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Toxoplasmosis in pregnancy: test, treatment and outcome

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ABSTRACT

Objectives: The aim of this study was to share the results, follow-up, and treatment characteristics of our pregnant women who were followed-up with anti-*Toxoplasma gondii* Immunoglobulin (Ig) M positivity during pregnancy.

Methods: Anti-*T. gondii* IgM- and IgG-positive pregnant women were evaluated between 2014-2018. Demographic characteristics, treatment, and information about pregnancy were obtained from the electronic database. Pregnant women were divided into three groups; primary infection, no infection, and suspected infection in pregnancy. Primary and suspected infection in pregnancy were followed up congenital toxoplasmosis risky pregnancy. Fetal ultrasonography (USG), *T. gondii* DNA polymerase chain reaction (PCR) result in amniotic fluid were recorded.

Results: Twenty-four pregnant women with a mean age of 27.9 years were followed up. IgG avidity results were low in 37.5% (n = 9), intermediate avidity in 8.3% (n = 2), and high avidity in 54.2% (n = 13) of pregnant women. Eleven (45.9%) pregnant women had congenital toxoplasmosis risky pregnancy. Fetal USG was performed on ten pregnant women, and no signs of congenital toxoplasmosis were found. Amniocentesis was performed in 72.7% (n = 8) of the participants, and the amniotic fluid *T. gondii* DNA-PCR result was negative in all of them. Ten (90.9%) pregnancies resulted in mature birth and one (9.1%) resulted in miscarriage.

Conclusions: Anti-*T. gondii* IgM positivity is an indication of acute infection. But IgM can persist for years, and be false-positive in pregnancy. Therefore, additional tests are required, and leading to emotional distress and unnecessary interventions in pregnacy women. These results can aid in developing an approach to screening and diagnosis of *T. gondii* infection in pregnancy.

Keywords: Toxoplasmosis, pregnancy, avidity, congenital toxoplasmosis, *T. gondii* DNA polymerase chain reaction (PCR), fetal ultrasonography

Toxoplasmosis is a common parasitic disease worldwide and is caused by *Toxoplasma gondii.* Although it often causes a self-limited infection with asymptomatic or mild symptoms (such as fever, malaise, lymphadenopathy), it can have a severe course in immunosuppressive individuals (e.g., HIV). Besides, acute infection during pregnancy can pass to the fetus (congenital toxoplasmosis), miscarriage, premature birth, stillbirth may occur and may cause severe sequelae in live-born babies (such as mental

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retardation, chorioretinitis, epilepsy) [1, 2].

It is estimated that more than 30% of the world's population is infected with *T. gondii*. According to countries and regions, this rate varies between 10-80% due to differences in climate, nutrition, and hygiene habits [3, 4]. In the United States, seropositivity has been reported to be 23% in adolescents and adults and 14% in women of childbearing age [2].

In a study investigating the prevalence of *T. gondii* in the world in 2009, our country was among the countries with a high prevalence (30-60%) [4]. *T. gondii* IgG seropositivity was 24.6% in 17,751 women of childbearing age in Istanbul, Adana, Bursa, Kayseri, and Kocaeli, and 30.7% in a study including pregnant women from Denizli [5, 6]. Seropositivity was 69.5% in pregnant women in Şanlıurfa [7]. There are also regional differences in our country. It is noteworthy that these rates are similar to Italy, France, Finland, and Austria, where toxoplasma screening is mandatory [8-11]. The increase in the incidence of congenital toxoplasmosis presentation in newborns brings up a screening in the United States. Massachusetts and New Hampshire are two states that perform routine newborn screening [12]. In our country, information about screening needs to be clarified.

According to estimates obtained from regional data in the USA, 400-4,000 cases of congenital toxoplasmosis and 750 deaths have been reported annually. The fact that 50% of cases are food-borne makes toxoplasmosis the third leading cause of food-borne death in the United States [13]. Since congenital toxoplasmosis is a critical public health problem, the Centers for Disease Control and Prevention (CDC) has made recommendations to reduce the risk of congenital infection [14].

In our country, there is no recommendation for pregnancy screening in the Ministry of Health's Antenatal Care Management Guidelines for toxoplasmosis or the recommendations of the Turkish Perinatology Society [15, 16]. In the age-related prevalence study performed in the province of Hatay, the estimation of the primary infection risk in pregnant women was found to be 6/1,000 [17]. The World Health Organization (WHO) estimated the incidence of congenital toxoplasmosis for Europe in 2013 to be 1.5 per 1,000 births [18].

Enzyme immunoassay methods that detect anti-*T. gondii* Immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies are frequently preferred in clinical practice for the laboratory diagnosis of toxoplasmosis due to their high sensitivity and ease of application. Anti-*T.gondii* IgM may remain positive for a long time in the peripheral blood. Therefore, additional tests such as IgG avidity, *T. gondii* DNA polymerase chain reaction (PCR) in amniotic fluid, and fetal ultrasonography (USG) are required to diagnose acute infection in pregnant women. Sometimes, the diagnosis is unclear even with these, and it is tried to be interpreted with the previous test results.

Our study aimed to interpret the test results of our pregnant women who were followed up with anti-*T. gondii* IgM and IgG positivity, their pregnancy follow-ups, growth retardation in babies. Together with the seropositivity studies, these results were intended to shed light on the screening for toxoplasmosis in pregnancy and guide physicians in interpreting the tests.

METHODS

Pregnant women who applied to our Infectious Diseases and Clinical Microbiology outpatient clinic between 2014-2018 with anti-*T. gondii* IgM and IgG positivity were included in our study. The study was approved by Ankara City Hospital Ethical Committee. Demographic characteristics of the pregnant women, the treatment they received, and information about pregnancy were obtained from the electronic database. After gathering these data, information about the babies of the pregnant women was recorded. The ages of the babies, whether they had was growth retardation in their follow-ups.

The results were interpreted per the evaluation criteria of commercial kits. For anti- *T. gondii* IgM, < 0.8 COI values were considered as negative, COI values between 0.8-0.999 as intermediate, ≥ 1 COI values as positive, < 1 IU/mL values as negative for anti- *T. gondii* IgG, values between 1-2.999 IU/mL as intermediate, ≥ 3 IU /mL values as positive and for IgG avidity test < 50 index value as low avidity, index value between 50-50.9 as intermediate avidity, ≥ 60 index value as high avidity.

The results were interpreted according to the gestational week and previous test results. Low avidity result was interpreted as primary infection in pregnancy. High avidity result was considered as no infec-

tion in pregnancy if in the first 12 weeks of pregnancy, and as infection with undecidable timing- suspected infection- if after 12 weeks. Pregnant women who were evaluated as infection in pregnancy and suspected infection during pregnancy were followed up as congenital toxoplasmosis risky pregnancy. *T. gondii* DNA PCR and fetal USG results were recorded in the amniotic fluid of these pregnant women.

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 version and Microsoft excel. Descriptive statistics were presented as frequency and percentages for categorical variables and as mean ± standard deviation (SD) or median (minimum-maximum values) for continuous variables.

RESULTS

Twenty-four participants with a mean age of 27.9 years (20-38) were included in our study. There was a history of miscarriage in 3 and tuberculosis in one. There was no chronic disease or drug use. The median gestational week was 10.5 (range, 6-34) weeks. Nineteen pregnancies were in the first trimester, four were in the second trimester, and one was in the third trimester. None of the participants had any symptoms. IgG avidity results were low in 37.5% (n = 9) of the pregnant women, intermediate avidity in 8.3% (n = 2), high avidity in 54.2% (n = 13) (Fig. 1). Eleven (84.6%) participants with high avidity were in the first trimester, and it was interpreted as no infection in pregnancy. Two (15.4%) pregnant women were in the second trimester (15 and 16 weeks of gestation), and the timing for infection could not be determined (suspected infection). One of the pregnant women whose IgG avidity resulted as intermediate avidity was interpreted as a primary infection in pregnancy due to a 4-fold increase in *T. gondii* IgG titer, and the other pregnant woman as no infection in pregnancy due to previous results. Since 88.9% (n = 8) of the pregnant women with low avidity results had a primary infection in pregnancy and 11.1% (n = 1) had results from their previous pregnancy, it was interpreted as no infection in pregnancy (Fig. 1).

Spiramycin 3gr/day dose was initiated for all participants who applied to our outpatient clinic with anti-*T. gondii* IgM positivity, and an IgG avidity test was requested. Spiramycin treatment was discontinued in patients who were decided to have an infection before pregnancy.

Fetal ultrasonography results were available in 91.7% (n = 22) of the participants, and no fetal anomaly was determined in any of them. Amniocentesis was performed in 37.5% (n = 9) of the pregnant women,

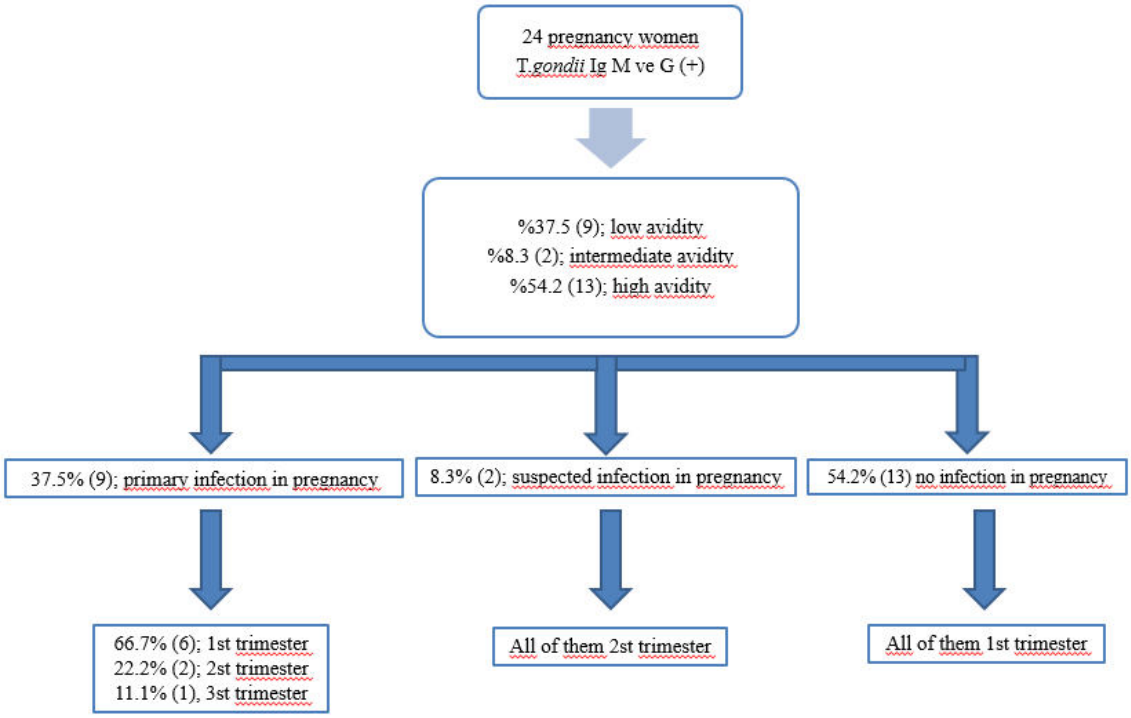

Fig. 1. Immunoglobulin (Ig) G avidity result and infection decision chart.

and the *T. gondii* DNA PCR result in the amniotic fluid of all of them was negative. Considering the pregnancy outcomes, miscarriage developed in 12.5% (n =3). One of the pregnant women who had a miscarriage was diagnosed with a primary infection in pregnancy, and the other two were diagnosed with no infection in pregnancy. 87.5% (n = 21) of babies were born mature.

Eleven (45.9%) pregnant women were congenital toxoplasmosis risky pregnancy (Table 1). Spiramycin treatment was continued in these pregnant women. The mean age of the pregnant women was 28 years. Of the pregnant patients with congenital toxoplasmosis risk, 54.5% (n = 6) were in the first trimester,

Table 1. Follow-up of congenital toxoplasmosis risky pregnant.

No	Age (years)	Pregnancy trimester	IgG avidity result	Infection definition	Fetal USG	Amniotic fluid T. gondii DNA PCR	Pregnancy termination
1	21	II	Low	Primary infection in pregnancy	Normal	Negative	Born mature
2	24	III	Low	Primary infection in pregnancy	Normal	No	Born mature
3	26	I	Low	Primary infection in pregnancy	No	No	Born mature
4	27	II	Low	Primary infection in pregnancy	Normal	Negative	Low
5	33	I	Low	Primary infection in pregnancy	Normal	Negative	Born mature
6	34	I	Low	Primary infection in pregnancy	Normal	No	Born mature
7	25	I	Low	Primary infection in pregnancy	Normal	Negative	Born mature
8	25	I	Low	Primary infection in pregnancy	Normal	Negative	Born mature
9	26	I	Intermediate	Primary infection in pregnancy	Normal	Negative	Born mature
10	34	II	High	Suspected infection in pregnancy	Normal	Negative	Born mature
11	33	II	High	Suspected infection in pregnancy	Normal	Negative	Born mature

IgG = immunoglobulin G, PCR = polymerase chain reaction, USG = ultrasonography

36.4% (n = 4) were in the second trimester, and 9.1% (n = 1) were in the third trimester. In the IgG avidity results, 72.7% (n = 8) had low avidity, 9.1% (n = 1) had intermediate avidity, 18.2% (n = 2) had high avidity. Fetal ultrasonography was performed on ten pregnant women, and no signs of congenital toxoplasmosis were found. Amniocentesis was performed in 72.7% (n = 8) of the pregnant women, and the amniotic fluid T.gondii DNA PCR result was negative in all of them. 90.9% (n = 10) of pregnancies resulted in mature birth, and 9.1% (n = 1) resulted in miscarriage. One of the babies was diagnosed with Bartter syndrome in the examinations performed due to growth retardation and died at sixth month due to aspiration pneumonia. The mean age of 9 living babies was 4.3 (3-5). None of the babies had developmental delay.

DISCUSSION

There is no worldwide consensus for screening for toxoplasmosis during pregnancy. While there are countries that advocate screening all pregnant women, some do not advise screening. Geographical location, cultural practices, feeding habits, socioeconomic status significantly affect the prevalence of the disease. European countries lead the primary toxoplasmosis infections in the world. France reported the highest infection rates in pregnant women (54%), while the remaining European countries reported lower infection rates (46%) [20].

After acute infection, the IgM titer starts to rise on the fifth day and reaches its maximum level in 1-2 months. While IgM antibodies become negative before the sixth month in 25% of cases, they may remain positive for a year or even up to 2 years in other patients, depending on the sensitivity of the test method used [19]. IgG titer begins to be detected 1-2 weeks after acute infection and remains high for life [20]. In pregnant women with positive *T. gondii* IgM and IgG tests, it is recommended to perform an IgG avidity test to determine whether the infection is in the early or late stages [21]. However, since antibodies with low avidity can remain in the serum for months, infection in pregnancy may not always be present when a low avidity value is detected [22, 23]. In such a case, laboratory diagnosis should be confirmed by PCR from amniotic fluid, and it should also be supported by clinical and ultrasonographic findings [22]. In interpreting serological tests, the time of requesting the tests is also important [24]. The high avidity result in the first trimester ensures the exclusion of infection. However, the examinations performed in the second and third trimesters make this decision difficult. In 20.8% (5/24) of the pregnant women in our study, tests were requested in the second and third trimesters. This also made the interpretation of the tests complicated. In this case, previous serological examinations are beneficial in making the diagnosis. No infection in pregnancy was decided because 8.3% (2/24) of the pregnant women who applied to us due to toxoplasmosis had a previous serology analysis. There is no recommendation for routine screening in our country. Furthermore, there is no consensus among doctors due to the lack of a common follow-up plan. These challenges encountered in the interpretation of the tests cause unnecessary tests in pregnant women and increase the anxiety of the prospective parents due to the uncertainty of the baby's prognosis [25, 26]. A study in Italy stated that 51.3% of pregnant women had previous results, making decision-making much easier [27]. They argued that more detailed studies on the tests used in screening policies should be done [27].

In pregnant women diagnosed with acute toxoplasmosis, the use of fetal USG is recommended after serological tests. Neurological anomalies (hydrocephalus, ventriculomegaly, and intracerebral calcifications), splenomegaly, congenital nephrosis, and ascites can be detected in fetal USG [28]. In our study, fetal USG was performed in 90.9% of pregnant women with congenital toxoplasmosis risk, and no finding suggestive of toxoplasmosis was detected in any of them. In the study of Italy, at least one finding suggestive of congenital toxoplasmosis was found in 10.4% of fetuses [27]. As the result of a multicenter study in France, the rate of an anomaly in fatal USG was reported as 4.2%. [29].

Amniocentesis is recommended at the earliest 18th week in pregnant women diagnosed with acute infection during pregnancy. *T. gondii* DNA PCR in amniotic fluid has a positive predictive value close to 100% in determining fetal infection [30]. In the study of Greco *et al.* [31], *T. gondii* DNA PCR was found to be 6% positive in amniotic fluid during primary infection. In a report from our country in 2021, *T. gondii* DNA PCR positivity in amniotic fluid was reported as

16.7% (1/6). This condition has been associated with initiating treatment late in pregnancy [32]. In our study, eight pregnant women underwent amniocentesis, and the *T. gondii* DNA PCR result in amniotic fluid was negative in all of them. This result supports the ultrasound findings showing that there is no fetal involvement.

Fetal transmission generally occurs at the rate of 29% (95% CI 25-33), while it is 6% at 13 weeks of gestation and 72% at 36 weeks of gestation. Congenital infection was determined in a pregnant woman who had seroconversion at 24-30 weeks of gestation, and it was reported that the incidence of her findings would be the highest (10%) [33]. As a result of the meta-analysis performed in 2014, the infection rate in the third trimester was 32% [24]. In the study of Avelino et al. [34], the rate of congenital toxoplasmosis was reported to be as high as 56% in women with suspected infection. However, it was reported that high rates might be due to delayed first-trimester screening of pregnant women [27]. This indicates the importance of antenatal screening time. Apart from this, the rates were reported to be much lower, such as 0.8-7%, in studies performed in pregnant women with Anti-*T. gondii* IgM (+)/ IgG (+) and low avidity [31, 35, 36]. Our study considered no fetal involvement since there was no problem in both the intrauterine tests and the follow-up of the babies after birth. Early treatment in pregnancy reduces fetal transmission by 50% [37, 38]. In our study, 54.5% (6/11) of pregnant women with congenital toxoplasmosis risk were in the first trimester, and all of them were initiated with spiramycin, which may be the reason why we did not see any signs of congenital involvement.

Some findings of fetal involvement of congenital toxoplasmosis can be easily missed at birth. Most babies develop late symptoms months after birth, such as chorioretinitis, seizures, mental retardation, and motor or cerebellar dysfunction. Furthermore, associations between congenital infection and sensorineural hearing loss, congenital nephrosis, hematological abnormalities, hepatosplenomegaly, various endocrinopathies, and myocarditis have been demonstrated [39]. We obtained information from the mothers about the outcomes of the babies and found that there was no developmental delay

One of the pregnancies diagnosed as primary infection in pregnancy ended in miscarriage. In the fetal USG performed in this pregnancy, no fetal anomaly was found to suggest congenital toxoplasmosis. Moreover, *T. gondii* DNA PCR was negative in amniotic fluid. Therefore, the miscarriage developed is not associated with toxoplasmosis, but it cannot be said clearly because the miscarriage material is not screened for toxoplasmosis.

Limitations

Our study has limitations such as being retrospective, the small number of patients, the fact that the miscarried baby was not examined in terms of toxoplasmosis, and it does not provide clear data on seroprevalence. However, it gives information about congenital transmission as it includes the long-term results of babies. A large-scale study has not yet been performed to determine the rate of congenital toxoplasmosis in Turkey [11]. Leading these studies was critical in justifying establishing a consensus on pregnancy screening and follow-up. It is also hoped that it will aid physicians in interpreting serological test results.

CONCLUSION

Toxoplasmosis is a preventable infection that affects millions of women and their children. The difficulty in interpreting serological results in the outpatient clinic causes significant difficulties for us, the physicians, and the mother and father-to-be with the stress it creates. Babies who are not correctly diagnosed and treated for congenital toxoplasmosis are at risk for lifelong brain and ocular abnormalities [20]. Considering the rates in our country, it is vital to evaluate women of childbearing age who are planning a pregnancy and pregnant women in terms of acute toxoplasmosis. In particular, systematic serological screening of pregnant women by establishing a national program will ensure that the cost-effectiveness of the screening is evaluated, and the problems experienced in diagnosis and follow-up will be minimized.

Authors' Contribution

Study Conception: RG, AKK; Study Design: AKK, İH; Supervision: AKK, İH, MA; Funding: N/A; Materials: FYA; Data Collection and/or Processing: AKK, MA, FE; Statistical Analysis and/or Data Inter-

pretation: AKK, BK; Literature Review: YO; Manuscript Preparation: AKK, RG and Critical Review: AKK, FE, RG, YO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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