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Is Routine Screening for Congenital Toxoplasma Infection Necessary During Pregnancy?

Konjenital Toksoplazma Enfeksiyonu Önlenmesi İçin Gebelikte Rutin Tarama Yapmak Gerekir mi?

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Question: *Is routine screening for congenital toxoplasma infection necessary during pregnancy?* **Yusuf Öztürk, MD.**

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Introduction and general information: To provide a sound answer to this question, many factors must be evaluated simultaneously. These include the prevalence of toxoplasma seropositivity among women of childbearing age in the country, factors influencing serological diagnostic methods, socioeconomic status, assessment of the risk of congenital toxoplasma infection (CTI) associated with toxoplasma infection during pregnancy, and the prognosis of CTI. Therefore, it is useful to recall some basic information on this subject.

Toxoplasma infection is a common zoonotic infection worldwide. It is caused by the parasite *Toxoplasma gondii*. There are multiple strains. Some strains (such as I and II) have a milder course, while atypical strains (other than I, II, and III) tend to have a more severe course (1). In children, consultation with a pediatric infectious disease specialist is generally recommended for the evaluation, diagnosis, and treatment of toxoplasma infection (2,3).

General clinical presentations of toxoplasmosis*:* Toxoplasma infection: a) Primary toxoplasma infection in immunocompetent postneonatal infants, children, and adults usually presents with fever, non-specific viral upper respiratory tract infection, lymphadenopathy, infectious mononucleosis-like syndrome, hepatitis, and other findings. If the findings are not serious, treatment is usually not required. In pregnant women, the findings are usually mild. However, if the pregnant woman has primary toxoplasma infection, treatment is given to the pregnant woman against the possibility of fetal involvement (congenital toxoplasma). In children with normal immunity, treatment is given if there is serious primary toxoplasma infection, albeit rare, or if ocular complications (active chorioretinitis) develop. b) In immunocompromised children, treatment is given if there is a severe primary (acute) toxoplasma infection or latent toxoplasma reactivation. c) In newborn infants with CTI (intrauterine fetal infection during pregnancy), treatment is required regardless of whether the infant has symptoms. Otherwise, existing neurological findings may worsen, and new neurological disorders (including

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visual impairment) may develop in asymptomatic infants. These complications are greatly reduced in those who receive treatment. 70-90% of newborns with CTI are asymptomatic. However, even if asymptomatic/subclinical, approximately 40% of infants with CTIs have been found to have findings such as chorioretinitis, intracranial calcification, hydrocephalus, and elevated CSF protein levels upon detailed evaluation, and have ultimately been considered symptomatic (4). Therefore, newborns suspected of having CTI should be carefully evaluated. A detailed pregnancy history (maternal primary toxoplasma infection during pregnancy; clinical and serological), physical examination, and laboratory tests (in addition to routine tests, eye evaluation of the infant, toxoplasma serology of the mother and infant, polymerase chain reaction of the infant if necessary, cranial and abdominal imaging) should be performed. Based on the results, treatment is administered to the infant and follow-up is initiated.

Toxoplasma infection; maternal and fetal pathogenesis, serological characteristics: The incubation period of toxoplasma infection is 4-21 days in postnatal infection and in adults (including pregnant women). After acute infection, the parasite (in the tachyzoite form) may persist in the blood for up to two weeks (5). Fetal infection during pregnancy develops through transplacental transmission of tachyzoites during the parasitemic phase following primary maternal infection (6). The parasitemic phase occurs before the development of maternal serological responses (7). After fetal infection develops, maternal (or fetal) IgG antibodies are not expected to reduce fetal/neonatal sequelae (8). In immunocompetent pregnant women, tachyzoites that could pose a risk of fetal infection in circulation are controlled by the immune system within a few days to a few weeks and remain latent in tissue cysts as bradyzoites for many years. Latent toxoplasma infection (tissue cysts containing bradyzoites) does not revert to the tachyzoite form in a pregnant woman with normal immunity and is not infectious to the fetus, therefore it does not pose a risk of CTI (9). In women who have had a previous toxoplasma infection (toxoplasma IgM -, toxoplasma IgG +), fetal toxoplasma infection (and CTI) is not expected in most cases (6).

In acute primary toxoplasma infection, IgM typically begins to become positive after the first week, increases over weeks, and may persist for months or even years. IgG typically begins to become positive after the second week, peaks around the second month, and remains positive for many years and often lifelong. High IgG avidity typically supports infection prior to four months (old infection). Low IgG avidity supports infection within 4 months (more recent infection). However, in some cases, low avidity may persist for longer periods, so additional testing may be needed to clarify the situation (10).

False-positive IgM results may occur in some cases. Considering primary toxoplasma infection, IgM false positives may be associated with certain viral infections (such as Epstein-Barr virus), autoimmune diseases and autoimmune antibodies, the standard used in commercial kits, or prolonged IgM positivity due to a toxoplasma infection that occurred months or years prior (2,10). Therefore, a comprehensive approach is appropriate when interpreting results.

Toxoplasma infection in pregnancy, epidemiology, and fetal risks: Primary toxoplasma infection in pregnancy leads to fetal infection and the risk of CTI through transplacental transmission. In a meta-analysis, the risk of CTI following primary toxoplasma infection in pregnant women was found to be approximately 50% overall. The risk of CTI was 15% [95% confidence interval (CI): 13-17%] in the first trimester (at 13 weeks), 44% (95% CI: 40-47%) in the second trimester (26 weeks), and 71% (95% CI: 61-76%) in the third trimester (36 weeks) (11). The risk of fetal infection increases in the later weeks of pregnancy. However, if transmission occurs during the first trimester, there is a higher risk of severe congenital toxoplasmosis (2.6). In women who have had toxoplasmosis before pregnancy (seropositive; IgG+) and have an intact immune system, the risk of reactivation and, consequently, the risk of congenital toxoplasmosis is not expected (6).

The prevalence of toxoplasma infection in the general population varies by country and country based differences should be considered when deciding on screening during pregnancy. The seroprevalence of toxoplasma (IgG positivity) in women of childbearing age is 10-50% in developed countries (7.5-11% in the United States, 10% in the United Kingdom, 19% in Italy, 32% in Spain, and 31% in France), and 78% in Brazil (5,6,12). In Türkiye, it was found to be between 30-40% in the evaluation of 58 studies (13). If a woman who is seronegative at the beginning of pregnancy becomes infected during pregnancy, her child may be at risk of CT. The incidence of acute primary toxoplasma infection during pregnancy varies between 0.1-2.5/1000 pregnant women worldwide. It is reported as 0.2-1.1/1000 in the United States, 0.1/1000 in the United Kingdom, and 2-2.5/1000 in France (5,6). Toxoplasma IgM positivity in pregnant women in Türkiye has been determined as 2.9% (13).

Toxoplasmosis surveillance is conducted in approximately half of European countries. Overall, the incidence of congenital toxoplasmosis in Europe was reported as 5-5.8 per 100.000 live births between 2017 and 2021. However, the reported cases are likely to be lower than the expected cases. The highest number of cases (78% of confirmed CTIs) in Europe has been reported from France, which conducts regular surveillance (14).

Evaluation of toxoplasma infection screening in pregnant women: The primary aim of toxoplasma screening in pregnant women is to prevent, detect, and treat potential CTIs early to improve outcomes. Although toxoplasmosis is an infection that can be transmitted to the fetus at a high rate in maternal primary infection and can have serious consequences such as CTIs, there are different practices worldwide regarding routine screening during pregnancy. Some countries (such as France) recommend monthly routine screening during pregnancy. In other countries (Austria, Belgium, Greece, Slovakia, Slovenia, etc.), screening is conducted at different intervals, such as every two months, every three months, or during the first trimester. Additionally, screening is recommended in cases of maternal symptoms and/or upon request (14). Routine screening is not recommended in countries such as the United States and the United Kingdom (6,14). In Türkiye, according to the Ministry of Health's recommendation, routine screening and surveillance for toxoplasmosis in pregnant women are not conducted.

The decision to implement a screening program should be based on a risk-benefit assessment. In some countries (such as South and Central America), more invasive and fetally risky toxoplasma strains (atypical strains) are more prevalent. In Europe and North America, however, milder-course type I and type II strains are more common (1). When making a decision, several factors must be considered. These include the prevalence of toxoplasmosis in the country (seroprevalence), the mother's adherence to preventive measures, whether regular prenatal care is available, the standard of the commercial serological method used, whether confirmatory tests can be performed in reference laboratories when necessary or in cases of repeated measurements, the recommendation for expert evaluation of atypical/controversial results, cost-effectiveness assessment, and consideration of the psychological stress caused by ambiguous laboratory results to the family. Careful and high-quality surveillance and rational evaluation of results are important in the decision to implement nationwide routine screening.

In women who have had toxoplasma infection (IgG seropositive) and are not immunocompromised before pregnancy, the risk of reactivation and therefore the risk of CTI is minimal, so routine screening is not necessary.

If there are maternal clinical symptoms (e.g., fever, infectious mononucleosis-like symptoms, and especially lymphadenopathy) or if routine fetal ultrasound during pregnancy shows findings consistent with CTIs (intracranial hyperechoic, cranial calcification, hydrocephalus, echogenic intestines, etc.) during pregnancy, the mother should be investigated for toxoplasma infection (6).

There is no CTI surveillance system in Türkiye, and there is insufficient information about the true burden and cost of the disease. Considering the epidemiological data in our country, the seroprevalence in women of childbearing age and the rate of primary toxoplasma infection during pregnancy appear to be similar to or even higher than those in France. However, unlike France, no surveillance is conducted in our country. Therefore, there is insufficient scientific data to justify routine screening during pregnancy. Considering the aforementioned epidemiology, fetal infection, and CTI risk, as well as potential confounding factors in serological diagnosis, it can be stated that a more accurate assessment can be made after conducting surveillance studies and cost-effectiveness analyses.

In summary, the authors' opinion in response to the question is that routine pregnancy screening is not necessary in Türkiye until qualifed epidemiological and surveillance data are available. It is important that pregnant women carefully follow preventive measures against toxoplasma infection and continue routine pregnancy follow-ups. Testing for toxoplasma IgG before pregnancy preferably (1-2 months prior) can largely rule out the risk of congenital toxoplasmosis in cases of IgG positivity. In the presence of findings consistent with toxoplasmosis in pregnant women or findings consistent with CTI in routine pregnancy ultrasounds, it would be appropriate to investigate the mother for primary toxoplasmosis infection, in addition to other causative factors, and to take the necessary measures based on the results.

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