haematogenous dissemination of the tachyzoites in an intermediate host until an adequate immune response occurs. It takes about 7 to 10 days for adequate immune response to occur. Following the development of immune response develops, the protozoa is contained within tissue cysts as bradyzoites, or slowly dividing T. gondii. Bradyzoites can remain dormant for the life time of the intermediate host in any of the body organs (lymph nodes, muscles, retina, lungs myocardium, brain and liver).36 However during immune suppression from any cause, bradyzoites can resume rapid division and haemotogenously disseminate as tachyzoites again.

T. gondii infection in human occurs through three routes of, ingestion of undercooked meat containing tissue cysts, fecal-oral contact with infective oocysts and blood transfusion of blood with circulating tachyzoites.
Mother to child transmission of T. gondii can occur resulting in congenital toxoplasmosis. This results from the transplacental passage of tachyzoites to the foetus. Transplacental transmission of T. gondii infection occurs only during primary infection in pregnancy. However in immunocompromised situation it may occur following reactivation of dormant tissue forms. Reinfection is rare in immunocompetent individuals. Although the risk of transplacental infection in mother with primary infection increases from 0-9% in the first trimester to 35 - 59% in the third trimester, the severity of the infection is less severe if the infection occurred during late pregnancy.

Clinical features.
Only 10-20% of pregnant women infected with T. gondii show clinical signs. Most pregnant women with acute acquired infection do not experience obvious symptoms or signs. A minority may experience malaise, low-grade fever, and lymphadenopathy. Rarely, pregnant woman will present with visual changes due to toxoplastic chorioretinitis as a result of recently acquired infection or reactivation of a chronic infection. In severely immunocompromised, chronically infected pregnant women, reactivation of latent T. gondii infection resulted in congenital transmission of the parasite to the fetus.

Congenital infection
Transmission to the fetus occurs predominantly in women who acquire their primary infection during gestation. In rare cases, congenital infection has occurred in chronically infected women whose infection was reactivated because of their immunocompromised state. The rate of transplacental transmission ranged from 25% in treated mothers to 55% in untreated mothers. Congenital Toxoplasmosis is the most serious form of intra-uterine infection. Classic congenital toxoplasmosis is characterized by chorioretinitis, hydrocephalus, intracranial calcification and convulsion. Signs such as intracranial calcification, microcephaly, hydrocephalus, and severe intrauterine growth restriction strongly suggest in utero infection. Congenital Toxoplasmosis is due to active parasitaemia during pregnancy and can cause severe and fatal damage to a foetus. Intrauterine infection may also result in fetal brain damage, mental retardation, blindness, epilepsy in infancy or much later in life, miscarriage or still birth. Congenital infection is most severe if acquired in the first or, in some cases, second trimester. Infection during the second or third trimesters tends to be asymptomatic. Over seventy percent infants born with congenital toxoplasmosis infection are asymptomatic, with less than ten percent showing severe CNS impairment. This may not manifest until several years later.

Diagnosis
More than 90 percent of primary toxoplasmosis infections in immunocompetent persons are
asymptomatic making the diagnosis of maternal infection difficult. During pregnancy, T. gondii infection can be identified with serologic testing, amniocentesis, or by the presence of abnormal ultrasound findings.

1. **Serological Testing.**

   Serologic testing using IgG and IgM antibodies are the first step in T. gondii diagnosis. However, the result is not only difficult to interpret but the differentiation of a primary from a chronic infection is a challenge too. The presence of IgM antibodies cannot be considered reliable for making a diagnosis of acute toxoplasmosis infection. IgM antibody titres rise from 5 days to weeks following acute infection, reaching a maximum after 1 to 2 months and decline more rapidly than IgG. In addition despite the general trend of IgM antibodies decreasing to low or undetectable levels within weeks, it may persist for years following the acute infection. IgG antibodies on the other hand appear later than IgM and are often detectable within 1 to 2 weeks after the infection, reaching peak within 12 weeks to 6 months after acute infection. IgG antibodies remain detectable for years after infection and often persists for life. The serological test results is interpreted as in the table below (table 1).

   The detection of IgM or IgA antibodies to T. gondii in an infant of a mother with primary toxoplasmosis is highly sensitive for diagnosis of congenital

<table>
<thead>
<tr>
<th>Serological Test Results</th>
<th>Interpretation</th>
<th>Next step</th>
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<tr>
<td>IgM antibody</td>
<td>IgG antibody</td>
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<tr>
<td>Negative</td>
<td>Negative</td>
<td>No infection</td>
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<tr>
<td>Negative</td>
<td>Positive</td>
<td>Old Infection</td>
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<tr>
<td>Positive</td>
<td>Positive</td>
<td>Recent Infection or a false positive Test result</td>
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2. **IgG Avidity test.**

   The IgG avidity test measures the strength of IgG binding to the organism. Avidity, in most cases but not all, shifts from low to high after about 5 months. If the avidity is high, this suggests infection occurred at least 5 months before testing. The presence of IgM level and low avidity index are highly suggestive of recent primary infection.

3. **Amniocentesis.**

   The examination of amniotic fluid for toxoplasma is another strategy for
diagnosis T. gondii infection in pregnancy using using polymerase chain reaction (PCR). The amplification of T. gondii DNA in amniotic fluid at gestational age of 18 weeks or later has been used successfully for prenatal diagnosis of congenital toxoplasmosis. Amplification of amniotic fluid or foetal blood samples obtained via amniocentesis can identify congenitally infected fetuses while still in utero, but is associated with certain inherent procedure-related risks. It should only be performed in women at very high risk for primary infection. Overall sensitivity of 64% for the diagnosis of congenital infection in the fetus, a negative predictive value of 88%, and a specificity and positive predictive value of 100% has reported [26]. It is not advisable for patients co-infected with T. gondii and HIV, because of the risk of infecting the fetus with HIV during the amniocentesis.

4. Detection of T. gondii DNA in neonates’ body fluids.
The amplification of T. gondii DNA by polymerase chain reaction (PCR) is almost 100 percent sensitive and specific and can be detected in most body fluid of a congenitally infected neonate [43].

5. Ultrasonography. If amniocentesis and antibody results are positive, sonographic follow up is indicated. Signs such as calcifications, microcephaly, hydrocephalus, and severe in utero growth restriction strongly suggest in utero infection in the presence of documented maternal infection.

Prevention
Toxoplasmosis like other food borne illness is prevented by cooking food to a safe temperature (71.1°C [160°F]). In areas endemic for toxoplasmosis, food thermometer should be used to ensure that meat is cooked all the way through. Fruits and vegetables should be peeled or thoroughly washed before they are eaten. Cutting boards, dishes, counters, utensils, and hands should be washed with hot soapy water after they have been in contact with raw meat, poultry, or seafood, or with unwashed fruits or vegetables.

Health education of women of childbearing age on how to prevent T. gondii infection. This should include the prevention of transmission from food and soil, food hygiene and avoidance of exposure to cat feces.

Women of child bearing age and most especially those pregnant should wear gloves when they are gardening or touching soil or sand, because of the possible presence of cat feces. Afterwards, they should wash their hands thoroughly.

In households that keep cats, the litter should be changed daily because T. gondii oocysts require more than 24 hours becoming infectious. Pregnant women should avoid changing the litter or in the alternative wears gloves. Cats should be fed only canned or dried commercial cat food or well-cooked table food; they should not be given raw or undercooked meat.
Prevention of Mother to Child Transmission of T. gondii infection.
Congenital toxoplasmosis can be prevented only by preventing maternal infection or by stopping transmission from mother to fetus. This can be done through a number of ways.

1. Preconceptional and early pregnancy counseling. Preconceptional and early pregnancy counseling can help women avoid personal exposure to T. gondii in undercooked food or material potentially contaminated by cat excrement. Educational materials that contain messages on how to prevent pregnant women from becoming infected have resulted in reduced rates of seroconversion. Ultimately it is the responsibility of health care policy makers and physicians to educate both pregnant women and women who are considering becoming pregnant, with regard to preventive measures.

2. Screening in pregnancy.
Whether or not pregnant woman should be screened for primary T. Gondii infection through serological testing remains controversial because of high false positive rate of IgM antibody detection, very low incidence of maternal primary infection and low seroconversion rates\(^{44,45}\). However, in high risk populations, with maternal infection rates of up to 3.5% routine, pregnant women should routinely be screened.

3. Treatment of maternal infection.
It is recommended that all pregnant women who have been diagnosed with primary toxoplasmosis infection be treated with spiramycin with or without pyrimethamine-sulfadiazine. Pyramethamine is teratogenic and contraindicated in the first trimester\(^{46}\). Prevention of transmission from mother to fetus by treating mothers with acute infection is a second way to prevent fetal infection. Maternal treatment is effective in blocking transmission in up to 60% of treated mothers\(^{47,48}\). If transplacental transmission occurs, manifestation of fetal infection can be managed and reduced substantially by diagnosing and treating fetal infection in utero.
There are 2 goals of drug therapy for toxoplasmosis, depending on whether or not fetal infection has occurred.

a. Fetal prophylaxis. Therapy here is aimed at preventing vertical transmission of T. gondii to the fetus. If the fetus of mother with primary infection is not infected, spiramycin should be administered to prevent the spread of organisms
across the placenta from mother to fetus. The macrolide antibiotic is concentrated in the placenta but does not readily cross it. It is given at a dose of 1 g orally every 8 hours for the duration of pregnancy.

Treatment is commenced once amniotic fluid polymerase chain reaction is confirmed negative for *T. gondii*.

b. Treatment of infected fetus. Pyrimethamine and sulfadiazine are used for treatment, if fetal infection has been confirmed or is highly suspected. Pyrimethamine is teratogenic as it is a folic acid antagonist that acts synergistically with sulphonamides, and should not be used in the first trimester. It must be combined with folinic acid. The combination of pyrimethamine and sulfadiazine results in a significant decrease in disease severity.

**Treatment beyond neonatal period**

Infants with congenital *T. gondii* infection should be treated with pyrimethamine and sulfadiazine. Infants treated with these drugs have been shown to have improved outcomes compared with untreated infants and children. The drug therapy should be continued for one year. Active and recurrent toxoplasmic eye disease also responds well to this drug therapy and may be given with steroids.

**Conclusion.**

Congenital toxoplasmosis is common in sub-Saharan Africa, and can have serious effects on the developing fetus. In high prevalence settings, routine screening for primary infection is recommended not because most primary infections during pregnancy are asymptomatic, primary prevention is also problematic.

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