ORIGINAL ARTICLE

Occurrence of Seropositivity of Toxoplasma gondii, Cytomegalovirus, and Rubella Infections in Pregnant Women

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ABSTRACT

Aim: To assess the seropositivity for Toxoplasma gondii, Rubella virus, and Cytomegalovirus among pregnant females in Hyderabad, Sindh, Pakistan

Methodology: A prospective study was undertaken at the Department of Gynecology and Obstetrics, Bahria University of Health Sciences, Karachi, Pakistan between March 2020 to June 2021. All women with confirmed pregnancies were eligible to participate in the study. Women with ectopic pregnancy or women who were not receiving prenatal care at our center were excluded. All participants underwent assessment for antibody Titres for Toxoplasmosis, Rubella, and CMV. Blood specimens of participating women were obtained in aseptic conditions for laboratory investigations. The IgM and IgG antibodies for Toxoplasma gondii, Rubella, and CMV along with IgG antibodies for CMV and Toxoplasma gondii were assessed comprehensively. Seropositivity was stratified with respect to age groups.

Results: A total of 336 women with a mean age of 26.88 ± 3.77 years were included. The rate of seropositivity for anti-Toxoplasma IgM, anti-Rubella IgM, and anti-CMV IgM was 1.2%, 0.6%, and 2.7%, consecutively. A total of four (1.2%) cases were positive for anti-Toxoplasma IgM. 126(37.5%) women were positive for Anti-Toxoplasma IgG. For the three positive cases of both IgM and IgG, avidity test showed high avidity. Overall, one case for toxoplasma gondii was detected. Two women were positive for anti-Rubella IgM only (positive cases). Overall, 291 (86.6%) individuals were positive for Rubella IgG. Overall, two cases of Rubella were detected in our study. All nine positive cases of anti-CMV IgM antibodies were also positive for anti-CMV IgG. For these nine cases, anti-CMV IgG avidity was reported which turned out to be intermediary or high. Overall, we did not detect a case of CMV in our study.

Conclusion: We found high levels of IgG antibodies for Rubella and CMV, indicating past infection/immunity. The present study highlighted the seroprevalence rate of Toxoplasma gondii, CMV, and Rubella in a cohort of pregnant women from Sindh. However, this rate could be under-reported as many women do not avail of antenatal services during pregnancy, especially from rural Sindh, Pakistan. Nevertheless, this study adds to the current literature. Furthermore, it is recommended to regularly screen pregnant females for these infections.

Keywords: Cytomegalovirus, rubella, seroprevalence, torch infections, toxoplasma gondii

INTRODUCTION

The infections including Toxoplasma gondii, Rubella, and Cytomegalovirus (CMV) are clumped together and are regarded as the TORCH infections. These infections are significantly associated with an increased risk of congenital infections[1].

Congenital malformations can result if a mother transmits it during pregnancy or delivery. Furthermore, it is a primary factor determining perinatal death and the burden of disease, mainly in less developed countries[2,3]. Toxoplasma gondii, CMV, and Rubella are leading factors of infection in people across any age group, and they do not show any symptoms, albeit disease in pregnant women during the first few weeks of pregnancy can result in fetal congenital abnormalities[4].

Congenital anomalies, recurrent abortions, preterm births, and stillbirths have all been implicated in these infections during gestation5. Early diagnosis of infections of Toxoplasma gondii, CMV, and Rubella in the mother and child is a critical element of prenatal care[6]. This is because of the fact that the majority of the women with existing infections do not show any presenting complaints and are therefore unlikely to report to the hospital thus, delaying the clinical diagnoses.

Diagnosis of such infections are mainly established on the basis of seropositive evidence[7]. The most widely used technique for detecting these infections is to screen for specific IgM antibodies. For the diagnosis of Toxoplasma gondii, CMV, and Rubella infections, there are a variety of analytical approaches available. The detection of IgM and IgG antibodies against these

pathogens using an enzyme-linked immunosorbent assay (ELISA) or an enzyme immunoassay (EIA) is considered to carry high sensitivity and specificity [5-7]. Furthermore, advances in IgG avidity assays have helped physicians discern between primary acute infection and recurring or previous infection[7-9].

The incidence of Toxoplasma gondii, Rubella, and CMV infections manifests major fluctuations based on a specific region, socioeconomic position, race, and age[9,10]. The objective of this cross-sectional study was to establish Toxoplasma gondii, Rubella virus, and CMV seroprevalence among pregnant females in Sindh, Pakistan, and to compare our data with that of other similar investigations.

METHODOLOGY

A prospective study was undertaken at the Department of Gynecology and Obstetrics, Bahria University of Health Sciences, Karachi, Pakistan between March 2020 to June 2021. After ethical approval was obtained from the institutional review committee, data acquisition was initiated. A non-probability consecutive sampling technique was employed to recruit participants. All women with confirmed pregnancies who visited the facility for the first prenatal visit during the first trimester were eligible to participate in the study. Women with ectopic pregnancy or women who were not receiving prenatal care at our center were excluded.

The sample size estimation was done using OPENEPI sample size calculator. By using the anticipated proportion of toxoplasmosis infection as 68.37% as reported by Gonjito da Silva et al[11], the confidence level of 95%, absolute precision of 5%, design effect as 1.0, the sample size was estimated as 333. The following formula was used Sample size n = [DEFF*Np(1-p)]/

[(d2/Z21-α/2*(N-1)+p*(1-p)]. Here, the absolute precision refers to the width of the confidence interval.

IgG, IgM antibody titres, and IgG avidity titres for Toxoplasma gondii, Rubella, and CMV were documented. Only the first reports of each patient were recorded along with demographic parameters including mean maternal age, parity, ethnicity, socioeconomic status, and education status were documented in a predefined proforma.

Patients who were diagnosed with rubella were counseled about the risk of congenital malformation in the fetus and were offered medical termination of pregnancy. Patients with primary infection of CMV were offered medical termination of pregnancy. For recurrent CMV infections, termination was not considered; proper follow-up was maintained to monitor fetal development.

To minimize bias, all the blood work for each woman was performed by a trained nursing staff. All the reports were read and analyzed by an experienced personnel who remained blinded to the study objectives. The investigations were sent to the same laboratory. This way the authors ensured that bias was minimized.

All participants underwent assessment for antibody titres for Toxoplasma gondii, Rubella, and CMV. After narrating the objectives of the study to women and their family members, informed consent was obtained prior to data acquisition.

Blood samples of women with confirmed pregnancies who were receiving prenatal care in our center were obtained in aseptic conditions for laboratory investigations. Specifically, the IgM or IgG for anti-Toxoplasma gondii, IgM or IgG anti-Rubella, IgM, or IgG for anti-CMV were assessed comprehensively. A five milliliter sample from the cubital vein of all pregnant women was extracted by a trained staff nurse for the serological detection of IgM and IgG. Using the Enzyme-linked immunosorbent assay (ELISA) kit by SERION diagnostics, antibody titres were tested.

Toxoplasma gondii Antibody Test: Toxoplasma gondii virus antibody test including Toxoplasma gondii IgG (SERION ELISA classic, ESR110G) and Toxoplasma gondii IgM (SERION ELISA classic, ESR110M) was performed as per manufacturer's instructions, which permitted quantitative as well as qualitative immunoassays for the detection of human antibodies in the blood plasma directed against Toxoplasma gondii. The sensitivity and specificity for SERION ELISA classic Toxoplasma gondii IgG was 98.2% and 99.8% while, for SERION ELISA classic Toxoplasma gondii IgM it was 97.7% and 98.4%, respectively[12].

For the confirmation of IgM positivity, another 5 ml blood sample was extracted and by using the corresponding avidity reagent the ELISA test was performed again anti-T. gondii IgG avidity. High avidity indicates past infection before pregnancy.

For Toxoplasma IgG, a value of more than or equal to 12 IU/mL was considered as positive. For IgM titres for Toxoplasma infection values greater than 0.6 ratio was considered as seropositive[11]. The avidity index (AI) results were interpreted in avidity percentage and were stratified into low avidity ≤ 30%, intermediary avidity between 31-60%, and high avidity ≥ 60%[13].

Interpretation was done as follows:

High titres of IgM and low titres for IgG suggested a very recent infection

High titre of IgM and IgG suggested a recent infection however, required avidity tests to confirm.

Low titre of IgM and IgG suggested a past infection.

Patients with intermediate and high avidity levels who were positive for IgM and IgG were labeled as having past infection prior to pregnancy[13].

Rubella Virus Antibody Test: Rubella virus antibody test including Rubella Virus IgG (SERION ELISA classic, ESR129G) and Rubella Virus IgM (SERION ELISA classic, ESR129M) was performed as per manufacturer's instructions, which permitted quantitative as well as qualitative immunoassays for the detection of human antibodies in the blood plasma directed against rubella virus. The sensitivity and specificity for SERION ELISA classic Rubella virus IgG was 99.7% and >99% while, for SERION ELISA classic Rubella virus IgM it was >99% and 96.8%, respectively[14].

For IgM against Rubella levels of 1.6 or higher and IgG Rubella antibody levels of > 10 IU/ml were regarded as positive[15].

For further confirmation, avidity tests for IgG antibodies were performed using the complementing SERION ELISA classic Avidity Reagent kit. Recent infection of rubella was confirmed if low avidity was detected. The avidity levels were translated in terms of relative avidity index (RAI) and were expressed as follows[16]:

RAI < 40% indicating low avidity
RAI 40% - 60% indicating intermediate range
RAI > 60% indicating high-avidity antibodies

Cytomegalovirus Antibody Test: Cytomegalovirus antibody test including Cytomegalovirus IgG (SERION ELISA classic, ESR109G) and Cytomegalovirus IgM (SERION ELISA classic, ESR109M) was performed as per manufacturer's instructions, which permitted quantitative as well as qualitative immunoassays for the detection of human antibodies in the blood plasma directed against Cytomegalovirus. The sensitivity and specificity for SERION ELISA classic Cytomegalovirus IgG was >99% and >99% while, for SERION ELISA classic Cytomegalovirus IgM it was 97.1% and 99.0%, respectively [17]. For CMV IgM values higher than 1 and CMV IgG values > 6 AU/mL were established as positive [18]. Furthermore, antibody avidity was also measured for patients with positive antibodies to confirm the diagnosis using the complementary Cytomegalovirus avidity reagent (SERION DIAGNOSTICS, B109AVID). High avidity meant non-primary infection while low avidity indicated primary infection. The cut-offs used in our laboratory for Avidity index (AI) for CMV were as follows: low avidity ≤ 35%, intermediary avidity between 36-49%, and high avidity ≥ 50%[19].

Patients were labeled as "Positive" for Toxoplasma gondii, Rubella, and CMV if following conditions were met[14,17,18]:

IgM levels were positive, IgG antibody titres were negative, and IgG avidity was low according to the cut-off values defined above.

Statistical methods: SPSS version 21 was utilized to conduct data analysis. Categorical variables, that is seropositive quantities, were compared by performing a Chi-squared test. A p-value of < 0.05 was taken to be statistically significant.

RESULTS

A total of 336 women with a mean age of 26.88±3.77 years were assessed for seropositivity for Toxoplasma, Rubella, and Cytomegalovirus in our center. The mean body mass index was 30.37±4.02kg/m2. The majority of the women were multiparous. Other demographics are presented in Table 1.

Table 1: Characteristics of study participants

Parameters	Mean ± SD
Age (years)	26.88 ± 3.77
Height (cm)	154.59 ± 5.42
Weight (kg)	72.58 ± 10.24
Body mass index (kg/m2)	30.37 ± 4.02
Age (years)	
≤ 20	59 (17.6%)
21-35	160 (47.6%)
>35	117 (34.8%)
Parity	
Nullipara	61 (18.2%)
Primipara	51 (15.2%)
Multipara	224 (66.4%)
Socioeconomic status	
Low	207 (61.6%)
Middle	127 (37.8%)
Upper	2 (0.59%)
Mode of delivery	
Cesarean section	83 (24.7%)
Vaginal delivery	253 (75.2%)

The rate of seropositivity for anti-Toxoplasma IgM, anti-Rubella IgM, and anti-CMV IgM was 1.2%, 0.6%, and 2.7%, consecutively. The confidence intervals against the corresponding proportions are mentioned in Table 2.

A total of four (1.2%) cases were positive for anti-Toxoplasma IgM. 126 (37.5%) women were positive for anti-Toxoplasma IgG. For the three positive cases of both IgM and IgG, avidity test showed high avidity. Overall, one case for toxplasma gondii was detected (0.29%).

Two women were positive for anti-Rubella IgM only. 291(86.6%) individuals were positive for Rubella IgG. Overall, two cases of Rubella were detected in our study (0.59%).

All nine positive cases of anti-CMV IgM antibodies were also positive for anti-CMV IgG. For these nine cases, anti-CMV IgG avidity was reported which turned out to be intermediary or high. Overall, we did not detect a case of CMV in our study. See Table 2 and 3 for detail. Age distribution revealed that women with IgM positivity against Toxoplasma gondii and Rubella were all aged between 21 to 35 years. At least more than half of the women in age group of 21-35 years were positive for IgG against Toxoplasma gondii, Rubella, and CMV (Table 4).

Table 2: Proportion of individuals with positive antibody titres

Antibody Titres	N (%)	95% CI (LL, UL)
Anti-Toxoplasma IgM	4 (1.2%)	(0.33, 3.02)
Anti-Rubella IgM	2 (0.6%)	(0.07, 2.13)
Anti-CMV IgM	9 (2.7%)	(1.23, 5.02)
Anti-Toxoplasma IgG	126 (37.5%)	(32.31, 42.92)
Anti-Rubella IgG	291 (86.6%)	(82.49, 90.06)
Anti-CMV IgG	336 (100%)	(98.91*, 100)
Toxoplasma Positive	1 (0.29%)	(0.01, 1.65)
Rubella Positive	2 (0.59%)	(0.07, 2.13)
CMV Positive	0	0

*One-sided 97.5% confidence interval

Table 3: The avidity test results of IgM & IgG positive cases against Toxoplasma gondii, Rubella and Cytomegalovirus

Parameter	Anti-Toxoplasma IgG avidity	Anti-CMV IgG avidity	Anti-rubella IgG avidity
Low avidity	0	0	0
Intermediary	0	1 (11.1%)	0
High avidity	3 (1.41%)	8 (88.8%)	0
Not tested (IgG -ve)	210 (62.5%)	0	45 (100%)
Total	213	9	45

Table 4: Distribution of Age With Respect to Antibody Titres of Toxoplasmosis, Rubella, and CMV infections.

Age (years)	Toxoplasmosis		Rubella		CMV	
	IgM(+)	IgG(+)	IgM(+)	IgG(+)	IgM(+)	IgG(+)
≤ 20	0 (0%)	5 (4%)	0 (0%)	52 (17.9%)	0 (0%)	59 (17.6%)
21-35	4 (100%) (50%)	116 (92.1%)	2 (100%)	148 (50.8%)	8 (88.9%)	160 (47.6%)
>35	0 (0%)	5 (4%)	0 (0%)	91 (31.3%)	1 (11.1%)	117 (34.8%)
Total	4	126	2	291	9	336

DISCUSSION

The idea of high seroprevalence of Toxoplasma gondii, Rubella, and Cytomegalovirus (CMV) during pregnancy has been reinforced by various studies. Early detection, treatment, and preventive interventions of infectious agents that can induce fetal damage are critical. Common ways for the spread of infections during pregnancy are ingestion of food items like raw, undercooked, or infected meat, consumption of rotten fruits and vegetables, and coming in contact with contaminated water or soil having oocytes from cat feces, as well vertical transmission[20,21].

We reported zero cases of CMV, one case of Toxoplasma gondii, and two cases of Rubella. Nevertheless, a large proportion of the women in our study were still susceptible to both Toxoplasma gondii and Rubella. Our findings are in line with the current evidence from the developing nations. For instance, a study by Sirin et al. revealed that even though most pregnant women were positive for IgG Rubella and CMV, many pregnant women were susceptible to Toxoplasma gondii virus[22]. In another study by Aynioglu et al. it was found that 2.5% and 43.9% women in the study population were positive for Toxoplasma IgM and IgG, respectively[23]. The subset of 21-30 years manifested the highest IgM positivity rate of 52.1% and 57.9% for Toxoplasma and CMV, respectively. The overall prevalence of rubella and CMV surpasses the prevalence of toxoplasma[23].

However, in contrast to our findings, a previously conducted study by Chopra et al., showed that out of the 200 serum assessed for Toxoplasma, Rubella, and CMV, 53(39%) were positive for Toxoplasma IgM alone while 13(9.5%) were positive for Rubella IgM alone[24]. This contrast in the prevalence of the disease could be because of decrease in disease over time. Furthermore, another reason for the differences could be attributed to the fact that the study sample in the study by Chopra et al. was much more diversified than our sample population. Furthermore the study established a substantial correlation between bad obstetric history and these infective agents. This was reflected by the statistics of Toxoplasma seropositivity being 42.5%, Rubella 17.5%, and CMV 29.5% in the subset of participants with BOH. The research identifies abortions as the most common etiology for the detection of immunoglobulins against Toxoplasma, Rubella, and CMV at 71.8%, 59.9% and 61% respectively. Thus, early detection and screening for these microbes in women can aid in the effective management of these infections[24].

In our study, those pregnant women with both IgM and IgG positivity underwent avidity testing. Intermediary or high anti-CMV and anti-toxoplasma gondii IgG avidity was reported in all women. Prasoona et al. revealed that the seroprevalence of toxoplasma gondii, rubella, and CMV, were 28%, 84%, and 92%, consecutively for IgG antibodies in women with high risk pregnancy[25]. Sahu et al. reported that Rubella was the most frequent infection that was found in 69.1% of the women followed by CMV and Toxoplasma infection[10]. These statistics are in line with our current findings. In most developed countries, successful immunization programmes have been launched, and vaccination has yielded increased seropositivity rates[26]. The rubella vaccine has been a part of Turkey's national childhood immunization regime since 2006. Research has shown increased levels of rubella super positivity in Turkey, ranging from 86.5% to 96.2%[18,26,27]

A recent primary infection does not necessarily have to always be associated with T. gondii, Rubella virus, and CMV IgM positivity. Individuals with autoimmune conditions may have false-positive IgM findings owing to the presence of antinuclear factors and rheumatoid factors. Also, there is a possibility that IgM heterotropic reactivity may be present in patients recently infected with certain viral infections[27] This can possibly contribute to the strong seropositivity rates of these conditions in particular regions.

The elevated levels of immunity against Toxoplasma, Rubella, and CMV, reported in discussed and present studies, in pregnant women lend credence to the case against frequent screening for the causative pathogens. However, this rate could be under-reported as many women do not avail of antenatal services during pregnancy, especially from rural Sindh, Pakistan. Therefore, it is recommended to regularly screen pregnant females for these infections.

There are several limitations of the current study as no research is without flaws. For instance, the current study is only single-centered which means that external validity is in question.

Future multi-center studies should be conducted to ensure that our results are similar to other hospital settings as well. Due to resource constraints, we could not maintain proper follow-up of patients and many patients with positive status were lost to follow-up. Thus, further research on the matter is warranted.

CONCLUSION

The seropositivity for IgG antibodies for Rubella, Cytomegalovirus (CMV), and Toxoplasmosis gondii were 37.5%, 86.6%, 100% indicating past infection/immunity. However, many women were still susceptible to both Rubella and Toxoplasma gondii. The present study highlighted the seroprevalence rate of Toxoplasma gondii, CMV, and Rubella in a cohort of pregnant women from Sindh. Further large scale studies are recommended to assess the risk factors associated with the infections.

Conflict of interest: Nil

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