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Toxoplasmosis: Seroprevalence in Women of Reproductive Age and Approach in Pregnancy

Toksoplazmoz: Doğurganlık Çağındaki Kadınlarda Seroprevalans ve Gebelikteki Yaklaşım

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ABSTRACT

Objective: *Toxoplasmosis is a parasitosis that is mostly asymptomatic. It can lead to severe clinical conditions in immunosuppressed patients and fetal infections. Since it is possible to prevent congenital toxoplasmosis with appropriate follow-up and treatment, our study aimed to determine the susceptible population and seroprevalence of our region and to evaluate the course of infections in this group.*

Material and Method: *Patients who applied to our tertiary hospital in the last five years and to whose Anti Toxoplasma IgM and IgG tests were performed were included in our study. Toxoplasmosis seroprevalence, the course of primary infection in pregnant women, the treatments applied, and also acute toxoplasmosis infections in non-pregnant patients were examined.*

Results: *The seropositivity rate was found to be 30.7% (n=1703) in 5545 women included in the study, and the seropositivity rate was 31% (n=1399) in 4503 pregnant women. Sixteen pregnant women with primary infection were followed up in our hospital; one underwent medical abortion at the request of the family, and only four used the recommended treatment. Congenital toxoplasmosis was not detected in any newborn. Of the patients included, 26 (0.4%) were examined to investigate the etiology of fever, 37 (0.6%) for lymphadenopathy (LAP), and 29 (0.5%) for elevated liver enzymes. Among the patients with LAP, four (10.8%) were diagnosed with acute toxoplasmosis.*

Conclusion: *As a result, it is important to determine the seroprevalence of toxoplasmosis, to detect possible primary infections, especially in pregnant women, and ensure close monitoring of these patients.*

ÖZET

Amaç: *Toksoplazmoz çoğunlukla asemptomatik seyreden paraziter enfeksiyon hastalığıdır. Bağışık yanıtı baskılanmış konaklarda ve fetal enfeksiyonlarda ağır klinik tablolara yol açabilmektedir. Özellikle konjenital toksoplazmozun uygun takip ve tedavi şekliyle engellenebilmesinin mümkün olması nedeniyle çalışmamızda bölgemizin duyarlı popülasyonunun ve seroprevelansının belirlenmesi ve bu grupta enfeksiyonların seyrinin değerlendirilmesi amaçlanmıştır.*

Gereç ve Yöntem: *Çalışmamıza son beş yılda üçüncü basamak hastanemize başvuran ve Anti Toxoplasma IgM ve IgG testi çalışılan hastalar dahil edildi. toxoplasmosis seroprevelansı, gebelerdeki primer enfeksiyonun seyri ve uygulanan tedaviler, ayrıca gebe olmayan hastalardaki akut toksoplazmoz enfeksiyonları incelendi.*

Bulgular: *Çalışmaya dahil edilen 5545 kadında seropozitiflik oranı %30.7 (n=1703), 4503 gebede ise seropozitiflik oranı %31 (n=1399) olarak tespit edilmiştir. Primer enfeksiyonu olan 16 gebeden birine ailenin isteğiyle tıbbi abortus uygulanmış, gebelerin yalnızca dördü gebelik sonuna kadar önerilen tedaviyi kullanmış, izlem sırasında hiçbir yenidoğanda konjenital toksoplazmoz tespit edilmemiştir. Çalışmaya dahil edilen hastaların 26'sı (%0.4) ateş, 37'si (%0.6) lenfadenopati (LAP) ve 29'u (%0.5) karaciğer fonksiyon testlerindeki yüksekliğinin sebebinin araştırılması için tetkik edilmiş, LAP ile izlenen hastalardan 4'üne (%10.8) akut toksoplazmoz tanısı* ***koyulmuştur.***

Sonuç: *Toksoplazmoz seroprevelansının belirlenerek özellikle gebelerdeki olası primer enfeksiyonların tespiti ve bu grup hastaların izlem ve tedavilerinin aksamaması uğruna klinisyenlerin hastaları doğru yönlendirmesi konjenital toksoplazmozun engellenmesi adına oldukça önemlidir.*

Keywords:
Congenital Toxoplasmosis
Serology
Fever
Lymphadenopathy

Anahtar Kelimeler:
Konjenital Toksoplazmoz
Seroloji
Ateş
Lenfadenopati

INTRODUCTION

Toxoplasmosis; is a zoonosis caused by *Toxoplasma gondii* (*T. gondii*). The final host of this obligate intracellular parasite, which causes infection in humans and many animals, is felines. Toxoplasma infection can develop through the consumption of raw or undercooked meat and shellfish, contaminated raw vegetables or water, or direct contact with contaminated products or oocysts found in cat feces. It can also be transmitted vertically from mother to baby or through organ transplantation. Clear data on the seroprevalence of the infection are not available. It is estimated that 30% of the world's population is infected with toxoplasma, the prevalence of latent toxoplasmosis in pregnant women worldwide is 33.8%, and the congenital

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infection rate is less than 0.1% (1,2). Centers for Disease Control and Prevention (CDC) stated toxoplasmosis is one of the five neglected parasitic diseases of the United States and it is estimated that approximately 40 million people are infected (3).

While 80-90% of patients are asymptomatic or have mild symptoms, flu-like symptoms, lymphadenitis, myalgia, headache, and sore throat may occur in mild cases (4). Cervical lymph nodes are often affected, and the disease usually limits itself within months. It can cause serious clinical conditions, especially in immunosuppressed patients, or congenital infections that develop after the primary infections of seronegative pregnant women. Central nervous system, lung, eye involvement, or disseminated toxoplasmosis may be seen in immunosuppressed patients. In severe cases of congenital toxoplasmosis, hydrocephalus, intracranial calcifications, retinochoroiditis and fetal death may occur (5). Serological tests, molecular methods, histological examinations, and isolation of the microorganism can be used in the diagnosis of toxoplasma infection. It is possible to minimize fetal effects by following diagnostic-treatment algorithms developed especially to detect mothers with primary infection and to prevent vertical transmission (6-8).

This study aims to determine the seropositivity rate of women of reproductive age in our province, to examine the course of pregnant women who are thought to have primary infection and acute toxoplasmosis infections in the study population, and to raise the awareness of clinicians by identifying our situation and deficiencies in this process.

MATERIALS AND METHODS

Our study is a retrospective observational study. In this study, female patients of reproductive age between the ages of 18 and 45 who applied to Recep Tayyip Erdoğan University, Training and Research Hospital in the five-year period between 01.01.2018 and 31.12.2022 and underwent Anti-*T. gondii* IgM or Anti-*T. gondii* IgG testing were included. Patients for whom only IgM testing was performed were excluded. The results of serological tests, the infection status of pregnant women, and treatments applied to patients thought to have primary infection, the course of these patients and pregnancy outcomes were evaluated. In addition, the reason for requesting tests from patients and the evaluation for toxoplasmosis in non-pregnant women were also examined. Examination results and follow-up and treatment information of the patients were accessed from the hospital information system. Patients for whom only IgM testing was performed were excluded from the study because it was insufficient to evaluate the presence of infection and did not contribute to the seroprevalence study. The results of serological tests, especially the infection status of pregnant women, advanced tests and treatments applied to patients thought to have primary infection, the course of these patients, and pregnancy outcomes were evaluated. Examination results, follow-up and treatment information of the patients were accessed from the hospital information system.

Pregnancy follow-up: Anti *T. gondii* IgM and IgG tests are performed on pregnant women followed in our hospital at their first admission, and patients with IgM positivity or intermediate values are referred to our clinic. Avidity test is applied to patients with positive anti *T. gondii* tests, and patients with negative tests are monitored for IgG seroconversion. Patients who are thought to have a primary infection are informed about follow-up, antimicrobial treatment, and termination of the pregnancy, and when necessary, appropriate medical treatment is initiated to prevent congenital infection and patients are monitored together with the gynecology and obstetrics departments.

Serological Analysis: Quantitative measurement of Anti Toxoplasma gondii IgM and IgG antibodies and avidity measurement of IgG antibodies were performed with ARCHITECT® *T. gondii* IgM, IgG, and Avidity kits working with the chemiluminescence microparticle immunoassay (CMIA) method.

Statistical Analysis: The IBM Statistical Package for the Social Sciences (SPSS) version 26.0 (Armonk, NY: IBM Corp) program was used to evaluate the data of the study. The suitability of the variables to normal distribution was examined using analytical methods (Kolmogorov Smirnov/Shapiro Wilk tests). Descriptive analyses were given using mean ± standard deviation for data that conformed to normal distribution, and median (lowest value-highest value) for data that did not comply with normal distribution. The data of the patients were calculated as a ratio.

Ethics Committee Approval: Approval for the study was received from Recep Tayyip Erdoğan University ethics committee with decision number 2023/156 dated 15.06.23.

RESULTS

We identified 6590 patients who underwent Anti-*T. gondii* IgM or IgG tests during the defined period. Of these, 1045 patients were excluded from the study because IgG testing was not performed, 5545 patients were included, and 4503 of them were pregnant. The median age of the patients was 32 (range 18-45) years. Serological tests were most commonly performed due to pregnancy (n=4503, 81.2%), and in 26 (0.4%) patients to investigate the etiology of fever, 37 (0.6%) patients to investigate the etiology of lymphadenopathy and in 29 (0.5%) patients to examine abnormal liver function tests. The remaining patients were scanned before pregnancy or for other reasons. The seronegativity rate (both Anti-*T. gondii* IgG and IgM negativity) was determined as 66.3% (n=3681), IgG positivity rate was 30.7% (n=1703), isolated IgG positivity rate was 28.7% (n=1590), and IgM positivity rate was 1.6% (n=90) (Table 1).

Anti *T. gondii* IgG and IgM results of pregnant women were examined, 3007 (66.7%) of them were seronegative, 1399 (31%) had IgG positivity, and 1327 (29.4%) had isolated IgG positivity (Table 1). Four of the eight patients with IgG (-), and IgM (+) test results were considered false positive because IgG seroconversion didn't happen during the 4-6 week follow-up. Twenty-three of 57 patients who were IgG and IgM positive were not referred to the infectious diseases outpatient clinic and no further examination was requested. The IgG avidity of 11 patients who underwent further evaluation was found to be 'low' and early infection was considered in these patients (Figure 1). One of the patients with low avidity underwent

Table 1: Results of anti-*T. gondii* IgM and IgG tests.

All patients		**Anti-*T. gondii* IgM**				
		Negative	Positive	Borderline	None	Total
Anti-*T. gondii* IgG	Negative	3683	12	4	45	3744
	Positive	1590	77	18	18	1703
	Borderline	96	1	0	1	98
	Total	5369	90	22	64	5545
Pregnant women		**Anti-*T. gondii* IgM**				
		Negative	Positive	Borderline	None	Total
Anti-*T. gondii* IgG	Negative	3007	8	3	4	3022
	Positive	1327	57	13	2	1399
	Borderline	82				82
	Total	4416	65	16	6	4503

T. gondii: Toxoplasma gondii

medical abortion voluntarily, three patients were started on spiramycin treatment, and the treatment continued until the end of pregnancy, one did not receive any treatment voluntarily, three did not complete the treatment, and three continued to be followed up in another center. The IgG avidity test of 23 patients resulted as 'high'. Twenty patients with high avidity were considered to have latent infection as their gestational age was less than 18 weeks and one of them also had IgG positivity in previous pregnancies. One of our patients, whose "high avidity" test result was detected in the examinations performed on the 24th week, used spiramycin for six weeks. At the 30th week, intrauterine growth retardation secondary to preeclampsia was detected and premature labor occurred. The newborn was evaluated for postpartum congenital toxoplasmosis, and no involvement was detected as a result of eye and central nervous system evaluations. (Figure. 1, Table 2). In the follow-ups to date, no findings in favor of congenital toxoplasmosis have been detected in the babies of any of the pregnant women with possible primary infection who were followed up in our hospital and gave birth.

Non-pregnant patients were also evaluated. Anti-Toxoplasma IgM and IgG were detected positive in six of the 37 patients examined for LAP, and with further evaluation, four patients (10.8%) were diagnosed with acute toxoplasmosis. Two of these patients were followed up without treatment because they had a mild course, and their clinical findings resolved spontaneously, while two of them were treated with antimicrobial treatment (trimethoprim sulfamethoxazole and spiramycin) and responded to the treatment. None of the 29 patients were examined due to abnormal liver function tests and the 26 patients were examined to investigate the etiology of high fever diagnosed with acute toxoplasmosis.

DISCUSSION

While toxoplasmosis generally causes asymptomatic or self-limiting clinical conditions in immunocompetent individuals, it may present with serious conditions in

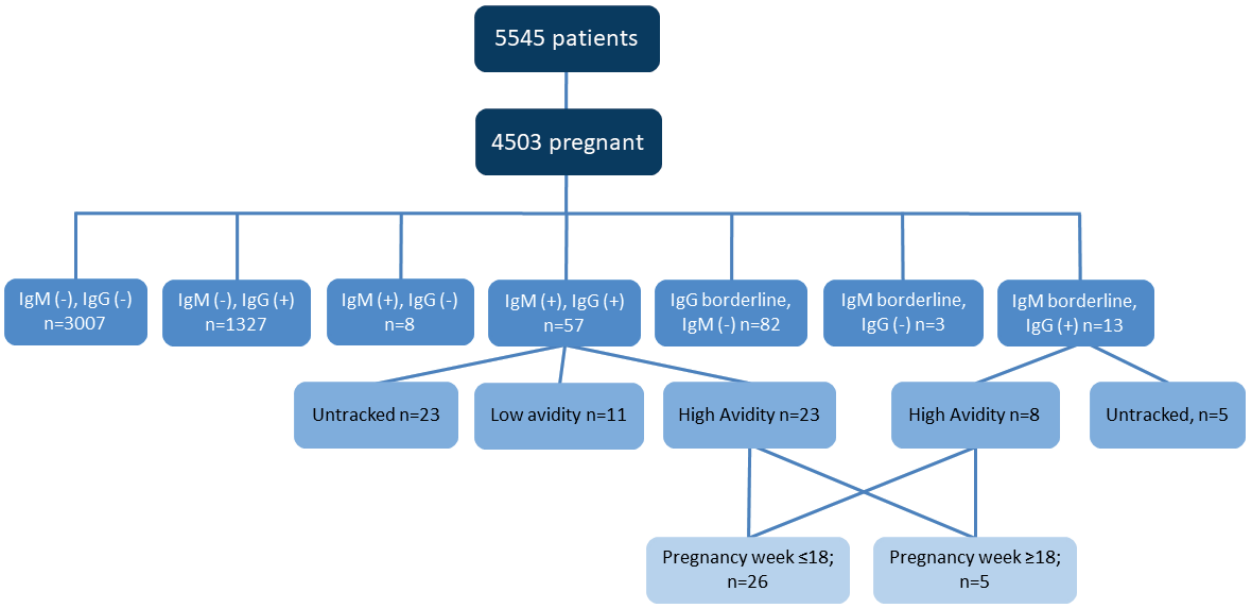

Figure 1: Anti-*T. gondii* IgM, IgG and IgG Avidity test results in pregnant women.

Table 2: Evaluation, follow-up and results of possible primary *T. gondii* infection in pregnant women.

Anti *T. gondii* IgM (+), IgG (-) (n=8)		4 false positives 4 untracked
Anti *T. gondii* IgM (+), IgG (+) (n=57)		
IgG Avidity	Not evaluated (n=23)	
	Low (n=11)	1 is terminated at the request of the mother 1 did not receive treatment voluntarily 3 completed the treatment until the end of pregnancy 3 did not finish treatment 3 untracked
	High (n=23)	20 pregnant women with a gestational age of ≤ 18 weeks had an infection before pregnancy 3 pregnant women with gestational age ≥ 18 weeks 1 infection before pregnancy 1 premature birth due to IUGR after 6 weeks of spiramycin use 1 untracked
Anti *T. gondii* IgM (borderline), IgG (+) (n=13)		
IgG Avidity	Untracked (n=5)	
	High (n=8)	6 pregnant women with a gestational age of ≤ 18 weeks had an infection before pregnancy. 2 pregnant women with gestational age ≥ 18 weeks 1 untracked 1 was followed without treatment

T. gondii: Toxoplasma gondii

cases of acute infection or reactivation of latent infection or congenital infections in immunosuppressants. For this reason, it is very important to closely monitor risk groups in terms of toxoplasma infections and to take effective interventions when necessary.

The seroprevalence of toxoplasmosis, a zoonotic disease, varies according to the climatic conditions of the regions and the nutritional and hygiene habits of the communities. In a review evaluating *T. gondii* seroprevalence in blood donors, anti-*T. gondii* IgG positivity rate was found to be 7.8% in Asia, 32.8% in America, 40.7% in Africa, 34% in Antarctica, and 38.1% in Europe (9). In a study conducted by Karakullukçu et al., which included 1066 people over the age of 20 living in Trabzon/Turkey, the anti-*T. gondii* IgG positivity rate was found to be 58.8% (10). In a study by Sert et al., among 84,587 pregnant women in Ankara/Turkey, the anti-*T. gondii* IgG positivity rate was found to be 22.3%, whereas in another multicenter study by Kul et al. the seropositivity rate was found to be 21% (11,12). In a study by Demiray, Emine Kübra Dindar et al. investigating the Toxoplasmosis seroprevalence in pregnant women from Turkey by pool analyses method; the anti- Toxo IgG rate was found to be 36.76% in Turkey and 31.8% in Black Sea Region (13). In our study, toxoplasma seroprevalence among women of childbearing age in our city was determined to be 30.7% which was similar to the last-mentioned study. It is thought that both regional differences and the inclusion of only women in a certain age range may be effective in the difference in seroprevalence rates.

Toxoplasma serological tests are mostly performed on pregnant women to detect acute infection and prevent possible congenital infections and to detect latent infection and determine the risk of reactivation in people with suppressed immune systems who are susceptible to the disease. Tests can also be performed to investigate the etiology of LAP, elevated liver enzymes, and high fever. As expected, since the group included in our study was women of reproductive age, the rate of patients examined due to pregnancy was quite high (n = 4503, 81.2%), however, we could not find any study that evaluated the reasons for requesting Anti-*T. gondii* tests and the rates of requesting tests according to etiology.

Congenital toxoplasmosis can develop as a result of primary infection experienced by the mother during pregnancy, reactivation in a highly immunosuppressed mother, or re-infection with a virulent strain. With early detection of acute infection and rapid treatment, the risk of transmission to the fetus can be significantly reduced (14). When maternal infection occurs in the early gestational weeks, the probability of transmission is lower, and the risk of sequelae is higher. These rates reverse as the gestational week progresses. In a study evaluating 603 confirmed maternal toxoplasmosis cases, the vertical transmission rate was found to be 29%, and the risk of transmission, which was 6% in the 13th week, reached 72% in the 36th week (1). While toxoplasmosis screening during the antenatal period is not recommended in some countries because it is not cost-effective, in some countries it is recommended to include it in routine pregnancy follow-up and monitor seronegative pregnant women at regular intervals (15-17). In our country, it is recommended that the decision to screen for toxoplasma infection in the antenatal period be made according to regional prevalence (5). In the first 18 weeks (4 months) IgG positive and IgM negative test results suggest an infection acquired before pregnancy. Patients with isolated IgM positivity are monitored for 2-6 weeks for IgG seroconversion, and if seroconversion does not occur, this situation is considered to be false positive. In patients with positive results for both tests, IgG avidity and gestational age are evaluated, and antibiotic treatment is recommended to prevent congenital transmission in pregnant women who are thought to have acute infection. If the fetus gets infected during follow-up, it is appropriate to use drugs for the treatment of fetal infection (5,18). As a result of the evaluations, only four of the pregnant women who were considered to have primary toxoplasma infection and were followed up in our hospital completed

prophylactic antibiotic treatment as recommended, and no congenital toxoplasma infection was detected in the babies of any of the pregnant women. However, it was observed that some of the pregnant women requiring further evaluation based on the examination results were not referred to our clinic, some of the pregnant women for whom prophylaxis was recommended after further evaluation did not use the treatment voluntarily, and usually, difficulties were encountered regarding both the clinical approaches of the physicians and the treatment compliance of the patients.

In immunocompetent patients, acute toxoplasmosis can usually present with an asymptomatic or self-limiting clinic. LAP with bilateral cervical pain is one of the most common clinical findings, cervical LAP can be seen in 20-30% of cases (4, 5). Anti-Toxoplasma IgM was found to be positive in 6.7% of 138 patients in a study examining the etiology of LAP by Güreser et al. (19). Similarly, in our study, acute toxoplasmosis was detected in 6.25% of the patients examined to investigate the etiology of LAP. In addition to lymphadenopathy in acute toxoplasmosis, serious conditions such as pneumonia, encephalitis, myo-pericarditis, and hepatitis may also be observed in some patients. Although it is a rare complication, it is recommended that toxoplasmosis be evaluated in the differential diagnosis of acute hepatitis. Serological evaluation and histopathological examination of the liver can guide the diagnosis (20). In addition, there are studies showing a relationship between Anti-*T. gondii* IgG positivity and chronic liver disease (21,22). Toxoplasmosis was not detected in any of the patients included in our study and examined due to disorders in liver function tests. The most common cause of fever of unknown origin (FUO) is infections. While toxoplasmosis is a rare infection in classical FUO, it can cause high fever more frequently, especially in HIV-infected individuals (20,23,24). Toxoplasmosis should also be kept in mind as one of the causes of fever in patients presenting with lymphadenopathy or hepatosplenomegaly and in contact with cats or consumption of potentially contaminated food. Acute toxoplasmosis was not detected in any of the febrile patients evaluated in our study.

The most important limitation of our study is that it is retrospective. In addition, since most of the pregnant women with possible primary infection were not referred to the infectious diseases department and some of them were followed up in different centers, no information could be obtained about the pregnancy outcome of this group of patients. It is also an important deficiency that the recommended follow-up algorithms could not be followed in some patients, due to clinician or patient-related reasons. However, a large number of patients were included in our study, important information about local seroprevalence was obtained, the course of acute infections in women of childbearing age could be monitored and, unlike other studies, infections in non-pregnant patients were also evaluated.

CONCLUSION

To know the local incidence of toxoplasma infections, which can cause serious diseases, especially in pregnant women and immunosuppressed patients, to create follow up algorithms for risk groups, and to start antimicrobial drugs when necessary, is important in terms of preventing morbidity and mortality. Although, as far as we know, we did not have a baby diagnosed with congenital toxoplasmosis during the study period, there were many pregnant women whom we could not follow up. Working together between obstetricians and infectious disease specialists to identify and follow-up pregnant women with primary infection will ensure more accurate approach to these patients. In addition, informing seronegative pregnant women about possible transmission routes is very important in order to prevent new primary infections and congenital infections.

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Ethics: This study was approved by the Recep Tayyip Erdoğan University ethics committee with decision number 2023/156 dated 15.06.23.

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