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Investigation of *Toxoplasma Gondii*, Rubella virus and Cytomegalovirus Infections in Pregnancy, Retrospective Evaluation of Avidity Tests and Perinatal Follow-up Results

Gebelikte *Toxoplasma Gondii*, Rubella virus ve Cytomegalovirus Enfeksiyonlarının Araştırılması, Avidite Testlerinin Perinatal Takip Sonuçlarının Retrospektif Değerlendirilmesi

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Abstract

Aim: In this study, it was aimed to investigate *Toxoplasma Gondii*, Rubella virus and Cytomegalovirus (CMV) IgM and IgG results, the avidity tests and perinatal follow-up results retrospectively.

Material and Method: Test results of pregnant women who applied to Gynecology and Obstetrics Polyclinics in 2017-2018 were analyzed retrospectively.When IgM result was positive for any of these infections, IgG avidity indices, ultrasound (USG) findings, prenatal screening results, amniocentesis results, week of gestation that IgM positivity was observed, and if any treatments applied for these infections, were examined from the file records of pregnant women.

Results: It was observed that 24.1% of 6719 patients were Toxoplasma IgG, 98.9% were Rubella IgG and 98.7% were CMV IgG positive. When the IgM positivity was examined, it was seen that this rate was 0.46% (n=31) for Toxoplasma, 0.16% (n=11) for Rubella and 0.7% (n=47) for CMV. There was only 9 low avidity test results for *Toxoplasma Gondii*. But there was no evidence of perinatal infection associated with these infectious agents .

Conclusion: In conclusion, screening for toxoplasma, rubella and CMV infections during pregnancy is still a controversial subject and there is no national screening programme in Turkey. Knowing the seroprevalence is of great importance in establishing national screening strategies and providing consultancy to pregnant women about protection from these infections. From this point of view our study is valuable in that it contributes to these data as the first study conducted in Balıkesir region on this subject.

Keywords: TORCH, congenital infection, avidity

Öz

Amaç: Bu çalışmada *Toxoplasma Gondii*, Rubella virus ve Cytomegolovirus (CMV) IgM ve IgG sonuçları, avidite testleri ve perinatal takip sonuçlarının retrospektif olarak araştırılması amaçlandı.

Gereç ve Yöntem: 2017-2018 yıllarında Kadın Hastalıkları ve Doğum Polikliniğine başvuran gebelerin *Toxoplasma Gondii*, Rubella virus, CMV IgG ve IgM test sonuçları ve IgG avidite indeksleri retrospektif olarak incelendi. Bu enfeksiyonlardan herhangi biri için IgM sonucu pozitif olduğunda, IgG avidite indeksleri, ultrason (USG) bulguları, doğum öncesi sonuçları, amniyosentez sonuçları, IgM pozitifliği görülen gebelik haftası ve bu enfeksiyonlara yönelik uygulanan tedaviler geriye dönük olarak araştırıldı. Bu gebelerin bebeklerinin doğum şekli ve ağırlığı, APGAR skoru ve yoğun bakım ihtiyacı gibi bilgiler incelendi.

Bulgular: 6719 hastanın %24,1'inin Toxoplasma IgG, %98,9'unun Rubella virus IgG ve %98,7'sinin CMV IgG pozitif olduğu görüldü. IgM pozitifliği incelendiğinde bu oranın Toksoplazma için %0,46 (n=31), Rubella virus için %0,16 (n=11) ve CMV için %0,7 (n=47) olduğu görüldü. Sadece *Toxoplasma Gondii* için 9 düşük avidite testi sonucu saptandı ancak TORCH ile ilişkili perinatal enfeksiyon kanıtı bulunamadı.

Sonuç: Sonuç olarak, gebelikte Toksoplazma, Rubella virus ve CMV enfeksiyonlarının taranması halen tartışmalı bir konu olup, ülkeler arasında farklı öneriler ve uygulamalar mevcuttur ve Türkiye'de ulusal bir tarama programı bulunmamaktadır. Seroprevalansın bilinmesi ulusal tarama stratejilerinin oluşturulmasında ve gebelere bu enfeksiyonlardan korunma konusunda danışmanlık verilmesinde büyük önem taşımaktadır. Bu açıdan bakıldığında çalışmamız bu konuda Balıkesir bölgesinde yapılmış ilk çalışma olması açısından bu verilere katkı sağlaması açısından değerlidir.

Anahtar Kelimeler: TORCH, konjenital enfeksiyon, avidite

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INTRODUCTION

Perinatal infections are among the common causes of congenital anomalies.*Toxoplasma Gondii*, Rubella virus, Cytomegalovirus (CMV), which are among the TORCH group infections, are the most common infections associated with congenital anomalies.[1] Congenital infections can cause various anomalies, especially hepatosplenic,cardiac and central nervous system malformations, as well as abortion and stillbirth.[1,2] CMV is the most common congenital viral infection affecting 2% of live births. It has been reported that 10-15% of affected fetuses show symptomatic congenital infection at birth.[1,3] CMV can cause malformations such as hepatosplenomegaly (HSM), cardiac problems, petechiae/purpura, microcephaly, periventricular calcification, hearing loss and chorioretinitis.[4] CMV is the most common cause of non-hereditary hearing loss.[1]

A 95% reduction in congenital rubella syndrome (CRS) was observed with routine rubella vaccination in parallel with the decrease in infection frequency from 2000 to 2014.[5] When rubella infection occurs in the first trimester, the risk of developing CRS (80-100%) is highest; this risk is 10-20% in the second trimester and 60% in the third trimester.[1] Rubella infection during pregnancy can cause serious malformations such as HSM, patent ductus arteriosus, pulmonary artery stenosis, myocarditis, petechiae/purpura, chorioretinitis, cataracts, microphthalmia, and hearing loss.[4,5]

Worldwide, approximately 201,000 cases of congenital toxoplasmosis are reported annually.[6] Toxoplasmosis can cause fetal HSM, petechiae/purpura, maculopapular rash, hydrocephalus, chorioretinitisand diffuse intracranial calcifications.[4,6]

The serological diagnosis of *Toxoplasma Gondii*, Rubella virus and CMV is based on the detection of IgM and IgG antibodies and IgG avidity tests are used to determine the time of infection. There are low-avidity antibodies in the early stages of the immune response and high-avidity antibodies in the late stages of the immune response and avidity tests are widely used to differentiate reactivation, re-infection or primary infection in TORCH infections that cause congenital infections during pregnancy. The practice of screening pregnant women for TORCH infections varies geographically.[7] The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women should be screened for rubella and syphilis at the first prenatal visit. In other countries, pregnant women also may be screened for toxoplasmosis. In Turkey there is no recommendation for screening in the Antenatal Care Management Guideline of the Turkish Ministry of Health but in practice most of the pregnant women are screened for these infections during their pregnancy.[8]

In this study, it was aimed to investigate *Toxoplasma Gondii*, Rubella virus and CMV infections in pregnant women to evaluate the avidity tests and perinatal follow-up results retrospectively.

MATERIAL AND METHOD

The study was carried out with the permission of Balıkesir University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 11.11.2020, Decision No: 2020/206). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Toxoplasma Gondii, Rubella virus, CMV IgG and IgM test results and IgG avidity indices of pregnant women who applied to Gynecology and Obstetrics Polyclinics in 2017-2018 were analyzed retrospectively. Only the first result of each patient was included in the study. When IgM result was positive for any of these infections, IgG avidity indices, ultrasound (USG) findings, prenatal screening results, amniocentesis results, week of gestation that IgM positivity was observed, and if any treatments applied for these infections, were examined from the file records of pregnant women.Information such as delivery type and weight, APGAR score and need for intensive care of the babies of these pregnant women were analyzed retrospectively.

Toxoplasma Gondii, Rubella virus, CMV IgG and IgM values were studied by the chemiluminescent enzyme immunoassay method (CMIA) (Architect i2000SR, Abbott, Germany) according to the manufacturer's instructions. 3 IU/mL,10 IU/mL and 5 IU/mL were accepted as threshold values for *Toxoplasma Gondii*, Rubella virus and CMV IgG positivity, respectively. For *Toxoplasma Gondii* IgMvalues between 0.5-0.6 IU/mL were grayzone and values >0.6 IU/mL werepositive; for Rubella IgM values between 1.0-1.2 IU/mL were grayzone and values >1.2 IU/mL were positive; for CMV IgM values between 0.85-1.0 IU/mL were grayzone and values >1.0 IU/mL were positive. IgM test results that were positive orgrayzone were studied twice. Results of the patients whose IgM and IgG positivity were observed and IgG avidity test were requested, were interpreted according to the values recommended by the manufacturer. For *Toxoplasma Gondii* avidity index values between 0.2-0.3 were grayzone and values <0.2 low avidity; for CMV avidity index values between 0.4-0.65 were grayzone and values <0.4 low avidity; for Rubella avidity index values between 0.4-0.5 were grayzone and values<0.4 were low avidity.

RESULTS

The mean age of 6719 pregnant women who were included in the study was determined as 27.8±5.4 (18-45 years).

Table 1. *Toxoplasma Gondii*, Rubella virus, CMV IgM and IgG results

	IgM positive n (%)	IgG positive n (%)	Total n
Toxoplasma Gondii	31 (0.46)	1618 (24.1)	6719
Rubella virus	11 (0.16)	6650 (98.9)	6719
CMV	47 (0.70)	6634 (98.7)	6719

CMV: Cytomegalovirus

Table 2. *Toxoplasma Gondii*, Rubella virus, CMV IgM and avidity results

	IgM grayzone n (%)	IgM positive n (%)	Low avidity n (%)	Grayzone avidity n (%)	High avidity n (%)	Avidity unknown n (%)
Toxoplasma IgM Positive (n=31)	1 (3.2)	30 (96.7)	9 (29.0)	1 (3.2)	17 (54.8)	4 (12.9)
Rubella IgM Positive (n=11)	1 (9.1)	10 (90.9)	0	0	6 (54.5)	5 (45.5)
CMV IgM Positive (n=47)	29 (61.7)	18 (38.3)	0	1 (2.1)	22 (46.8)	24 (51.1)

CMV: Cytomegalovirus

It was observed that 24.1% of 6719 patients were Toxoplasma IgG, 98.9% were Rubella IgG and 98.7% were CMV IgG positive. When the IgM positivity was examined, it was seen that this rate was 0.46% (n=31) for Toxoplasma, 0.16% (n=11) for Rubella and 0.7% (n=47) for CMV.

When the results of 31 pregnant women with grayzone\ positive Toxoplasma IgM (IgM value ranging between 0.56-9.30) and whose ages were between 19-40 (mean age±SD:26.1±5.5) were examined, one of them was found to be grayzone and 30 were positive. Among 31 Toxoplasma IgM positive pregnant women-4 (%12.9) avidity results cannot be found and other's avidity results were as follows;17 (54.8%) high avidity,1 (3.2%) grayzone, 9 (29.0%) low avidity.

When the results of 11 pregnant women with Rubella IgM positivity (IgM value varying between 1.02-6.47) and between 21-40 years (mean age±SD:28.2±6.1) were examined,it was seen that one of them was grayzone and 10 of them were positive. Among these for 5 (45.5%) pregnant women there were no avidity test results, and 6 (54.5%) of them were found to have high avidity.

When the results of 47 pregnant women with CMV IgM positivity (IgM value varying between 0.85-3.88) and aged between 18-41 (mean age±SD:27.7±5.5) were examined, 29 of them were found to be grayzone and 18 were positive. It was observed that in 24 (51.1%) of 47 pregnant women, the avidity results were not found, 22 (46.8%) had high avidity and one (2.1%) had a grayzone.

Sixteen pregnant women and their babies for Toxoplasma, 6 for Rubella virus, and 19 for CMV, whose IgM positivity was observed and IgG avidity indexes and regular follow-up records could be reached, were evaluated in detail. Low avidity was not detected for Rubella virus and CMV in our study. There is only one pregnant woman with a grayzone avidity value for CMV, but her follow-up records were not available. Therefore, all pregnant women whose follow-up records for CMV and Rubella can be reached werehigh avidity. In their prenatal follow-up and delivery, no evidence of perinatal infection associated with TORCH was found. Of the 9 low avidity results detected only for Toxoplasma, the clinical data of 4 could be reached: all of them had IgM positivity detected in the first three months of pregnancy, amniocentesis was not applied to any of the pregnant women with low avidity, there was no finding suggestive for toxoplasma infection in the fetal USG findings, three of these pregnant women had spiramycin treatment and the birth weights and APGAR scores of the babies were normal.

DISCUSSION

Toxoplasma, Rubella, CMV infections are seen in all age groups and are usually asymptomatic, but primary infections, especially during pregnancy, can cause very serious consequences in the fetus, ranging from many systemic diseases, malformations to premature birth, abortion and stillbirth.[1-6] Therefore, it is of great importance to prevent or diagnose early and to treat them if possible during pregnancy.[9] Among these three infectious agents, there is only vaccine for Rubella, and the frequency of CRS has decreased in parallel with the decrease in the frequency of infection with the Rubella immunization.[5] For this reason, pre-pregnancy vaccination of those who are not immune to Rubella by screening women of reproductive age is the most effective way of preventing infections and therefore CRS during pregnancy. In Turkey, the Rubella vaccine has been included in childhood vaccination programs since 2006.[10] The frequency of these infections varies between regions and countries, and knowing the seroprevalence is of great importance in establishing national screening strategies and providing consultancy to pregnant women about protection from these infections.

Many studies have been conducted in Turkey and in the world about this subject. Our study is important in being the first study in Balıkesir region and determining the seroprevalence in this region. It was observed that 24.41% of 6719 patients included in our study were Toxoplasma IgG, 98.9% Rubella IgG and 98.7% CMV IgG positive. Considering the Toxoplasma IgG positivity, this rate was found to be 34.7% in the study conducted in 2020, which included Brazil, Mexico, Germany, Poland, China and Turkey. Among these countries the lowest rate was 1% in China and the highest rate was 59% found in Brazil. In the same study this rate was reported as 26% for Turkey, and the rate of 24.41% found in our study is very close to this rate.[9] Toxoplasma IgG positivity was reported as 9.1% in England, 18% in Italy and 67.7% in India.[10] It is known that this ratio is generally higher in low socioeconomic levelsand in developing countries. When we look at the studies conducted in Turkey, it is seen that this rate varies between 18.8% and 68.9% and is lower in the west and north of the country.[11] In the study conducted by Sirin et al. between 2014 and 2016 in Izmir, it was stated that this rate was 32.2% and it was emphasized that Toxoplasma IgG positivity varied between 30.3% and 69.5% in studies conducted in Turkey.[10] Toxoplasma IgG positivity was reported as 22% in a study covering 2015-2017 in Bolu and

37.6% in a study covering the years 2012-2013 in Van.[12,13] This rate is 23.6% in Afyon and 63.4% in Kilis.[14,15] As stated in the literature, there are differences in the seroprevalence of these infections according to geographic regions, socioeconomic level, lifestyle and eating habits. The fact that the results of our study show similarities with İzmir, Bolu and Afyon, which are more similar to Balıkesir province both geographically and socioeconomically, and that this ratio is higher in Van and Kilis supports these data. In our study, it was found that only 24.1% of the pregnant women were Toxoplasma IgG positive and most of the pregnant women were sensitive to infection. As stated above there are different recommendations screening for toxoplasmosis in pregnancy. Since the prevalance of the disease and incidence of maternal infection are low, national societies in the United States, Canada, the United Kingdom, and some parts of Europe do not recommend routine screening for toxoplasmosis in pregnancy but in other parts of Europe screening is performed.[7] In some countries diagnostic testing using serology for toxoplasmosis should be performed if there is clinical suspicion of acute toxoplasmosis during pregnancy[16] or ultrasonographic abnormalities in the fetus that suggest congenital toxoplasmosis. There is no national screening programme for toxoplasmosis in Turkey but most of the pregnant women in our study and in other studies are seronegative and sensitive to infection. Among congenital infections, the only infection with a treatment option is Toxoplasma. For this reason, we think that it is important to detect Toxoplasma IgG negative pregnant women, to inform them about infection prevention methods and to be followed up in terms of acute infection.

In a study conducted in 2020 in terms of CMV IgG and Rubella IgG and including Brazil, Mexico, Germany, Poland, China and Turkey, the positivity rate was found to be 98.4% and 94.1%, respectively.[9] Although very high Rubella IgG positivity has been achieved worldwide and in Turkey due to the Rubella vaccination program, it is known that this rate can decrease to 86.5% in the east of Turkey and reaches 98% in other regions.[10,13] In our study, 98.9% of pregnant women were Rubella IgG positive. Although quite high rates have been reached, it is still necessary to identify women susceptible to Rubella infection, which is more common in some regions, and should be included in the pre-pregnancy vaccination program if possible. American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women should be screened for rubella at the first prenatal visit.[7] If the pregnant women is immune, repeat testing is unnecessary butif nonimmune, the patient should be informed to avoid contact individuals with rubella and should be vaccinated after pregnancy.

CMV infection is the most common among congenital viral infections and unlike other congenital infections, it is known to infect the fetus during reactivation and reinfections, rarely. CMV seroprevalence is closely related to low socioeconomic conditions, low hygiene and crowded living conditions similar to toxoplasma infections.[11] While this rate is generally between 50-60% in developed countries, it is between 90-100% in developing countries.[17-20] In parallel with these data, this rate was 98.4% for Turkey, 28.3% for Germany and 98.1% for Brazil.[9] Differences can be observed within the countries according to geographical regions and socioeconomic conditions. Although there are differences between regions in studies conducted in Turkey, generally CMV IgG positivity is over 90%.[11] In our study,CMV IgG positivity was found to be 98.7%.CMV infection is usually asymptomatic and transmissible to the fetus, some suggest that all women of childbearing age should know their CMV serostatus.[21-24] But on the other hand, American College of Obstetricians and Gynecologists[25] and Society for Maternal-Fetal Medicine,[26] recommend against routine serologic screening for CMV since there is no vaccine is available to prevent infection in seronegative women and in seropositive pregnant women, it is difficult to distinguish between primary infection, reinfection or reactivation and it is also diffucult to determine the time of the infection. Testing pregnant people for CMV is indicated if there is mononucleosis-like illnesses, if a fetal anomaly suggestive of congenital CMV infection is detected on prenatal ultrasound examination or if the patient requests the test. In a study in Japan, universal screening of pregnant women using CMV-IgG and IgG avidity identified only three of the 10 infants with congenital CMV infection.[27] There is no evidence that antiviral treatment of primary infection in pregnant women prevents sequelae of CMV infection in the newborn, so it is suggested that routine screening can lead to unnecessary, and potentially harmful, intervention. But on the other hand, some authorities think that knowing that the patient's serology is negative for CMV antibodies and CMV counseling increase some patients'motivation to practice good hygiene and thus decrease the risk of seroconversion during pregnancy.[28-30] Although the majority of the population is CMV IgG positive in our study, it is important to detect the pregnant women who are still seronegative, albeit in a small proportion, provide consultancy for protection from CMV infection throughout pregnancy.

Another important point in terms of congenital infections is to be able to determine whether the infection was during pregnancy or before. Although Toxoplasma, Rubella and CMV IgM positive and IgG negative are considered in favor of acute infection, the results should be interpreted with caution. Autoimmune diseases, RF positivity, ANA positivity, or any other viral infection may cause false IgM positivity. False positivity can be excluded by showing seroconversion within 15 days in only IgM positive pregnant women or by showing the infection in fetus with aminosynthesis. While screening during pregnancy, IgM positive and IgG negative patients are evaluated as acute infections. In our study, there were no pregnant women who wereonly IgM positive. Another confusing situation in terms of congenital infections is the situations where both IgM and IgG are positive. It is known that IgM positivity may persist for months or even years after an acute infection, or false IgM positivity may be

encountered due to the reasons mentioned above.[31] At this stage, it is of great importance to determine whether the infection detected in the pregnant woman has been acute or recently passed, and the avidity tests come into play. While high IgG avidity indicates an infection passed approximately four months ago for CMV and T.gondii infections, it is less reliable for Rubella infections due to the rapid maturation of its antibodies.[32] When the IgM positivity of 6719 pregnant women included in our study was examined, it was seen that it was 0.46% for Toxoplasma, 0.16% for Rubella and 0.7% for CMV. In similar studies conducted in pregnant women or women of childbearing age in Turkey, Toxoplasma IgM was 0.8-4.0%, Rubella IgM was 0.2-1.3% and CMV IgM was 0.4-3.2% found to be positive.[11,13-15,33,34] In our study, it was thought that the low Toxoplasma IgM positivity rate might be related to the seroprevalence of the infection, the serological method used, and the socioeconomic and geographical characteristics of the region. However, considering that some of the positive IgM results found in all studies were probably false positive, it was concluded that these rates would not fully reflect the truth.

In 37.1% of 89 pregnant women who were Toxoplasma, Rubella, CMV IgM and IgG positive, avidity tests were not performed or their results could not be reached. Of the 31 pregnant women's avidity results who were positive for Toxoplasma IgM and IgG, for 4 (12.9%) we could not reach any avidity result, 17 (54.8%) was high avidity,1 (3.2%) was grayzone, and 9 (29.0%) was low avidity. Five (45.5%) of 11 pregnant women positive for Rubella IgM and IgG did not have any avidity test result, 6 (54.5%) of them had high avidity. Of the 47 pregnant women who were CMV IgM and IgG positive, we could not reach the avidity result for 24 (51.1%) women, 22 (46.8%) were found to have high avidity and 1 (2.1%) was grayzone. Of the 9 low avidity results detected only for Toxoplasma, the clinical data of 4 could be accessed: all of them had IgM positivity in the first trimester of pregnancy, amniocentesis was not performed in any in of the patients with low avidity, there was no finding suggestive of toxoplasma infection in their fetal USG findings and three of these pregnant women were treated with spiramycin. Birth weights and APGAR scores of babies were found to be normal. In a study conducted in Switzerland, it was stated that the most common abnormal ultrasound findings in terms of TORCH infections were intrauterine growth retardation, polyhydramnios, and intrauterine fetal death.[35] With the ultrasonographic findings oravailable data of any of the pregnant women whose clinical data could be accessed, no picture that would suggest these infections was found.

In our study, since the avidity test results and clinical information of the most of the pregnant women with Toxoplasma, Rubella or CMV IgM positivity could not be reached; in patients with low avidity for Toxoplasma, the presence of these infections was not confirmed by amniocentesis and we did not have postnatal follow-up information about the babies for congenital infections, no comparison could be made regarding the accuracy of the low or high avidity test results in showing whether the infection detected in the pregnant was acute or recent. However, in light of the information in the literature, it is known that high IgG avidity indicated an infection about four months ago. In our study, high avidity was detected in 50.6% of 89 pregnant women who were positive for Toxoplasma, Rubella and CMV IgM and IgG, and acute or undergoing infection was excluded without the need for invasive interventions. Spiramycin treatment was initiated for three pregnant women who were found to have low avidity for Toxoplasma.

CONCLUSION

Screening for TORCH infections during pregnancy is still a controversial subject and there are different recommendations and practices between countries and there is no national screening programme in Turkey. The frequency of these infections varies between regions and countries,and knowing the seroprevalence is of great importance in establishing national screening strategies and providing consultancy to pregnant women about protection from these infections. Form this point of view our study is valuable in that it contributes to these data as the first study conducted in Balıkesir region on this subject. But of course in order to develop national screening programs more comprehensive studies are needed in Turkey.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 11.11.2020, Decision No: 2020/206).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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