Original Article / Araştırma Makalesi

COMPARISON SEROPREVALENCE OF TOXOPLASMA GONDII, RUBELLA, AND CYTOMEGALOVIRUS IN MUŞ PROVINCE BEFORE AND DURING THE COVID-19 PANDEMİC

Muş İlinde Covid-19 Pandemisi Öncesi ve Sürecinde Toxoplasma Gondii, Rubella ve Sitomegalovirüs Seroprevalansının Karşılaştırılması

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ABSTRACT

The aim of this study is to determine the seroprevalence of *Toxoplasma gondii (T. gondii)*, rubella and cytomegalovirus (CMV) and the primary infection rates of these agents with avidity test in pregnant women in Muş province. Additionally, the effect of prevention and protection measures implemented during the Covid-19 pandemic on the prevalence of T. gondii, rubella and CMV in pregnant women was also investigated. Between 2018 and 2021, IgG and IgM antibodies in the serum samples of pregnant women who applied to the Department of Gynecology and Obstetrics polyclinic of Muş State Hospital were examined by enzyme-linked immunosorbent assay (ELISA) and chemiluminescence immunoassay (CLIA). High and low avidity assays were examined by enzyme linked fluorescence assay (ELFA). Low seroprevalence of T. gondii IgG antibody (28%) and the detection of low avidity detection in 38 of 102 pregnant women indicate that this parasite may be a risk for intrauterine life. Rubella IgG (89%) and CMV IgG (99%) antibodies were found to carry a low risk due to their high seroprevalence and avidity. It was determined that Covid-19 prevention and protection measures caused a significant decrease in the prevalence of rubella and CMV, but had no effect on the prevalence of T.*gondii.*

Keywords: Covid-19, Cytomegalovirus, Rubella, Seroprevalence, *Toxoplasma gondii.*

ÖZ

Bu çalışmanın amacı Muş ilindeki gebelerde *Toksoplazma gondii* (*T. gondii*), rubella ve sitomegalovirüs (CMV) seroprevalansını ve avidite testi ile bu etkenlerin primer infeksiyon oranlarını belirlemektir. Ek olarak, Covid-19 pandemisi sırasında uygulanan önlem ve koruma tedbirlerinin hamile kadınlarda T. gondii, rubella ve CMV prevalansına etkisi de araştırıldı. 2018-2021 yılları arasında, Muş Devlet Hastanesi Kadın Hastalıkları ve Doğum polikliniğine başvuran gebelerin serum örneklerinden IgG ve IgM antikor düzeyleri enzim bağlı immünosorbent tahlili (ELISA) ve kemilüminesans immünolojik tahlili (CLIA) ile incelendi. Yüksek ve düşük avidite testleri, enzim bağlantılı floresans tahlili (ELFA) ile incelendi. Gebelerde *T. gondii* IgG antikorunun (%28) seroprevalansının düşük olması ve 102 gebenin 38'inde düşük avidite tespiti bu parazitin intrauterin hayat için risk oluşturabileceğini göstermektedir. Rubella IgG (%89) ve CMV IgG (%99) antikorlarının seroprevalansının ve de aviditesinin yüksek olmasından dolayı düşük oranda risk taşıdığı saptandı. Covid-19 önlem ve koruma tedbirlerinin rubella ve CMV prevalansında anlamlı bir azalmaya neden olduğu ancak *T.gondii* prevalansına etkisi olmadığı belirlendi.

Anahtar kelimeler: Covid-19, Sitomegalovirüs, Rubella, Seroprevalans, *Toxoplasma gondii*.

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INTRODUCTION

Congenital infections are one of the most important causes of perinatal morbidity and mortality, especially in developing countries (Aynıoğlu, Aynıoğlı & Altunok, 2015). Due to the temporary immunosuppression that occurs during pregnancy, pregnant women's defense against various infectious agents is inadequate (Parlak et al., 2015; Sebastian, Zuhara& Sekaran, 2008). Among the infectious agents, *T. gondii*, rubella, and CMV are factors that can cause congenital malformations, recurrent miscarriages, premature births, and stillbirths during pregnancy (Parlak et al., 2015; Sharma et al., 2015). *T. gondi* acquired during pregnancy can have effects including fetal death and hydrocephalus, microcephaly, cerebral calcification, jaundice, chorioretinitis, microphthalmia, and hepatosplenomegaly. In addition to fetal death, Rubella can cause clinical conditions such as hepatomegaly, jaundice, cataracts, hearing loss, microcephaly, and congenital heart malformations, especially seen in the first trimester of pregnancy. Although CMV is the viral agent most commonly associated with congenital infections, it may cause effects on the fetus such as mental retardation, chorioretinitis, or cerebral calcifications (Feldman, Timms & Borgida, 2010).

In pregnant women, prenatal diagnosis of *T. gondii*, rubella, and CMV can be made with serological tests including IgG, IgM, and IgG avidity tests (Chiopris et al., 2020; Mendelson et al., 2006). Although *T. gondii*, rubella, and CMV IgM levels indicate primary infection, they do not always mean the same (Mendelson et al., 2006). In addition, since pregnant women are often asymptomatic and have false IgM positivity during pregnancy, IgG avidity testing is recommended to distinguish acute, recurrent, or past infections. Avidity values have been shown to be effective in differentiating between primary and secondary infections when IgG+ and IgM+ antibodies are determined together in the first trimester of pregnancy(Liesenfeld et al., 1997). If maternal blood is IgM and IgG positive, the next step is to perform an IgG avidity test on the same blood sample to estimate the time of infection. A low avidity index indicates a recent infection, while a high index indicates a past or recurrent infection (Mendelson et al., 2006).

The determination of the seroprevalence of *T. gondii*, rubella, and CMV provides important data for establishing national screening strategies. The differentiation of these infections as primary or secondary by the IgG avidity test prevents unnecessary abortions in secondary infections, while primary infections pose a risk to intrauterine life and determines the necessary medical treatment. For this purpose, in our study, the seroprevalence of *T. gondii*, rubella, and cytomegalovirus antibodies and low and high IgG avidity test results were

determined retrospectively in pregnant women in Muş province. In order to prevent the spread of these infections in pregnant women, educating them and taking precautionary measures are of vital importance for intrauterine life. To determine the effectiveness of precautionary measures applied during Covid-19, the seroprevalence rates of IgG and IgM antibodies before and during the pandemic period were compared.

MATERIAL AND METHOD

Objective and Type

An analytical and retrospective investigation was conducted to determine the seroprevalence of *T. gondii*, rubella, and CMV as well as whether Covid-19 restrictions prevented the spread of these infections in pregnant women who applied to the department Mus State Hospital Obstetrics and Gynecology Clinic between January 1, 2018, and January 1, 2022.

Laboratory Analysis

Serum separated after centrifugation from blood samples of pregnant women was analyzed by enzyme-linked immunosorbent assay (ELISA) (Cobas 6000 E601, Roche, Germany) and chemiluminescence immunoassay (CLIA) at the Microbiology Centre Laboratory of Muş State Hospital. The kits' instructions were followed in order to determine the reference values. Pregnant women who tested positive for *T. gondii,* rubella, and CMV IgG+ and IgM+ between 2018 and 2021 underwent avidity testing utilizing the VIDAS (BioMérieux, France) instrument with the Enzyme-Linked Fluorescent Assay (ELFA) in in a contracted external laboratory. Avidity tests were evaluated as high and low according to the threshold values specified in the instructions of the kits used. While positive test results were included, uncertain (gray zone) test results that fell between the limit values were not included in the study.

Collection and Analysis of Data

In the analysis of the data, IgG and IgM serological test results were examined based on the positivity rate of the tests for the detection of seroprevalence, which was expressed as a percentage (%). In patients with both IgG+ and IgM+ positive results, IgG avidity test results were evaluated as high or low. The number of pregnant women with low IgG avidity was determined, and seroprevalence rates before and during Covid-19 were determined to assess the effect of preventive measures. Statistical analyses were performed using the chi-squared test in SPSS 25, and values with $p<0.05$ were considered statistically significant.

Ethics

This study has been approved by the Scientific Research and Publication Ethics Committee of Muş Alparslan University (approval date: 12.10.2022, approval number: 41).

RESULTS

During the period from January 1, 2018 to January 1, 2021, the incidence of avidity testing in seropositive pregnant women was examined, considering both high and low values. Additionally, IgG and IgM antibody levels were determined from 10 April 2018 to 1 July 2019 (before the Covid-19 pandemic) and from 10 April 2020 to 1 July 2021 (during the pandemic). The SPSS 25 statistical package program was used to evaluate IgG and IgM antibody results before and during the pandemic, aiming to determine the significance level of Covid-19 prevention measures in preventing the spread of these agents.

In 10501 serum samples from pregnant women, 3002 (28.5%) tested positive for *T. gondii* IgG. 10400 serum samples showed 81 (0.7%) cases of *T. gondii* IgM, 9166 serum samples revealed 8213 (89.6%) cases of rubella IgG, 10494 serum samples showed 247 (2.3%) cases of rubella IgM, and 9773 serum samples indicated that 9757 (99.8%) were positive for CMV IgG. Additionally, among 10565 serum samples, 105 (0.9%) were positive for CMV IgM (Table 1).

Table 1. Seropositive Seroprevalence of IgG and IgM Antibodies Against *T. Gondii*, Rubella, and CMV Agents Among Pregnant Women

ELISA Tests	Total Number of Pregnant Women (n)	Seropositive Pregnant Women(n)	Seronegative Pregnant Women (n)	Seropositive Seroprevalence (%)
T.gondii IgG	10501	3002	7499	28.5
T.gondii IgM	10400	81	10319	0.7
Rubella IgG	9166	8213	953	89.6
Rubella IgM	10494	247	10247	2.3
CMV IgG	9773	9757	16	99.8
CMV IgM	10565	105	10565	0.9

Among 278 pregnant women, 102, 68, and 108 individuals were screened for *T. gondii* IgG, rubella IgG and CMV IgG avidity tests, respectively. It was determined that *T. gondii* IgG avidity was negative for 1 pregnant woman, high for 64 pregnant women, and low for 38 pregnant women. It also had high rubella IgG avidity for 66, and low avidity for 2 women. However, CMV IgG was determined to have high avidity for all screened individuals (Table 2).

Table 2. Results of *T.gondii* IgG avidity, Rubella IgG avidity, and CMV IgG avidity tests in 278 pregnant women between January 2018 and January 1, 2021.

Avidity Tests	The number of avidity in pregnant	High Positive	Low Positive	Negative
T.gondii IgG avidity	102	64	38	1
Rubella IgG avidity	68	66	2	-
CMV IgG avidity	108	108	-	-

We also evaluated the seroprevalence of IgG and IgM antibodies against *T. gondii*, rubella, and CMV before and during Covid-19. Between April 10, 2018 and July 1, 2019 (before Covid-19), it was determined that 659 (26%) and 17 (0.7%) pregnant women were seropositive in terms of T. gondii IgG and IgM among 2444 and 2424 patients, respectively. It was also found that rubella IgG was positive in 848 (89%) pregnant women among 950 women, and the number of IgM positive women was 35 (1.4%) among 2428 pregnant women. In addition, CMV seropositivity was detected in all (100%) of 1844 pregnant women, and IgM seropositivity was detected in 43 (1.7%) of 2429 pregnant women (Table 3).

Between 10 April 2020 and 1 July 2021 (during Covid-19), 1247 (27%) and 42 (0.9%) pregnant women were found to be seropositive for *T. gondii* IgG and IgM, respectively, among 4523 and 4519 pregnant women. Rubella IgG was also found to be positive in 4053 (89%) of the 4532 pregnant women and IgM positive in 39 (0.8%) of the 4525 pregnant women. In addition, CMV seropositivity was detected in 4525 (99%) of 4533 pregnant women and IgM seropositivity in 4332 (0.6%) of 4530 pregnant women (Table 3). The significance level of the preventive measures in the spread of agents was determined based on the pre-pandemic and during pandemic IgG and IgM seropositive antibody data. When comparing pre-pandemic and pandemic IgG and IgM antibody levels, a significant decrease was observed in rubella IgG ($p=0.000$), IgM ($p=0.027$), CMV IgG ($p=0.018$), and IgM ($p=0.000$). However, no significant difference was observed in *T. gondii* IgG ($p=0.697$) and IgM ($p=0.319$) (Table 3).

Table 3. Seropositive Seroprevalence of IgG and IgM Antibodies Against *T. gondii*, Rubella, and CMV Agents Before and During Covid-19.

ELISA Tests	Covid-19 Pre-pandemic			Covid-19 Pandemic process			Chi-square Results	
	Total number of pregnant (n)	Seropositive Pregnant Women (n)	Seropositive Seroprevalence (%)	Total number of pregnant (n)	Seropositive Seroprevalence (n)	Seropositive Seroprevalence (%)	χ2	Asymp. Sig. (*p*)
T.gondii IgG	2444	659	26	4523	1247	27	0.151	0.697
T.gondii IgM	2463	21	0.7	4689	42	0.9	0,993	0.319

Rubella IgG	950	848	89	4532	4053	89	622.9	0.000
Rubella IgM	2428	35	1.4	4594	42	0.8	4.999	0.027
CMV IgG	1844	1844	100	4533	4525	99	5.645	0.018
CMV IgM	2429	43	1.7	4530	4053	0.6	16.43	0.000

DISCUSSION

CMV infection is the most common congenital infection worldwide, with rates ranging from 0.2 to 2% of live births (Diogo et al., 2020). Toxoplasmosis is the second most common congenital infection after CMV, with a prevalence ranging from 0.1 to 1 per 1000 live births in endemic countries (Züber & Jacquier, 1995). Rubella is also among the leading causes of birth defects (Çopur Çiçek et al., 2012). For this reason, pregnant women are widely screened for *T. gondii*, rubella, and CMV both in the embryonic and fetal periods. Considering both their prevalence and cost, serological screening of these agents is still controversial among researchers. Evaluating the *T. gondii*, rubella, and CMV seropositivity and seroprevalence rates in a particular area is essential for making screening decisions (Çopur Çiçek et al., 2012). The goal of the study was to determine whether the precautions taken during COVİD-19 had any effect on the transmission of T. gondii, Rubella, and CMV among expectant mothers.

Anti-*T.gondii* IgG positivity was found in the range of 18.3–37% in previous studies conducted in various regions of Turkey, including Edirne (Varol, Sayın & Soysüren, 2011), Afyon (Aşık et al., 2013), Van (Efe & Kurdoglu, 2009; Parlak et al., 2015), Uşak (Doğan Toklu, 2013), Çanakkale (Gencer et al., 2014), Kayseri (Kayman & Kayman, 2010), Yozgat (Kiriş Satılmış, 2014), Artvin (Inci, Yener & Güven, 2014), İzmir (Sirin et al., 2017), İstanbul (Alaçam et al., 2020) and Konya (Ezer et al.,2023). The positivity rate for anti-*T. gondii* IgG detected in our study was found to be compatible with these cities. However, anti-*T. gondii* IgG positivity was detected as 60.4%, 52.1%, 48.4%, 48.3%, 47.1%, and 43.9% in Şanlıurfa (Harma et al., 2004), Hatay (Ocak et al., 2007), Adıyaman (Kölgelier et al., 2009), Kocaeli (Sonmez, Dundar & Caliskan, 2009), Kahramanmaraş (Bakacak et al, 2014) and Zonguldak (Aynıoğlu, Aynıoğlı & Altunok, 2015), respectively but a lower positivity was obtained in our study. Anti-*T.gondii* IgM positivity has been found in the range of 0.2-3% in various studies conducted in our country (Alaçam et al., 2020; Aşık et al., 2013; Aynıoğlu, Aynıoğlı & Altunok, 2015; Bakacak et al., 2014; Dündar, 2009; Doğan Toklu, 2013; Efe & Kurdoglu, 2009; Gencer et al., 2014; Gonca, Serin, Halepliler & Erden Ertürk, 2019; Harma et al., 2004; Inci, Yener &

Güven, 2014; Kayman & Kayman, 2010; Kiriş Satılmış, 2014; Ocak et al., 2007; Sirin et al., 2017; Sonmez Tamer, Dundar & Caliskan, 2009; Varol, Sayın & Soysüren, 2011). However, our results revealed that anti-*T.gondii* IgM positivity was lower at 0.7% compared with previous studies. Based on the results of meta-analysis research on *T. gondii* seroprevalence over the previous 30 years, anti-*T. gondii* IgG and IgM seroprevalence were found to be 36.76% and 2.91%, respectively, in our nation in 2022 (Demiray et al., 2022). On the other hand, anti-*T. gondii* positivity was found to be 28.5% for IgG and 0.7% for IgM in our study (Table 1).

Studies carried out in different parts of our country have found anti-rubella IgG positivity in the range of 89.1-98.13%, and our results are consistent with previous studies, which have found a rate of 89.6% (Table 1) (Alaçam et al., 2020; Aşık et al., 2013; Aynıoğlu, Aynıoğlı & Altunok, 2015; Bakacak et al, 2014; Ezer et al., 2023; Doğan Toklu, 2013; Dündar, 2009; Gonca, Serin, Halepliler & Erden Ertürk, 2019; Inci, Yener & Güven, 2014; Kiriş Satılmış, 2014; Ocak et al., 2007; Sirin et al., 2017; Sonmez, Dundar & Caliskan, 2009). Several studies conducted in our country have reported a positivity rate for anti-rubella IgM ranging from 0 to 1.9%; however, our study yielded a higher positivity rate of 2.8% (Table 1) (Aynıoğlu, Aynıoğlı & Altunok, 2015; Aşık et al., 2013; Ezer et al., 2023; Efe & Kurdoglu, 2009; Gonca, Serin, Halepliler & Erden Ertürk, 2019; Harma et al., 2004; Inci, Yener & Güven, 2014; Kiriş Satılmış, 2014; Körkoca & Berktaş, 2021; Sirin et al., 2017; Kölgelier et al., 2009; Sonmez, Dundar & Caliskan, 2009; Varol, Sayın & Soysüren, 2011;). Furthermore, studies conducted in our country have reported anti-CMV IgM positivity rates varying from 1 to 2%; our investigation showed lower results, at 0.9%. (Aynıoğlu, Aynıoğlı & Altunok, 2015; Doğan Toklu, 2013; Varol, Sayın & Soysüren, 2011; Inci, Yener & Güven, 2014; Sirin et al., 2017; Ezer et al., 2023). Another study reported positivity rates of 0.2-3.7% for anti-CMV IgM and 87.8-100% for anti-CMV IgG, similar to our study (Table 1) (Çetinkaya & Yenilmez, 2019).

We also evaluated the *T.gondii*, rubella and CMV specific IgG avidity test, which is an essential tool to help date the infection. Of the 102 pregnant women, 64 had a high avidity score, and 38 had a low avidity result (Tables 1 and 2). These results indicate that the low *T. gondii* seropositive IgG prevalence rate (28%) and *T.gondii* IgG avidity test results in 38 pregnant women may threaten pregnancy and intrauterine life. Of the 68 pregnant women who took part in the rubella IgG avidity test, 66 had high results and 2 had low findings. Among the 108 pregnant women who took the CMV IgG avidity test, all of them had high results.

In Muş province, the *T.gondii* positive seroprevalence rate in pregnant women is 28% for IgG and 0.7% for IgM. It was determined that 64 pregnant women were high and 38 pregnant

women were low in *T.gondii* IgG avidity tests (Tables 1 and 2). The low *T. gondii* seropositive IgG prevalence rate (28%) and the *T.gondii* IgG avidity test result in 38 pregnant women may threaten pregnancy and intrauterine life. It was also determined that rubella IgG was 89%, IgM was 2.3%, CMV IgG was 99%, and IgM was 0.9%. Among the 68 screened pregnant women, the rubella IgG avidity test results were high in 66 pregnant women and low in 2 pregnant women, and in CMV IgG avidity tests, it was high in all 108 pregnant women (Tables 1 and 2). Our results suggest that the risk of intrauterine life for CMV and rubella is low in accordance with these values.

In order to determine the effect of the precautionary measures implemented during Covid-19, IgG and IgM seropositive serum results before and during Covid-19 were compared. Our results showed that there is no statistically significant difference between seropositive IgG (p=0.697) and IgM (p=0.319) for *T. gondii*, but there are significant differences between rubella IgG (p=0.000), IgM (p= 0.027) and CMV IgG (p=0.018), IgM (p= 0.000) (Table 3). However it should be noted that, this study's primary limitation is that it is a retrospective, single-center study. The size of the study should be taken into consideration when extrapolating the results to a broader community, in spite of the relatively high number of patients involved in the research. Nonetheless, it is noteworthy that the results reported here correlate with the experiences of other medical centers in Turkey.

In conclusion, as *T. gondii* and its cysts are transmitted by eating undercooked meat, water, or food contaminated with oocysts excreted in cat feces, Covid-19 prevention measures are not effective in preventing the spread of *T. gondii*. However, since rubella and CMV are transmitted to the susceptible host by infected droplets from the upper respiratory mucosa, precautionary measures such as masks, social distance, and semi- and full-closure significantly reduce the spread of these infections. But despite the extraordinary precautionary measures of Covid-19, it was determined that they could not completely prevent the spread of rubella and CMV.

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