Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Antenatal Toxoplasma Gondii, Rubella and Cytomegalovirus Infection Screening Among Pregnant Women Attending Tertiary University Hospital

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ABSTRACT

OBJECTIVE: The present study was designed to determine the seroprevalence of *Toxoplasma gondii, Rubella*, and *Cytomegalovirus*, to investigate the frequency of low and high avidity results among pregnant women and to contribute to the data of our country with the results obtained.

STUDY DESIGN: In the present study, the hospital records of the women who applied to the antenatal outpatient of the Rize Recep Tayyip Erdogan University Medical Faculty during the first trimester between January 2016 and October 2018 were retrospectively reviewed. *Toxoplasma gondii, RRubella* and *Cytomegalovirus* IgM, IgG and IgG avidity results were evaluated.

RESULT: IgM positivity was found to be 0.83% (29/3490) for *Toxoplasma gondii,* 0.92% (32/3459) for *Rubella* and 1.90% (65/3404) for *Cytomegalovirus*; IgG positivity was found to be 33.64% (1174/3490) for *Toxoplasma gondii,* 90.70% for *Rubella* (3140/3459), and 99.17% (3376/3404) for *Cytomegalovirus*. Avidity of *Toxoplasma gondii* was found to be low (3.70%) in 1 patient, borderline (11.11%) in 3 patients, and high avidity in 23 patients (85.18%). Avidity of *Cytomegalovirus* was found to be low (1.75%) in 1 patient, borderline (3.50%) in 2 patients and high avidity (94.73%) in 54 patients. Avidity of *Rubella* was found to be low (4%) in 1 patient, and high avidity (96%) was found in 24 patients.

CONCLUSIONS: In our study, although the prevalence of acute infection with *Rubella*, *Cytomegalovirus* and *Toxoplasma gondii* was shown to be low in pregnancy in Rize province, serological screening tests for monitoring and informing high-risk groups that are particularly seronegative appear to be important.

Keywords: *Cytomegalovirus*, Pregnancy, *Rubella*, Seroprevalence,*Toxoplasma*

Introduction

Perinatal infections are diseases which may result in congenital infections and they may be one of the most important causes of perinatal mortality and morbidity, although the severity of them varies according to the maternal immunity and gestational week. The most common perinatal infections are *Toxoplasma gondii*, *Rubella* and *Cytomegalovirus* (CMV) infections, which are included in TORCH group diseases. Infection agents that are shown to be associated with congenital malformation, abortion, premature birth, mental retardation, and stillbirth, can pass through mother by the transplacental way, poor hygiene, contaminated blood, water, soil and respiratory tract (1). Studies have shown that the management of perinatal infections in the antenatal period has not yet been fully standardized and that the algorithms applied for prevention or treatment do not prevent poor pregnancy outcomes (2).

Cytomegalovirus is one of the most detected perinatal infectious agents with a frequency of 0.2-2.5% in newborns. The fetus may be affected by both primary and secondary infections of CMV. The antibodies of the mother cannot prevent reactivation or reinfection of CMV. Ninety percent of the primary infections and most of the secondary infections of mothers are asymptomatic. Mononucleosis-like syndrome with prolonged fever and lymphadenopathy, nausea, myalgia, and hepatitis may be seen in symptomatic patients. The vertical transition is 30-50% after primary infection and is less than 1% after secondary infections. Most of the newborns are in-

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fected primarily during pregnancy and almost all those infected with secondary infection are initially asymptomatic. In addition, the perinatal infections caused by CMV may lead to diseases that may result in severe sequelae such as optic atrophy, microcephaly, hypotonia, intracranial calcifications, sensorineural hearing loss, pneumopathy, thrombocytopenia with 5% mortality in the following months (3).

Rubella is one of the most important teratogenic viruses. Despite the vaccination programs implemented with the recommendations of the World Health Organization, it has not been completely eradicated. The risk of infection is 10-54% for the fetus if mother is infected with *Rubella* in the first three months of pregnancy (4). It may be asymptomatic in the newborn or may result in poor pregnancy outcomes such as abortion, preterm birth, stillbirth, and congenital malformations including deafness, blindness, cataract, microcephaly and heart diseases (5).

Toxoplasma gondii is a mandatory intracellular parasite that can cause infection in humans and many mammals. Most pregnant women infected with *Toxoplasma gondii* are asymptomatic. When symptoms occur, there may be nonspecific findings such as headache, fever, fatigue and muscle pain in pregnant women (6). In 10-15% of infected newborns, there are significant findings including skull and encephalic anomalies, neurological diseases, hydrocephalus, microcephaly, cerebral calcifications, chorioretinitis, and microphthalmia. Only 5% suffer from severe complications such as thrombocytopenia, anemia, jaundice, and hepatomegaly (3).

Early diagnosis of perinatal infections in both mother and fetus is an important component of prenatal follow-up. Since maternal infections are initially asymptomatic, clinical findings are not reliable. The diagnosis of acute infection in pregnant women is usually based on serological tests such as specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, which are screened during routine screening. In the detection of IgM and IgG antibodies, "Enzyme-linked immunosorbent assay (ELISA)" and "Enzyme immunoassay (EIA)" are the most sensitive and precise methods in diagnosis (7). Avidity indicates the aggregation power of the antibody to a specific antigen. IgG avidity plays a role in the investigation of whether the infection is acute, chronic or recurrent. In the presence of low avidity, the risk of intrauterine transition is high, while high avidity means a low risk of fetal infection. Borderline avidity is also thought to be important for the fetal transition. It is recommended to manage the cases with borderline avidity in the first trimester as high avidity and to be interpreted and followed as low avidity in the second and third trimester. In this low avidity cases, the parents should also be informed about complications (8). If serological tests show acute infection or suspicious ultrasonographic markers are detected, a definitive diagnosis of infection in the fetus is necessary. In these suspected cases, the pathogen is investigated by polymerase chain reaction (PCR) in the amniotic fluid with amniocentesis.

Discussions on the routine screening of TORCH group infections during pregnancy still continue. The low prevalence of perinatal infections, the positive retention of serological tests in the latent phase, the risk of re-infection, low treatment success, and the cost of tests are the main reasons for the debate on routine screening. In high prevalence, it is recommended to continue screening in the region where the disease is seen. Therefore, it is decided whether or not perinatal infections will be screened as a part of routine antenatal care in a region, according to the results of the disease's seroprevalence.

This study in Rize province in the eastern Black Sea region of Turkey was carried out on women who applied for pregnancy follow-up to the tertiary university hospital.

The study aims to investigate the seroprevalence of *Toxoplasma gondii*, *Rubella*, and CMV, to investigate the frequency of low and high avidity results and to contribute to the data of our country with the results obtained.

Material and Method

In this study, the hospital records of the women who applied to the antenatal outpatient of the Department of Obstetrics, Recep Tayyip Erdogan University School of Medicine, Rize, Turkey, between January 2016 and October 2018 were retrospectively reviewed.

The study meets the ethical guidelines, including adherence to the World Medical Association's Declaration of Helsinki. Approval was obtained from Recep Tayyip Erdogan University Ethics Committee of Non-invasive Clinical Trials (No:2018/163). Administrative approval was consented for using data.

IgM, IgG, and IgG avidity results of *Toxoplasma gondii*, *Rubella* and CMV were recorded. Only patients with both IgM and IgG results were included in the study.

In serum samples taken from pregnant women, immunoglobulin analyzes were performed on the automatic Abbott i1000SR device (Abbott Diagnostics, USA) by chemiluminescent immunoassay method and avidity analyzes were performed by VIDAS (bioMerieux, France). All positive and borderline IgM results were double checked.

Antibody titers were considered to be positive for *Toxoplasma* IgM at a dose of 0.5 mg/dL and for *Toxoplasma* IgG 1.6 mg/dL and above. For the *Rubella* IgM, 1.2 mg/dL and for *Rubella* IgG 10.0 mg/dL and above were considered positive. For CMV IgM values of 0.85 and for CMV IgG 6.0 mg/dL and above were considered positive. *Toxoplasma gondii*, *Rubella*, CMV IgG avidity results were interpreted as <30% low, 30% borderline or 40% high avidity according to the manufacturer's recommendations.

According to the results of blood samples taken from pregnant women, it was defined as primary infection if low IgG avidity or low IgG seroconversion was detected in the presence of specific IgM positivity for *Rubella* and *Toxoplasma gondii*. In the presence of specific IgM positivity for CMV, low IgG avidity or low IgG seroconversion were identified as primary infection.

In cases where CMV IgM positivity is associated with high IgG avidity, it can't be understood whether the perinatal infection is reinfection or reactivation.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 (SPSS, Chicago, IL, USA). Data were presented with the number and percentage of patients. In the evaluation of data, numbers and percentages were used as descriptive statistical methods.

Results

The data of pregnant women who applied to the outpatient clinic in the first trimester between January 2016 and October 2018 were analyzed retrospectively. Serological results of 3490 pregnancies for *Toxoplasma gondii*, 3459 for *Rubella* and 3404 for CMV were collected from the hospital records.

In the study, IgM positivity was found to be 0.83% (29/3490) for *Toxoplasma gondii*, 0.92% (32/3459) for *Rubella* and 1.90% (65/3404) for CMV; IgG positivity was found to be 33.64% (1174/3490) for *Toxoplasma gondii*, 90.70% for *Rubella* (3140/3459) and 99.17% (3376/3404) for CMV (Table I). Avidity test results are given in Figure 1, in cases with *Toxoplasma gondii*, CMV and *Rubella* IgM positive. In our study, IgG result was positive for all patients who were positive for *Toxoplasma gondii* IgM. *Toxoplasma gondii* avidity test was performed in 27 of 29 patients who were positive for both IgM and IgG. The results of the other two patients' hospital records could not be reached. Avidity was found to be low (3.70%) in one patient, borderline (11.11%) in three patients, and high avidity in twenty-three patients (85.18%). All patients with positive CMV IgM result had positive IgG results. CMV avidity test was used in 57 of 65 patients who were positive for both IgM and IgG. The results of the other eight patients' hospital records could not be reached. Avidity was found to be low

(1.75%) in one patient, borderline (3.50%) in two patients and high avidity (94.73%) in fifty-four patients. All patients who were positive for *Rubella* IgM were also positive for IgG. *Rubella* avidity test was used in 25 of 32 patients who were positive for both IgM and G. The results of the hospital records of the other seven patients could not be reached. Avidity was found to be low (4%) in one patient, and high avidity (96%) was found in twenty-four patients. There were no acute infections or congenital malformations in the neonates of three pregnant women who had low avidity results.
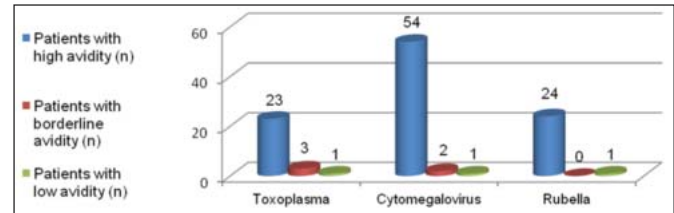
Figure 1: *Avidity test results in patients with Toxoplasma gondii, cytomegalovirus, Rubella IgM positive*

Discussion

Severe birth defects may be seen early in fetuses infected with *Toxoplasma gondii*, *Rubella* or CMV in the intrauterine life. In addition, in the age of growth, system abnormalities may develop in newborns who are initially asymptomatic. In the literature, the cost-effectiveness ratio of screening programs for perinatal infectious diseases during pregnancy is still ongoing. Due to the nature of infectious diseases, reinfection and reactivation processes cause the risks to continue to be detected in pregnant women who were initially screened and accepted as seropositive. This situation reduces the effectiveness of the negative result of the test. In addition, test results are insufficient to predict fetal and neonatal complications (9). *Rubella*, hepatitis B, HIV, and syphilis are the infectious diseases in which screening is recommended in our country. Other perinatal infectious agents should continue to be screened in areas where the disease is endemic due to poor pregnancy outcomes. Seroprevalence results are significant in understanding whether a pathogen is endemic or not. This study aimed to investigate the seroprevalence of perinatal infections with the most frequent and important results in Rize and to provide data to national screening plans. To the best of our knowledge, it is the first study in Rize that investigated the

Table I: *Toxoplasma, Cytomegalovirus, Rubella screening results in pregnant women in Rize province*

Test	Negative	Borderline	Positive	Positivity	Total
			Percentage (%)		
Toxoplasma IgM	3451	10	29	0.83	3490
Toxoplasma IgG	2146	170	1174	33.64	3490
Cytomegalovirus IgM	3304	35	65	1.90	3404
Cytomegalovirus IgG	28	0	3376	99.17	3404
Rubella IgM	3382	45	32	0.92	3459
Rubella IgG	175	144	3140	90.70	3459

seroprevalence of a microorganism in the three most frequently sees TORCH groups.

It is estimated that one-third of the world's population is infected with *Toxoplasma gondii* and that only 0.01% to 1% of newborns are affected by infection (10-13). Living conditions and quality of life, such as dietary habits, socioeconomic status, and hygiene conditions are determinant in the seroprevalence of *Toxoplasma gondii* in the community. In our country, although it varies according to the city and age group in the study, IgG positivity varies between 18.8-63% and IgM positivity varies between 0-3.7% (Table II) (14-29). In our study which was performed in Rize province, *Toxoplasma gondii* IgM seropositivity was determined as 0.83% and IgG 33.64% in pregnant women. Only one patient had low avidity rates and acute infection was not detected in this mother's newborns. Our result is consistent with other regions of our country. Agriculture and fishery are commonly performed in this region of the country because of the geographic features of the eastern Black Sea region. This may affect the attitudes of nutrition. People living in Rize consume less red meat but vegetables such as corn, cabbage, beans, and fish is widely consumed. This may be the reason why the risk of seropositivity doesn't exceed the average for the country. Although antibiotic treatment started in the early gestational week in the presence of infection decreases the transplacental fetal transition, routine *Toxoplasma gondii* screening in many countries of the world is not performed due to the low rate of acute infection in pregnancy, the inadequate efficacy of treatment and the cost of screening. However, determining the rates of seronegativity in countries with low socioeconomic status and high meat consumption, such as our country, may be important for prevention of infection in pregnancy. In particular, social awareness training about hygiene rules including washing hands upon contact with uncooked meat, avoiding of eating raw meat, flushing all vegetables and fruits and preventing contact with cat feces is recommended for childbearing age-women and pregnant who have seronegative test result.

Lack of hygiene increases the seropositivity of CMV infection in the community as well as low socio-economic level. Therefore, in the literature, wide range of seropositivity rates in different studies can be found. In China, IgM positivity was 0.5% and in France, it was found to be 4.1% (30,31). Generally, IgG seropositivity rates vary by 50-100%. When the studies performed on seropositivity in different region of Turkey were evaluated, it was observed that seropositivity for CMV IgM and IgG antibodies varied between 0.2-2.6% and 84-100%, respectively (Table II) (14-29,32). In our study, CMV IgM seropositivity rates was 1.9% which is similar to the other studies and CMV IgG seropositivity rates was 99.17% which is higher than most of the rates reported in previous studies. Such high rates are understandable when factors such as crowded living conditions, low socio-economic level, eating habits, weather conditions, poor hygienic conditions, and the inadequate infrastructure of our province are considered.

Table II: *Results of studies evaluating Rubella, Toxoplasma gondii and cytomegalovirus seroprevalences from different regions of Turkey*

Authors	District	Time interval	*Toxoplasma* seropositivity (%)		CMV seropositivity (%)		*Rubella* seropositivity %	
			IgM	IgG	IgM	IgG	IgM	IgG
Uyar et al. (14)	Samsun	2004-2005	-	-	1	97.3	1.7	94.3
Tamer et al. (15)	Kocaeli	2005-2007	0.4	48.3	0.7	96.4	0.2	96.1
Karabulut et al. (16)	Denizli	2008-2009	1.4	37	1.2	98.7	0	95.1
Dogan et al. (17)	Istanbul	2008-2013	0.8	31.4	0.8	99.3	0.2	95.7
Çeltek et al. (18)	Tokat	2009-2012	1.1	32	1.7	99.4	0.3	95.4
İnci et al. (19)	Artvin	2009-2012	1.3	30.3	1.6	98.6	0.3	95.2
Karacan et al. (20)	Istanbul	2009-2013	0.4	23.1	0.4	84	0.5	95
Nazik et al. (21)	Bingol	2011-2016	2	63	-	-	0.8	91.1
Parlak et al. (22)	Van	2012-2013	1.1	37.6	2.6	100	0.5	86.5
Bakacak et al. (23)	K.Maras	2012-2013	2.2	47.1	0.2	93.2	3.2	99.3
Aynıoğlu et al. (24)	Zonguldak	2012-2014	2.5	43.9	1.5	93.8	2	91.5
Şimşek et al. (25)	Afyon	2012-2014	1.5	23.4	2.3	96	2.5	94.5
Numan et al. (26)	Istanbul	2013-2015	0	31	0.5	99.5	0.2	94.2
Kasap et al. (27)	Mugla	2014-2015	3.7	18.8	0.3	90.4	0.8	89.5
Sirin et al. (28)	Izmir	2014-2016	1.9	32.3	1.2	93.5	1.5	98.9
Madendağ et al. (29)	Kayseri	2017-2018	1	28.9	0.2	98.2	0.59	97.3
Our study	Rize	2016-2018	0.8	33.6	1.9	98.1	0.9	90.7

To the best of our knowledge, in literature, there is only one study which conducted in eastern Black sea region in Turkey, same region with Rize. In this study which was conducted by Uyar et al. in Samsun, the rate of CMV IgM was 1% and the CMV IgG ratio was reported to be 97.3%. In another study conducted with 32188 pregnant women in Ankara province between 2008 and 2017, 62% seropositivity rates were found for CMV IgG and IgM positivity was reported as 0.22%. Most of these patients had high avidity and only one infant had signs of congenital CMV infection at the time of birth (32). In our study, only one patient had low avidity rates and acute infection was not detected in this particular newborn.

"American College of Obstetrician and Gynecologists (ACOG)" does not recommend routine screening for CMV (33). However, screening can be considered in pregnant women who describe influenza symptoms during pregnancy, have abnormal ultrasonographic findings such as microcephaly, intrauterine growth retardation, echogenic bowel, periventricular calcification, and ventriculomegaly and working with children and contacting their body fluids. Considering the re-infection, it is important to reduce the rate of CMV infection with serious pregnancy complications not only during pregnancy but also in the whole society.

Rubella is one of the most teratogenic virus causing "Congenital *Rubella* Syndrome (CRS)". In line with the goals of the World Health Organization (WHO), in some developing and developed countries, CRS has been significantly reduced, and in some regions, it has been eliminated. However, in 2010, 100,000 children with CRS were reported. WHO aims to completely eradicate the *Rubella* infection in 2020 with the vaccination programs initiated all over the world (34). In Turkey, vaccination has been in place since 1995. Since 2006, under 18 years of age have been included in the routine vaccination program. Despite vaccination programs, *Rubella* seropositivity was reported to be 71.6-98% in women of reproductive age in different countries (24). In our country, IgG positivity is between 86.5-99.3% and IgM positivity varies between 0-3.2% (Table II) (14-29). In a study conducted with 94508 pregnant women in Ankara province between 2008 and 2017, 89% seropositivity rates were found for *Rubella* IgG and IgM positivity was reported as 0.19% (35). In our study, the vaccination status of pregnant women was unknown, but seropositivity was found to be 90.7% and IgM positivity was found as 0.92%. Only one patient had low avidity rates and acute infection was not detected in this mother's newborns. The obtained seropositivity rates are similar to other studies conducted in our country, but it is far from the target of the WHO 2020. Seronegative women should be advised to have *Rubella* vaccination before pregnancy in order to prevent CRS. It's important to wait a month after getting vaccinated, for the pregnancy. In a study conducted in our country in 2009, pregnancies of 57 women who had been vaccinated with *Rubella* vaccines were followed because they did not report their pregnancies in early pregnancy period and no CRS or vaccine complications were encountered (36).

The seropositivity of *Rubella* in the first trimester during pregnancy is screened all over the world. Pregnant women with low levels of antibody or non-immunized should be informed about avoiding contact with suspected or diagnosed infected individuals. Until the whole community in Rize has fully benefited from the vaccination program, the 10% pregnancy status, still seronegative, makes it reasonable to continue screening programs.

Due to the retrospective design of our study and the inadequacies in our hospital records; living conditions, socio-economic status, dietary habits, vaccination status of pregnant women could not be recorded. The fact that we could not reach long-term neonatal outcomes in patients with suspected acute infection during pregnancy and all data were based on a single center were the other limitations.

Conclusion

In our study, although the prevalence of acute infection with *Rubella*, CMV and *Toxoplasma gondii* was shown to be low in pregnancy in Rize province, serological screening tests for monitoring and informing high-risk groups that are particularly seronegative appear to be important. The most important way to reduce mortality and morbidity of perinatal infections in the newborn is to prevent the infection. Therefore, we think that education programs and vaccination practices covering not only pregnant women but also the whole community are the most effective preventive health services.

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