Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Original Article

Is routine TORCH screening necessary for pregnancy follow-up?

Gebelikte rutin TORCH taraması gerekli midir?

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Abstract

Aim: This study aimed to determine the seroprevalence rates of Toxoplasma gondii, Rubella and Cytomegalovirus (CMV) among the pregnant women who presented to the Ümraniye Training and Research Hospital and to compare the seroprevalence rates with the other studies fromTurkey.

Material and method: The antibody levels of all pregnant women presented to the prenatal outpatient clinic between January 1, 2017 and October 30, 2019, for Toxoplasma gondii, Rubella, CMV were obtained retrospectively. Only pregnant women with immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody results of the three viruses were included in the study. If IgM and IgG were both found to be positive, the IgG avidity results were obtained using the Abbott Architect i2000 SR device with enzyme-linked immunosorbent assay (ELISA), following the manufacturer's recommendations.

Results: Serological results of pregnant women for Toxoplasma gondii (n = 7535), Rubella (n = 9093), and CMV (n = 2652) were obtained from the hospital records. IgM positivity was found to be 0.6% for Toxoplasma gondii, 0.3% for Rubella, and 2.3% for CMV. IgG positivity was found to be 24% for Toxoplasma gondii, 86.4% for Rubella, and 99% for CMV. IgG avidity test results for Toxoplasma gondii were 5.3% low, 10.5% borderline, and 84.2% high. Rubella IgG and CMV IgG avidity results were all determined following high avidity.

Conclusion: Because Toxoplasma IgG seroprevalence is not high, and the treatment of acute toxoplasmosis infection during pregnancy is possible, Toxoplasma screening should be recommended to all pregnant women. Because the immunity to the Rubella virus is still not at the desired level in our country, we believe screening against Rubella is vital during pregnancy. We also believe that routine CMV screening is unnecessary in pregnant women owing to the high seroprevalence of CMV IgG in our country.

Key words: Antenatal screening; Toxoplasma; Rubella; Cytomegalovirus

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Öz

Amaç: Ümraniye Eğitim ve Araştırma Hastanesi'nin gebe polikliniğine başvuran gebelerde Toksoplasma gondii, Rubella ve Sitomegalovirus'a karşı olan bağışıklık durumunu tespit etmek ve Türkiye'nin diğer bölgelerindeki seroprevalans oranları ile karşılaştırmaktır.

Gereç ve Yöntem: 01/01/2017- 30/10/2019 tarihleri arasında hastanemizin gebe polikliniğine başvuran tüm gebelerin Toksoplasma gondii, Rubella ve Sitomegalovirus'e karşı olan antikor düzeyleri retrospektif olarak hastane kayıtlarından çıkarıldı. Çalışmaya sadece her üç virus için IgM ve IgG antikorlarının birlikte bakıldığı gebeler dahil edildi. IgM ve IgG birlikte pozitif olduğu gebelerin varsa IgG avidite sonuclarına ulaşıldı. Bu serolojik testler enzyme-linked immunosorbent assay (ELISA) yöntemi ile Abbott Architect i2000 SR cihazında üretici firmanın önerileri doğrultusunda çalışıldı.

Bulgular: Hastane kayıtlarından Toxoplasma gondii için 7,535, Rubella için 9,093 ve CMV için 2,652 gebenin test sonuçlarına ulaşıldı. Toxoplasma gondii IgM pozitifliği %0.6, Rubella IgM pozitifliği %0,3 ve Cytomegalovirus IgM pozitifliği %2,3, Toxoplasma gondii IgG pozitifliği %24, Rubella IgG pozitifliği %86,4 ve Cytomegalovirus IgG pozitifliği %99 olarak saptandı. Toxoplasma gondii IgG Avidite test sonuçları %5,3 düşük, %10,5 sınır ve % 84,2 yüksek değer olarak saptandı. Rubella IgG ve CMV IgG avidite sonuçlarının hepsi yüksek avidite olarak tespit edildi.

Sonuç: Toksoplazma IgG seroprevalansı yüksek olmadığı için ve gebelikte geçirilen akut Toksoplazma enfeksiyonun tedavisi olduğu için gebelere Toksoplazma taraması önerilmelidir. Ülkemizde Rubella virusüne karşı bağışıklığın halen istenilen düzeyde olmamasından dolayı gebelikte Rubella virusüne karşı taramanın önemli olduğunu, CMV IgG seroprevalansının yüksek olmasından dolayı ise gebelikte rutin CMV taramasının gereksiz olduğunu düşünmekteyiz.

Anahtar kelimeler: Antenatal tarama; Toksoplazma; Rubella; Sitomegalovirus

1. Introduction

Toxoplasma gondii (T. gondii), Rubella, Cytomegalovirus (CMV), and Herpes Simplex Virus (HSV) are grouped under TORCH infections. These are infections in which similar clinical symptoms are observed, be vertically transmitted, and can result in fetal morbidity and mortality (1,2). There is currently no clear consensus on the routine screening of TORCH infections during pregnancy. HSV screening is not recommended in pregnant women because there is no evidence that HSV screening would effectively reduce the incidence of fetal infection (3). Toxoplasmosis, which is a widespread disease around the world and in our country, is mostly asymptomatic. Symptoms such as headache, fever, fatigue, and muscle pain are rare (4). Although T. gondii causes ventriculomegaly, intracranial and intrahepatic calcifications, hepatomegaly, acid, pleural effusion in the fetus, and increased thickness in the placenta during the intrauterine period, it may also cause hydrocephaly, motor intellectual disability, seizure, hearing and vision loss, hepatosplenomegaly, anemia, thrombocytopenia, and even death in newborns (5).

In cases of Rubella infection in pregnant women, the risk of fetal infection has been observed to be between 10% and 54%. Congenital Rubella infections demonstrate a broad spectrum, ranging from asymptomatic findings to premature birth, stillbirth, cataract, blindness, deafness, microcephaly, and heart diseases known as congenital rubella syndrome (6,7).

Congenital CMV infections generally occur when a woman is infected with CMV during pregnancy or shortly before conceiving. The fetus may be affected by either primary (30%) or recurrent (50%) CMV infection, with a vertical transmission rate of less than 1%. Intrauterine growth retardation, polyhydramniosis, pericardial and pleural effusion, ventriculomegaly, hydrocephaly, and intracranial and placental calcifications can be seen in affected fetuses. Congenital CMV infections may result in severe sequelae such as microcephaly, optic atrophy, sensorineural hearing loss, pneumopathy, and thrombocytopenia in newborns (8,9).

Routine TORCH screening during pregnancy remains a controversial issue. In this study, we aimed to investigate the seroprevalence rates of T. gondii, Rubella, and CMV among pregnant women who presented to the Umraniye Training and Research Hospital's outpatient clinic and to compare our results with those of previous studies in Turkey.

2. Material and Method

Antibody levels for T. gondii, Rubella, and CMV of pregnant women who presented to the Ümraniye Training and Research Hospital prenatal outpatient clinic for the first time in their first

or second trimester between January 1, 2017, and October 30, 2019, were retrospectively screened using hospital records. This study was conducted in compliance with the Helsinki Declaration of the World Medical Association's ethical rules and was approved by the Local Ethics Committee of Umraniye Training and Research Hospital (No: B.10.1.TKH.4.34.H.G. P.0.01/204).

Only patients with Immunoglobulin M (IgM) and Immunoglobulin G (IgG) results for T. gondii, Rubella, and CMV were included in the study. Besides, IgG avidity results were recorded for patients who were positive for IgM and IgG. Samples obtained from pregnant women were screened with an Abbott Architect i2000 SR device using an enzyme-linked immunosorbent assay method (ELISA), following the manufacturer's recommendations.

Index values lower than the 0.5 for Toxoplasma IgM are negative, values between 0.5 and 0.6 are borderline, and values of 0.6 and greater are positive. For Toxoplasma IgG, values lower than 1.6 IU/ml are negative, values between 1.6 and 3.0 IU/ml are borderline, and values of 3.0 IU/ml and more significant are positive. For Rubella IgM, values lower than 1.2 are negative, values between 1.2 and 1.6 are borderline, and values greater than 1.6 are positive. For Rubella IgG, values lower than 5 IU/ml are negative, values between 5 and 10 IU/ml are borderline, and 10 IU/ml and greater are positive. For CMV IgM, values lower than 0.84 are negative, values between 0.85 and 0.99 are borderline, and values greater than 0.99 are positive. For CMV IgG, values lower than 5.99 AU/ml are considered negative and values of 6 AU/ml and greater are considered positive. In our hospital, no borderline value is given for CMV IgG. All positive and borderline IgM results were checked twice. T. gondii, Rubella, and CMV IgG avidity results were interpreted as low (<20%), borderline (20%–30%), or high (30%) avidity, following the manufacturer's recommendations.

Primary infection of T. gondii, Rubella, and CMV was identified if IgG was negative and IgM was positive, low IgG levels and low IgG avidity, or positive specific IgM. Previous T. gondii, Rubella, and CMV infections, postvaccination immunity for Rubella were identified with IgG positivity and IgM negativity.

Statistical Analysis

The data were analyzed using Microsoft Office Excel 2016. Variable frequencies and rates of descriptive statistical methods were used to evaluate the study data.

3. Results

The data of pregnant women presented to the Umraniye Training and Research Hospital prenatal outpatient clinic during their first and second trimester between January 2017, and October 2019 were analyzed retrospectively. Serological results were obtained from the hospital records of pregnant women for T. gondii (n = 7535), Rubella (n = 9093), and CMV (n = 2652). The most recent results were compared with previous blood results of the same patient. In our study, IgM positivity was found to be 0.6% (48 of 7535) for T. gondii, 0.3% (23 of 9093) for rubella, and 2.3% (61 of 2652) for CMV. IgG positivity was found to be 24% (1806 of 7535) for T. gondii, 86.4% (7857 of 9093) for rubella, and 99.0% (2626 of 2652) for CMV **(Table 1)**.

Table 1. Toxoplasma, Rubella, Cytomegalovirus screening results

Test	Positive n (%)	Borderline n (%)	Negative n (%)	Total
Toxoplasma Ig M	48 (0.6)	12 (0.2)	7475 (99.2)	7535
Toxoplasma Ig G	1806 (24)	180 (2.4)	5549 (73.6)	7535
Rubella IgM	23 (0.3)	11 (0.1)	9059 (99.6)	9093
Rubella IgG	7857 (86.4)	633 (7.0)	603 (6.6)	9093
CMV Ig M	61 (2.3)	14 (0.5)	2577 (97.2)	2652
CMV Ig G	2626 (99.0)	0	26 (1.0)	2652

The number of patients with both Toxoplasma IgM and IgG positivity was 46. Among these 46 patients, only 19 were investigated for IgG avidity. Of these 19 patients, 16 were found to have high IgG avidity, two were found to have borderline IgG avidity, and one was found to have low IgG avidity. Patients with low and borderline IgG avidity were considered to have acute Toxoplasma infection and received spiramycin treatment until delivery. One patient was found to have a positive toxoplasma IgM result and negative IgG result. Another was found to have a positive IgM result and borderline IgG result. These two patients received spiramycin treatment until delivery. Antibody titer was not monitored, and the subsequent toxoplasma IgG antibody status was not investigated in patients who received spiramycin treatment. Amniocentesis was not performed in any patient for toxoplasma polymerase chain reaction. No congenital infection or congenital anomaly was noted newborns' records after birth for the patients who received spiramycin treatment.

The number of patients with both Rubella IgM and IgG positivity was 22. Only 6 of these patients were examined for IgG avidity, all of whom were found to have high avidity. The remaining 16 patients were not examined for IgG avidity. There were no patients with positive Rubella IgM results and negative IgG results. There was one patient whose rubella IgM result was positive and the IgG result was borderline. When the newborn was examined, no congenital infection or congenital anomaly was detected in the baby.

The number of patients with both CMV IgM and IgG positivity was 61. Only 20 of these patients were examined for IgG avidity; all of whom were found to have high avidity. The remaining patients were not examined for CMV IgG avidity. Amniocentesis was not performed for CMV polymerase chain reaction investigation in any patient with positive CMV IgM and IgG. No congenital CMV

infection or congenital anomaly was determined in the newborn records after birth among these 61 patients. There were no patients with positive CMV IgM results and negative IgG results or borderline IgG results concurrently **(Table 2)**.

Table 2. Toxoplasma, Rubella and Cytomegalovirus avidity test results

Test	High	Borderline	Low	Total
Toxoplasma IgG avidity	16	2	1	19
Rubella IgG avidity	6	0	0	6
CMV IgG avidity	20	0	0	20

4. Discussion

It has been shown that a large number of infectious agents may vertically transmit and infect the fetus during pregnancy. Whether the fetus will be affected by these infections depends on the gestation week in which the infectious agent is encountered, the mother's immune status, and the infection agent's virulence. Permanent sequelae may occur in affected fetuses, and these perinatal infections may result in loss of pregnancy or neonatal death (6,10).

Toxoplasmosis is a widespread zoonosis in our country and around the world. Its seroprevalence may vary depending on age, geographic location, hygienic conditions, life habits, nutritional status, and contact with animals such as cats and dogs. The risk and severity of the congenital infection depend on the trimester in which the disease develops. The rate of vertical transmission of Toxoplasmosis in the first trimester is 7% and may increase as high as 24% in the second trimester and 60% to 81% in the third trimester. By contrast, the risk of fetal exposure is 75% in the first trimester and close to 0% in the last trimester (11). The effect of acute infection to the fetus, lasting 3 months or more before conception, is almost nonexistent (12). In our study, the birth records of 35 out of 46 pregnant women who were positive for both Toxoplasma IgM and IgG antibodies were reviewed. When the neonatal documents were scanned, no neonatal infection or congenital anomaly was reported to suggest vertical transmission in any of the newborns. Spiramycin treatment used in pregnant women with acute Toxoplasma infection is believed to prevent vertical transmission.

Not every country recommends routine prenatal toxoplasma screening. Seroprevalence rates, screening and treatment costs, and health policies are important issues regarding Toxoplasma screening. Although toxoplasma screening is not recommended for pregnant women in countries such as the United States, United Kingdom, Norway, Canada, and the Netherlands where seropositivity rates are low, it is legally required in other countries such as France and Austria (13). In Turkey, many studies have been conducted to determine the seroprevalence of TORCH infectious agents **(Table 3)**. In these studies, the seroprevalence rates of Toxoplasma varied between provinces reported to range between 18% and 63%. In the current study, we found the Toxoplasma IgG seroprevalence rate to be 24%.

Table 3. The summary of TORCH seroprevalence studies in Turkey

			Toxoplasma Seropositivity		Rubella Seropositivity		CMV Seropositivity	
Authors	**City**	**Time Interval**	**(%)**		**(%)**		**(%)**	
			IgM	IgG	IgM	IgG	IgM	IgG
Aynıoğlu et al. (27)	Zonguldak	2012-2014	2.5	43.9	2	91.5	1.5	93.8
Bakacak et al. (28)	K.Maraş	2012-2013	2.2	47.1	3.2	99.3	0.2	93.2
Çeltek et al. (29)	Tokat	2009-2012	1.1	32	0.3	95.4	1.7	99.4
Dogan et al. (20)	Istanbul	2008-2013	0.8	31.4	0.2	95.7	0.8	99.3
Duran et al. (17)	Bingöl	2011-2016	2	63	0.8	91.1	-	-
Gurlek et al. (16)	Rize	2016-2018	0.8	33.6	0.9	90.7	1.9	98.1
Inci et al. (30)	Artvin	2009-2012	1.3	30.3	0.3	95.2	1.6	98.6
Karabulut et al. (31)	Denizli	2008-2009	1.4	37	0	95.1	1.2	98.7
Karacan et al. (22)	Istanbul	2009-2013	0.4	23.1	0.5	95	0.4	84
Kasap et al. (18)	Mugla	2014-2015	3.7	18.8	0.8	89.5	0.3	90.4
Madendağ et al. (32)	Kayseri	2017-2018	1	28.9	0.5	97.3	0.2	98.2
Numan et al.(21)	Istanbul	2013-2015	0	31	0.2	94.2	0.5	99.5
Ocak et al. (33)	Hatay	2004-2006	0.5	52	0.5	95	0.4	94.9
Parlak et al. (19)	Van	2012-2013	1.1	37.6	0.5	86.5	2.6	100
Şimşek et al. (34)	Afyon	2012-2014	1.5	23.4	2.5	94.5	2.3	96
Şirin et al. (35)	Izmir	2014-2016	1.9	32.3	1.5	98.9	1.2	93.5
Tamer et al. (36)	Kocaeli	2005-2007	0.4	48.3	0.2	96.1	0.7	96.4
Our study	Istanbul	2017-2019	0.6	24.0	0.3	86.4	2.3	99.0

As long as they are not considered high-risk (e.g., pregnant women who are pet owners), screening tests for Toxoplasma are not performed again in the last weeks of pregnancy for those tested as seronegative in our hospital. However, it has been shown in a previous study that performing a screening test every month for early detection of acute infection in pregnant women, who were seronegative, significantly reduces the risk of congenital Toxoplasma infection (14). Because Toxoplasma IgG seroprevalence is not high in our country and the treatment of acute toxoplasmosis infection during pregnancy is possible, Toxoplasma screening should be recommended to all pregnant women in the first trimester.

The World Health Organization intends to eradicate Rubella around the world by 2020 through worldwide vaccination programs (15). Therefore, in many countries worldwide, Rubella seropositivity is screened before pregnancy and during the first trimester of pregnancy. Despite effective vaccination programs, Rubella seropositivity has been reported to vary from 71% to 98% in some countries (16). The vaccination against Rubella, which began in 1995 in Turkey, has been continuing since 2006 to include all individuals under 18 years. A notice issued by the Ministry of Health in 2008 aimed to achieve a 95% rubella vaccination rate and to ensure continuity throughout the country with the Rubella vaccine within the framework of an extended immunization program. In studies conducted in our country, the seroprevalence of rubella IgG varies between 86% and 99% (Table 3). Accordingly, in some of our provinces, the immunity rates against rubella have not yet reached the desired level (16-19). In 3 different seroprevalence studies conducted in Istanbul, Rubella IgG seropositivity was 95% (20-22). We have found the Rubella IgG seropositivity rate to be 86.4% in the current study. Unlike other studies conducted in Istanbul, we believe the decrease we observed in Rubella IgG seropositivity is the result of our hospital being located in a low sociocultural environment and providing extensive service to Syrian immigrants. Although there were no Rubella IgM positive and IgG negative pregnant women in our study, 22 women were both IgM and IgG positive for Rubella. Birth records of 9 of these 22 pregnant women were obtained and reviewed. No anomalies suggesting congenital Rubella syndrome were noted in any of the newborns.

It is our opinion that following up the mothers' immune status against Rubella and administering the Rubella vaccine to women before pregnancy is the most effective method to prevent congenital Rubella syndrome. Although women who are vaccinated with the Rubella vaccine are advised not to conceive for at least one month after vaccination, it is also not recommended to terminate the pregnancy if vaccinated accidentally.

Congenital CMV infections, which may cause many sequelae, generally occur when a woman is infected during pregnancy or shortly before conceiving. The fetus may be affected both primarily and recurrently (30%–50%), with a vertical transmission rate of less than 1% (9). Antiviral treatment of pregnant women is not recommended in CMV infections, mostly because there is no existing antiviral drug that can reduce transmission to the fetus. Socioeconomic status, living conditions, cultural and nutritional habits, and hygienic conditions are determinative factors in CMV seropositivity. Seropositivity rates were reported as high as 100% in Thailand, 91% in Iran, 78% in Russia, 56.8% in Australia, 56.3% in Finland, and 46.8% in France (23-25). Except for a study conducted by Karacan et al. (22), CMV seroprevalence greater than 90% was found in all other seroprevalence studies conducted in our country (Table 3). In the current study, we also found a CMV seropositivity rate of 99% in pregnant women. We believe the high CMV IgG seropositivity observed in our study was related to the population's low sociocultural status served in our hospital. The American College of Obstetricians and Gynecologists does not recommend routine screening for CMV (26). Considering the high rate of seropositivity in our study, we also do not routinely recommend CMV screening to every pregnant woman. As an exception, however, prenatal CMV screening may be considered for expectant women in groups at high-risk for CMV infection (e.g., those who work in hospitals, nursing homes, nurseries, and schools).

The limitations of the current study were that of its retrospective design with the lack of IgG avidity tests in some patients in which both IgM and IgG were positive, unknown Rubella vaccination status of pregnant women, and the lack of long-term results of the babies with suspected acute infections. In light of the seroprevalence studies of TORCH infections conducted in Turkey, we believe that pregnancy monitoring can be standardized throughout the country by creating of a proper TORCH infection screening algorithm in pregnant women.

5. Conclusion

We observed the seroprevalence rates of Toxoplasma, Rubella, and CMV in pregnant women who presented to our hospital between January 2017 and October 2019. Because Toxoplasma IgG seroprevalence is not high, and there is an effective treatment for acute toxoplasmosis infection, we believe that toxoplasma screening should be recommended to all pregnant women. Because the immunity to the rubella virus is still not

at the desired level in Turkey, we believe screening against rubella is vital during pregnancy. We believe rubella screening should be performed before pregnancy in women who intend to become pregnant. Women who are not immune to rubella and are not pregnant should be given the MMR vaccine before any future pregnancies. Finally, we believe that routine CMV screening is unnecessary in pregnant women owing to the high seroprevalence of CMV IgG in our country.

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Declaration of Interest

The authors report no conflicts of interest. No current sponsorship or financial support has been provided regarding the study.

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