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Review Article

Pregnancy and Toxoplasmosis: should screening be a routine practice?

Gebelik ve Toksoplazmoz: Rutin tarama yapılmalı mı?

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ABSTRACT

Because infectious agents can reach the fetus through the placenta, pregnancy is regarded as a particular period for contagious diseases. Identification of infections during pregnancy and appropriate treatment can prevent fetal disorders. For this purpose, to avoid their harmful effects on fetus and newborn, various infectious diseases are screened during pregnancy. Toxoplasma gondii infection in pregnancy is transmitted through the transplacental pathway leading to severe neurological sequelae such as fetal abortion, stillbirth, intrauterine growth retardation, cranial calcifications, blindness, deafness, and mental retardation. This can lead to serious social and economic problems for the family and the infant, as well as society. To prevent these sequelae, infections during pregnancy need to be identified and appropriately treated. There are different opinions and practices in the world regarding the screening of T. gondii during pregnancy follow-up. This review aimed to assess the seroprevalence of T. gondii infection during gestation in Turkey and the world, its effects on the fetus, ways of protection, and suggestions about screening in the world and in Turkey in light of the literature, so that this becomes a guide for clinical practice for physicians.

Keywords: Pregnancy, screening, transplacental transmission, toxoplasmosis

ÖZ

Gebelik, etkenlerin transplasental yolla fetüse ulaşıp, hastalık yapabilme potansiyelleri nedeniyle enfeksiyon hastalıkları için özel bir dönemdir. Enfeksiyon etkenlerinin anneden bebeğe geçerek hastalık oluşturmalarının önlenmesi, gebelik sırasında tanınmaları ve uygun şekilde tedavi edilmelerine bağlıdır. Bu amaçla, gebelik sırasında çeşitli enfeksiyon hastalıklar için tarama yapılmakta, fetüs ve yenidoğanda olabilecek hastalık ve olumsuz etkiler önlenmeye çalışılmaktadır. Gebelerde T. gondii taraması konusunda dünyada farklı görüş ve uygulamalar vardır. Bu derlemede, gebelikte T. gondii enfeksiyonunun dünyada ve Türkiye'de seroprevalansı, fetüs üzerine etkileri, korunma yolları, tarama konusundaki görüş ve önerilerin literatür eşliğinde gözden geçirilmesi, birinci basamak hekimleri için klinik uygulamalarda yol gösterici olması amaçlanmıştır.

Anahtar Kelimeler: Gebelik, tarama, transplasental bulaş, toksoplazmoz

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Introduction

T. gondii infection during pregnancy is subclinical or asymptomatic to the mother, but transplacental transmission to the fetus can lead to severe neurological sequelae and mental retardation [1]. This condition brings serious social and economic problems for the family, baby, and society. There are different views and approaches in the world about the screening of infections during pregnancy. In this review, guided by the literature, the course of toxoplasma infection during pregnancy, its effects on the fetus, and discussions on routine screening in Turkey and in the world are reviewed and aimed to establish a guide for primary care physicians who follow up pregnancies.

Cause and transmission

Toxoplasmosis is a protozoal infection caused by *Toxoplasma gondii* [2]. *T. gondii* is a compulsory intracellular parasite and has the three forms oocyst, bradyzoite, and tachyzoite. Oocyst is the form taken from feces; tachyzoite is the invasive form responsible for the infection, and bradyzoite is the form that the parasite takes after reaching the target organ. The bradyzoite form can be located in every tissue, particularly in the heart muscle, skeletal muscle, brain, and eye, and can survive throughout the lifespan of the host [3]. In the life cycle of this protozoan, cats are the main host, while the human is an accidental host. It is possible to encounter this disease wherever cats are found. The parasite excreted via cat feces is the oocyst form, which can retain its infectious nature for a year depending on the climate and weather conditions in the soil. Human transmission occurs by contaminated oocysts from cat feces through ingesting raw and undercooked meats carrying *T. gondii* cyst (bradyzoite), drinking raw milk, eating raw eggs, blood transfusion, and organ transplantation; it can also be transmitted transplacentally to the baby from the mother [4, 5]. After the oocysts are taken orally, they become tachyzoites. Tachyzoites spread to the organs with blood and lymph nodes and take the last form bradyzoite in the target organs (tissue cyst) [3].

In individuals with intact immune systems, the infection is usually asymptomatic and passes unnoticed. Subclinical and mild disease is self-limited. The most common symptoms seen in the human are lymphadenopathy and a flu-like clinical condition accompanied by fever, headache, sore throat, and muscle- and joint pain. However, it can cause severe symptoms in immunocompromised individuals and pregnant women [6, 7].

Prevalence

Toxoplasmosis is common worldwide (12-90%). It is known that approximately one-third of the world population is infected with *T. gondii* [2, 8]. The disease is more common in hot and humid areas. Its prevalence may vary according to geographical location, climate, eating habits, country, or even region. It is estimated that 16-40% of the population in England and America and 50-80% in Europe are infected with *T. gondii* [9]. Seroprevalence in pregnant women is reported to be low in China (10.6%) and Japan (10.3%) and between 15.33% - 40% in India [10-12]. However, serious regional differences are also mentioned within the same country. In Turkey, *T. gondii* prevalence is high due to the climatic and local characteristics, and seropositivity among pregnant women varies between 22-47% [6]. The highest seropositivity was reported in Kahramanmaraş (47.1%) in pregnant women and in Şanlıurfa (69.5%) in a mixed population [13, 14]. The raw meatball (çiğköfte) eating culture in both provinces is thought to contribute to these high rates.

The significance of toxoplasmosis in pregnancy

Infection in pregnancy is important because of the risk of transmission to the fetus. In case of infection in the mother, the parasite invades the placenta, proliferates there, and continues to infect the fetus during pregnancy if not treated [15]. Abortion, stillbirth, or congenital toxoplasmosis may be seen due to the transmission of the disease during pregnancy [16]. The incidence of congenital toxoplasmosis is between 1 and 16 in 1 000 to 10 000 live births [17]. Congenital toxoplasmosis may present as a symptomatic neonatal disease, mild or severe illness, or subclinical infection in the first month of life. If the infection is not diagnosed, the condition may be first recognized as sequelae in childhood or adolescence. Ultrasonography may demonstrate ventriculomegaly, intracranial calcifications, cataract, microcephaly, hepato-splenomegaly, hyperechogenic bowel, acid, placentomegaly, hydramnios, non-immune hydrops fetalis, and symmetric intrauterine growth retardation. The probability of sequelae is higher in symptomatic cases. As long-term sequelae, convulsions, spasticity, severe vision disorders, hydrocephalus, microcephaly, deafness, and mental retardation can be observed [4, 18].

Transplacental spread

When the mother is immune, she protects the fetus against infection. For the fetus to develop the disease, it is necessary for the mother to have an infection during her pregnancy [8]. The risk of infection in the fetus is directly proportional to the gestational age, and the risk of transmission increases as the pregnancy progresses [19]. While the risk of transmission to the fetus in the first trimester is 15%, this rate increases to 70% in the last trimester, and reaches to the highest level (90%) in the last two weeks of pregnancy [18, 20]. The effects that may occur in the fetus depend on the time of the mother's infection. In contrast to the possibility of infection, the likelihood of neurological damage and sequelae is highest in the first trimester. Although the risk of infection of the fetus increases with the progression of the gestational week, there is less risk of severe disease [6, 16, 17]. Seronegative pregnants carry the risk of infection during pregnancy [7]. For this reason, counseling on infection prevention should not be neglected in each follow-up visit. Women who are diagnosed with acute infection should be advised not to become pregnant for 6 months [21].

Diagnosis

The reference test for the diagnosis of toxoplasmosis is the “Sabin-Feldman Dye” test. However, serological tests are due to their ease of administration, high sensitivity and specificity, and the difficult and time-consuming isolation of the organism [6, 19]. The first emerging antibodies during an infection are *T. gondii*-specific IgM antibodies, which are usually positive on the 5th day of the infection, increase to the highest level in the first month, and become negative within a few months. However, since *T. gondii*-specific IgM positivity may last up to 15 months to two years, they do not always

show acute infection [16, 22, 23]. Only 40% of patients with positive IgM antibodies have been shown to have an acute infection. Thus, the American College of Obstetricians and Gynecologists (ACOG) recommends validation testing in reference laboratories to prevent false positive results [24]. *T. gondii*-specific IgG antibodies appear in the blood in the second or third week of infection after IgM antibodies, reach the highest titers within 3-6 months, and remain positive for life with varying titers. In the case of IgG antibody positivity, it is understood that the person has had an infection [16, 21-23]. When IgM positivity is detected, the test should be repeated after 1-3 weeks, and if positive again, anti-*T. gondii* IgG avidity test should be performed. The avidity test is an important test that provides information about the time of infection. High avidity indicates a past infection, while low avidity suggests recent acute infection. Since antibodies with high avidity occur at the earliest 12-16 weeks after infection, high avidity should suggest a past infection at least 16 weeks ago. By determining the time of infection with the avidity test, invasive procedures, unnecessary antibiotic use, amniocentesis, and medical abortion can be prevented [1]. In a pregnant woman with no information on her previous condition or who is IgM negative, IgM-positivity and IgG-negativity suggest a new infection. If IgM and IgG are positive together, the test should be repeated after 2-3 weeks, and at least a 4-fold increase in antibody titers should be expected to indicate that it is an active infection [1, 15]. Interpretation of the serological tests is summarized in Table 1 [7, 16, 21, 22].

Table 1. Interpretation of anti-*Toxoplasma gondii* IgM and IgG results.

Antibody Positivity	Interpretation
Anti- *Toxoplasma gondii* IgM (-) Anti- *Toxoplasma gondii* IgG (-)	No Active infection, No evidence of past infection
Anti- *Toxoplasma gondii* IgM (+) Anti- *Toxoplasma gondii* IgG (-)	Person susceptible to infection, IgM should be repeated after 1-3 weeks, If still positive, avidity test should be ordered
Anti- *Toxoplasma gondii* IgM (+) Anti- *Toxoplasma gondii* IgG (+)	Seroconversion present, should be evaluated with PCR for gestational infection

PCR: Polymerase Chain Reaction

The definitive diagnostic method for toxoplasmosis is polymerase chain reaction (PCR) in amniotic fluid (showing toxoplasmosis in amniotic fluid), and more invasive methods such as demonstration of cysts in placental and fetal tissues. Pregnant women with normal immunity have a risk of infection with strains of different genotypes of the parasite or re-infection, even if anti-*Toxoplasma gondii* IgG is (+) and anti-*Toxoplasma gondii* IgM is (-) [21]. If primary toxoplasmosis is suspected in pregnant women, and the serological tests are not sufficient to make a diagnosis or exclude the disease, and if there are findings suggesting toxoplasmosis on ultrasound, amniocentesis should be performed, and the amniotic fluid should be studied with PCR for *T. gondii*. Amniocentesis should not be performed before the 18th week of pregnancy because of the risks to the fetus. To prevent false negativity, four weeks should pass after acute maternal infection [7].

Treatment

The main aim in the treatment of acute toxoplasmosis during pregnancy is to prevent and minimize the effect of the agent to the fetus and to minimize tissue damage in case of infection [15]. Treatment initiated within three weeks after seroconversion reduces the risk of transmission to the fetus. When a maternal infection is detected, 3 mg/day oral Spiramycin treatment should be started. Combination of Pyrimethamine and Sulphadiazine can also be used in acute cases. When diagnosed as fetal toxoplasmosis, oral Pyrimethamine 50mg/day and 3 g/day Sulphadiazine (three weeks) followed by Spiramycin (three weeks) is recommended. Since Pyrimethamine is an antagonist of folic acid, it should be given with folic acid (5 mg twice a week) and should not be used in the first trimester of pregnancy because of its teratogenic effects. Treatment of the pregnant woman reduces both the risk of congenital toxoplasmosis and long-term sequelae. Neonatal treatment has also been shown to contribute positively to long-term outcomes. However, there are opinions defending pregnancy termination, when the diagnosis of maternal infection is made in the first 24 weeks of gestation [25, 26].

Screening

There are different approaches in screening for *T. gondii* in pregnant women [15]. In addition to those who recommend screening for all pregnant women, it is argued that screening should not be done; there is no consensus on this issue in the literature [1, 27, 28]. Those who recommend screening claim that it may provide early detection of the infection during pregnancy, enable a chance for treatment, prevent the transfer of the infection to the fetus, and prevent the disease and long-term sequelae in the fetus. The group that does not recommend screening does not support this idea because routine screening for all pregnant women is not a cost-effective approach, the effects of the infection on the baby are not as severe as in the theory, the effectiveness of the treatment is not clear enough, and may lead to unnecessary anxiety and terminations in pregnant women [15]. The incidence of congenital toxoplasmosis in the United States is one in 10,000 live births; no routine screening is performed [29]. Routine screening is not practiced nor recommended in the UK, Canada, and most of the European countries [1, 27, 28]. In countries such as France, Belgium, Norway, the incidence is 2-3/1000. Thus, routine screening is applied and recommended. Screening is carried out in France and Austria, compulsory by law [25, 30]. In France, besides routine screening, non-immune pregnant women are re-screened at each control until delivery [31]. In countries such as China, Japan, and India, routine screening is not performed due to low prevalence; instead, counseling is provided to pregnant women [10-12]. ACOG, the Royal College of Obstetricians and Gynecologists (RCOG), Centers for Disease Control and Prevention (CDC) do not recommend routine *T. gondii* screening during pregnancy, emphasize the importance of prevention, counsel and educate pregnant women [24, 32, 33]. Toxoplasmosis is not among the infections

that should be screened according to the Ministry of Health of Turkey, and also the Turkish Perinatology Association does not recommend routine toxoplasma screening to pregnant women [34, 35].

Prevention

Congenital toxoplasmosis is always associated with maternal infection. Therefore, prevention of the infection in the mother plays a key role in the prevention of the disease. Meat should be cooked well (internal temperature should be 67 degrees Celsius; no pink area should remain in the middle of the meat). Smoking, drying, and pickling of the meat does not kill the parasite. Since the parasite can maintain its vitality at +4 °C for 68 days, storing in the refrigerator does not kill the parasite either. Since microwave cooking does not kill the parasite cysts, the infectious property is maintained. However, freezing of meats at -200 °C kills bradyzoites [4, 21]. Pregnant women may have cats at home, but especially for seronegative women, it is not recommended to have a new cat during pregnancy. The most effective way to reduce oocysts release to the environment is the vaccination of cats. No vaccination is available for human. Women diagnosed with acute infection should be advised not to become pregnant for 6 months [21]. Preventive measures for toxoplasmosis are summarized in Table 2 [4, 21].

Table 2. Preventive recommendations for toxoplasmosis

Primary prevention recommendations
• Meat should be cooked until there is no pink area in the middle • Wash hands thoroughly after contact with raw meat • Animal slaughtering, flaying, and meat chopping should be avoided during pregnancy; in case of necessity gloves should be used • Smoked, dried, and pickled meat should not be consumed • Meat should not be cooked in the microwave • Vegetables and fruits should be thoroughly washed • Milk should not be consumed without boiling • Raw eggs should not be consumed • Water suspected of contamination should be avoided • Gloves should be used when handling soil and gardening • Cats should be vaccinated, cleaning the cat litter should be avoided, and gloves should be worn if necessary. • Cat toilet bowls should be washed with boiling water • No new cat should be adopted during pregnancy
Secondary prevention recommendations
• Pregnant women at risk should be serologically screened • Encountered diseases should be treated with antibiotics

Conclusion and suggestions

We conclude that routine screening of toxoplasmosis in pregnant women is not a cost-effective approach for Turkey, and education is the most crucial point in prevention. All pregnant women should be counseled about the disease and prevention in the first antenatal examination, and especially for seronegative pregnant women, patient education should be repeated until delivery. We think that screening should be done for pregnant women who live in regions with high seroprevalence, who are in risk groups, and who have suspicious findings on ultrasound.

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