Seroprevalence and Determinants of ToRCH Pathogens in Pregnant Women in the Sub-Himalayan Region

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Abstract

Introduction

Toxoplasma gondii (TG), rubella virus (RV), cytomegalovirus (CMV), and herpes simplex virus type 1 and 2 (HSV 1 and 2) cause mild maternal morbidity but have serious fetal consequences. The prevalence of these infections varies widely by country and population subgroup, and the paucity of data from the hilly state of Uttarakhand prompted us to undertake this study on their seroprevalence and association with potential risk factors.

Methods

Serum samples received from pregnant women attending the antenatal clinic of All India Institute of Medical Sciences, Rishikesh, between January 2016 to December 2019 were tested for TG-, RV-, CMV, and HSV-specific IgM and IgG by capture enzyme-linked immunoassay (ELISA). The data were then analyzed to determine the seroprevalence of the major ToRCH infections (toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes), and Fisher’s exact test was applied to check association with potential risk factors.

Results

Out of 165 pregnant women who were screened for the four major ToRCH pathogens, overall seroprevalence was 41.2% for TG (IgM=13.3%; IgG=38.2%), 80.0% for RV (IgM=3.0%; IgG=80.0%), 61.8% for CMV (IgM=1.8%; IgG=61.8%), and 42.4% for HSV (IgM=4.3%; IgG=40.6). TG was significantly associated with increasing maternal age (p-value=0.007). The seropositivity of RV was maximum in the drier and windy months of January-March (p-value=0.004), while that of TG in the warmer months of April-June (p-value=0.03). HSV prevalence was comparatively more common in Muslim women (p-value=0.05). Women presenting with bad obstetric history (BOH) and multiparous women were at higher risk for TG-RV-HSV and TG-RV-CMV, respectively.

Conclusion

Considering the high prevalence and risk of ToRCH infections in this region, we suggest disease-specific screening based on maternal history. Recognition of the burden of ToRCH infections in pregnant women is vital in clinicians’ decisions and implementing control measures.

How to cite this article

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Due to the mostly asymptomatic or mild clinical course of these four diseases, diagnosis during pregnancy is often missed [4,6]. So, the most effective way to control birth defects due to prenatal infection by these four microorganisms is preventive antenatal screening and counseling, leading to early diagnosis [6,7]. A screen for toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (ToRCH screen) is a panel of serological tests used to screen pregnant women for these infections. T, R, C, and H in the acronym ToRCH panel stand for TG, RV, CMV, and HSV, respectively.

TG, an apicomplexan parasite, is mainly caused by ingestion of T. gondii oocyst present on raw and unwashed vegetables or undercooked meat containing tissue cysts [7]. During pregnancy, primary TG infection or reactivation may cause congenital toxoplasmosis with serious fetal outcomes like hydrocephalus, retinitis pigmentosa, or even death in utero. Rubella or German measles is an airborne viral infection characterized by fever, upper respiratory infection, skin rash, lymphadenopathy, and joint pain. Congenital rubella syndrome (CRS) can include spontaneous abortion, stillbirth, IUGR (in up to 60% of newborns), hepatosplenomegaly, thrombocytopenia, and purple rash [1]. The infected newborn may have vision and/or hearing impairment, heart defects, and calcium deposits in the brain. CMV, regarded as human herpesvirus (HHV) type-5, usually causes asymptomatic infections in immunocompetent adults. But infected infants may present with microcephaly, hepatosplenomegaly, hepatitis, hemolytic anemia, and/or other abnormalities. Neonatal herpes, caused by HSV-1 and 2, is usually acquired from infected mothers with genital lesions during delivery. It may vary from cutaneous blisters, conjunctivitis, hepatitis, central nervous system manifestations.

Serological tests are the mainstay for diagnosing ToRCH infections [8]. The most commonly used test is enzyme-linked immunosorbent assay (ELISA) for detecting IgM and IgG antibodies against these pathogens. Other assays, like automated chemiluminescent immunoassay (quantitative), indirect immunofluorescence assay, and lateral flow chromatographic immunoassay (both qualitative), for detecting virus-specific immunoglobulins (IgM and IgG) can also be done [8,9,10]. IgG avidity test plays a vital role in differentiating patients with acute infection from those with chronic infection. Molecular assays like polymerase chain reaction (PCR) have high sensitivity and specificity but are applicable only for molecular typing and not for routine screening in resource-scarce settings.

As there is a paucity of studies on seroprevalence of ToRCH agents in pregnant women from the sub-Himalayan state of Uttarakhand, this study aimed to assess the seroprevalence of TG, RV, CMV, and HSV among pregnant women visiting All India Institute of Medical Sciences, Rishikesh, for an antenatal check-up and to find its correlation with socio-demographic characteristics and bad obstetrics history (BOH).

**Materials And Methods**

**Study area**

This cross-sectional study was conducted in the microbiology department of the All India Institute of Medical Sciences, Rishikesh, in Uttarakhand, India, between January 2016 and December 2019. It is a tertiary care teaching hospital offering healthcare services to patients from the sub-Himalayan state of Uttarakhand and adjoining areas. This area comprises both river valley plains and hilly terrains. Map of the area covered in the study, created using the QGIS application, is depicted in Figure 1.
Inclusion and exclusion criteria

All pregnant women attending the antenatal and gynecological outpatient department (OPD) of our institute for routine antenatal check-ups for four years (2016-2019) were considered for the study. Out of these, subjects who underwent screening for ToRCH pathogens, either as a routine antenatal screening process or had BOH or signs/symptoms compatible with those of ToRCH infections, were enrolled in the study. BOH implies previous unfavorable fetal outcomes in terms of two or more consecutive spontaneous abortions, history of fetal death/s, IUGR, early neonatal death, and/or congenital anomalies. Data used in the study were collected primarily from selected subjects or their attendants (carrying the samples). In case of any information gap, we referred to laboratory register/medical records maintained in the department or hospital information system (HIS). Cases with incomplete data were excluded from the study.

Laboratory methods

Blood samples were collected from the cases aseptically in plain vials. After half an hour, they were centrifuged and serum was separated. Aliquots sera were stored at a -20 degree centigrade deep freezer until further processed. IgG and IgM levels for TG, RV, CMV, and HSV were measured using Calbiotech IgG and IgM ELISA kits (Calbiotech R5EC 96 well ELISA, El Cajon, USA) individually for each organism. ELISA was performed on automated Euroimmune Analyzer 1 (Walkaway automated seven plate ELISA reader; Euroimmun, Lübeck, Germany), and the optical density (OD) was read at 450nm absorbance. All the ELISA kits had 99% Kappa agreement with reference ELISA method according to manufacturer’s kit insert. The interpretation of test results was based on the antibody index (AI) calculated by dividing the OD value of each sample by cut-off value (calibrator OD multiplied by calibrator factor). An AI of >1.1 was interpreted as positive and <0.9 was regarded as negative result. An AI of 0.9-1.1 was considered equivocal.

Statistical analysis

Data were entered into an Excel spreadsheet (Microsoft® Corp., Redmond, USA) separately by two researchers and checked for errors. The standard software package of SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY), was used for all statistical analyses. Mean and standard deviation was calculated for overall IgM and IgG levels against TG, RV, CMV, and HSV. The differences in the mean of dependent variable (IgM and IgG levels against pathogen) for each set of independent variables (age groups, year, months, religion, parity and BOH) were also checked. Associations of ToRCH infections with the independent variables were calculated using Fisher’s exact test. A two-tailed p-value of <0.5 was considered significant.

Ethical declaration

The present study protocol was reviewed and approved by the institutional review board of our institute (AIIMS/IEC/20/855 Date: 12/12/2020). Patient confidentiality was maintained by excluding their name and registration number while compiling the data and giving a specific identifier number.
Results

Patient characteristics

Altogether 4053 pregnant women attended the antenatal and obstetrics and gynecology OPD for routine antenatal check-ups between January 2016 and December 2019. Among them, 196 (4.8%) women, with or without any clinical presentations and/or BOH, were screened for the four major ToRCH infections. Thirty-one women were excluded from the study due to the unavailability of required data, and finally, the remaining 165 women were further analyzed in the study. The mean age of studied subjects was 27.6 ± 5.9 years. Table 1 shows the distribution of the study population. The majority of the cases belonged to 21-25 years (35.2%), followed by 26-30 years. The number of cases gradually increased from 14.5% in 2016 to 34.5% in 2019. The cases were equally distributed over the year, but a spike in cases was noticed in April and September. Most pregnant women belonged to the Hindu religion (78.8%), while 17.6 practiced Islam. About 27.3% of women were pregnant with their first viable child, while 29.1% of the women had presented with BOH.

| Characteristics  | No. of cases, n | Percentage % |
|------------------|----------------|--------------|
| Maternal age groups * |                      |              |
| <20              | 15             | 9.1          |
| 21-25            | 58             | 35.2         |
| 26-30            | 52             | 31.5         |
| >31              | 40             | 24.2         |
| Year             |                |              |
| 2016             | 24             | 14.5         |
| 2017             | 33             | 20.0         |
| 2018             | 51             | 30.9         |
| 2019             | 57             | 34.5         |
| Time of year     |                |              |
| Jan-Mar          | 36             | 21.8         |
| Apr-Jun          | 46             | 27.9         |
| Jul-Sep          | 45             | 27.3         |
| Oct-Dec          | 38             | 23.0         |
| Religion         |                |              |
| Hindu            | 130            | 78.8         |
| Muslim           | 29             | 17.6         |
| Others           | 6              | 3.6          |
| Parity           |                |              |
| Primipara        | 43             | 26.1         |
| Multipara #      | 122            | 73.9         |
| BOH              |                |              |
| Yes              | 48             | 29.1         |
| No               | 117            | 70.9         |

TABLE 1: Distribution of study participants according to socio-demographic characteristics

N= 165

* For the age category, the lower limit is the completed given age (in years) and the higher limit is completed given age (in years) up to one day less than the succeeding year.

# Women that have had more than one pregnancy resulting in viable offspring.

BOH, bad obstetrics history

Sero-prevalence of the ToRCH pathogens

The seroprevalence of the four main ToRCH pathogens is displayed in Table 2. The overall seropositivity of TG was 41.2%. Maximum total seropositivity was found in RV (80.0%), followed by CMV (61.8%) and HSV.
(42.4%). While IgG against TG, RV, CMV, and HSV was elevated in 38.2%, 80.0%, 61.8%, and 40.6%, respectively, IgM was raised only in 13.3%, 3%, 1.8%, and 4.3%, respectively. Both IgM and IgG were raised against TG, RV, CMV and HSV in 10.9%, 3%, 1.3%, and 2.4% cases, respectively.

### Table 2: Serological status of IgG and IgM antibodies with mean and standard deviation against Toxoplasma gondii, rubella, cytomegalovirus, and herpes simplex virus type 1 and 2 infections in pregnant women

| Associated factors | When demographic factors were taken into consideration, TG seroprevalence significantly increased with increasing age groups (p-value= 0.007), reaching the maximum rate at >31 years (62.5%) (Figure 2). The rate of TG and RV seroprevalence was higher during April–June and January–March, respectively (TG p-value=0.031, RV p-value=0.004) (Figure 3). However, no significant changes in prevalence were noticed in the four years (Figure 4). HSV was more prevalent in Muslim women (p-value=0.050) (Table 3). Multiparous women had a significantly higher risk of having anti-TG, -RV, and -CMV antibodies, whereas women with BOH were significantly associated with TG, RV, and HSV (Table 3). Table 4 describes the difference in means and standard deviations among the different categories.
FIGURE 2: Prevalence of Toxoplasma gondii (TG), rubella virus (RV), cytomegalovirus (CMV), and herpes simplex virus (HSV) infections in different age groups of pregnant women.

FIGURE 3: Trend of seropositivity of ToRCH infections in the different months of a year.

TG, Toxoplasma gondii; RV, rubella virus; CMV, cytomegalovirus; HSV, herpes simplex virus.
FIGURE 4: Trend of seropositivity of ToRCH infections in the four years of the study period

TG, Toxoplasma gondii; RV, rubella virus; CMV, cytomegalovirus; HSV, herpes simplex virus

| Characteristics       | Toxoplasma gondii | Rubella virus | Cytomegalovirus | Herpes virus |
|-----------------------|-------------------|---------------|-----------------|--------------|
|                       | Pos n, Neg n, %   | Pos n, Neg n, %| Pos n, Neg n, %| Pos n, Neg n, %|
| **Maternal Age Group**|                   |               |                 |              |
| <20                   | 4 (26.7) 11 (73.3)| 9 (60.0) 6 (40.0)| 6 (40.0) 9 (60.0)| 7 (46.7) 8 (53.8)|
| 21-25                 | 17 (29.4) 41 (70.7)| 17 (81.0) 11 (19.0)| 34 (58.6) 24 (41.4)| 30 (51.7) 26 (48.3)|
| 26-30                 | 21 (40.4) 31 (59.6)| 38 (73.1) 14 (26.9)| 31 (59.6) 21 (40.4)| 18 (36.4) 34 (63.6)|
| >31                   | 25 (62.5) 15 (37.5)| 32 (80.0) 8 (20.0)| 28 (70.0) 12 (30.0)| 15 (37.5) 25 (62.5)|
| **Year**              |                   |               |                 |              |
| 2016                  | 13 (54.2) 11 (45.8)| 22 (91.7) 2 (8.3)| 17 (70.8) 7 (29.2)| 10 (41.7) 14 (58.3)|
| 2017                  | 10 (30.3) 23 (69.7)| 21 (63.6) 12 (36.4)| 17 (51.5) 16 (48.5)| 13 (39.4) 20 (60.6)|
| 2018                  | 20 (39.2) 31 (60.8)| 41 (80.4) 10 (19.6)| 31 (60.8) 20 (39.2)| 22 (43.1) 29 (56.9)|
| 2019                  | 24 (42.1) 33 (57.9)| 42 (73.7) 15 (26.3)| 34 (59.6) 23 (40.4)| 25 (43.9) 32 (56.1)|
| **Time of year**      |                   |               |                 |              |
| 10                    | 26                | 34             | 20               | 20            |

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### TABLE 3: Results of Fisher’s exact test to check the association of ToRCH infections with probable risk factors

**BOH**: bad obstetrics history; **Pos**: Positive; **Neg**: Negative;  
*sig.*: significance (2-sided p-value) by Fisher’s exact test

| Characteristics | Mean + Standard Deviation |
|-----------------|--------------------------|
|                 | TG IgG | TG IgM | RV IgG | RV IgM | CMV IgG | CMV IgM | HSV IgG | HSV IgM |
| **Maternal Age** |        |        |        |        |        |        |        |        |
| groups*          |        |        |        |        |        |        |        |        |
| <20             | 0.6 +/- 0.8 | 0.5 +/- 0.4 | 68.5 +/- 257.7 | 0.2 +/- 0.2 | 2.7 +/- 4.5 | 0.2 +/- 0.2 | 1.8 +/- 2.6 | 0.2 +/- 0.2 |
| 21-25           | 19.5 +/- 95.7 | 0.5 +/- 0.5 | 58.7 +/- 211.5 | 0.3 +/- 0.4 | 3.7 +/- 4.8 | 0.3 +/- 0.6 | 5.9 +/- 23.8 | 0.4 +/- 0.3 |
| 26-30           | 51.9 +/- 143.6 | 0.7 +/- 1.1 | 95.7 +/- 313.2 | 0.7 +/- 2.1 | 4.5 +/- 12.9 | 0.3 +/- 0.3 | 1.1 +/- 1.6 | 0.3 +/- 0.2 |
| >31             | 72.3 +/- 167.6 | 1.3 +/- 1.8 | 99.9 +/- 287.2 | 0.3 +/- 0.2 | 10.9 +/- 23.8 | 0.3 +/- 0.2 | 3.1 +/- 9.1 | 0.2 +/- 0.1 |
| **Year**        |        |        |        |        |        |        |        |        |
| 2016            | 56.2 +/- 146.6 | 0.9 +/- 1.5 | 182.6 +/- 436.2 | 0.6 +/- 1.8 | 4.9 +/- 6.3 | 0.3 +/- 0.2 | 1.2 +/- 1.7 | 0.4 +/- 0.3 |
| 2017            | 34.1 +/- 107.6 | 0.6 +/- 0.9 | 42.4 +/- 146.9 | 0.3 +/- 0.2 | 3.0 +/- 4.2 | 0.2 +/- 0.2 | 4.6 +/- 16.7 | 0.3 +/- 0.3 |
| 2018            | 43.5 +/- 129.0 | 0.8 +/- 1.2 | 75.7 +/- 252.2 | 0.5 +/- 1.3 | 9.7 +/- 24.3 | 0.4 +/- 0.6 | 5.5 +/- 23.6 | 0.3 +/- 0.3 |
**TABLE 4: Comparison of the mean and standard deviation of IgG and IgM levels of the ToRCH pathogens between the different groups of each variable**

| Time of year | Religion | BOH | Parity |
|--------------|----------|-----|--------|
| **2019**     | **Jan-Mar** | **Apr-Jun** | **Jul-Sep** | **Oct-Dec** | **Hindu** | **Muslim** | **Others** | **Primigravida** | **Multiparous** | **Present** | **Absent** |
| **39.0 +/- 122.7** | **15.1 +/- 78.4** | **70.6 +/- 163.5** | **60.2 +/- 141.5** | **10.9 +/- 41.9** | **40.8 +/- 122.4** | **55.7 +/- 146.3** | **0.4 +/- 0.4** | **23.0 +/- 98.4** | **48.6 +/- 132.4** | **69.7 +/- 153.7** | **30.5 +/- 109.3** |
| **0.7 +/- 1.1** | **0.5 +/- 0.9** | **1.1 +/- 1.6** | **0.8 +/- 1.3** | **0.4 +/- 0.3** | **0.7 +/- 1.2** | **0.8 +/- 1.3** | **0.8 +/- 0.4** | **0.5 +/- 0.4** | **0.8 +/- 1.3** | **1.0 +/- 1.6** | **0.6 +/- 0.9** |
| **66.6 +/- 238.8** | **4.6 +/- 7.5** | **180.5 +/- 399.3** | **107.6 +/- 287.8** | **2.4 +/- 2.4** | **83.5 +/- 271.5** | **87.7 +/- 280.8** | **1.5 +/- 0.8** | **10.1 +/- 36.8** | **106.3 +/- 306.9** | **166.1 +/- 385.7** | **46.4 +/- 191.9** |
| **0.4 +/- 1.2** | **0.2 +/- 0.2** | **0.4 +/- 1.3** | **0.6 +/- 1.9** | **0.3 +/- 0.4** | **0.4 +/- 1.4** | **0.2 +/- 0.1** | **0.2 +/- 0.1** | **0.2 +/- 0.2** | **0.5 +/- 1.4** | **0.6 +/- 1.8** | **0.3 +/- 0.9** |
| **3.8 +/- 5.2** | **1.9 +/- 1.4** | **11.1 +/- 25.4** | **5.5 +/- 6.6** | **0.3 +/- 0.4** | **5.4 +/- 13.9** | **7.2 +/- 17.5** | **2.3 +/- 2.3** | **2.6 +/- 4.2** | **6.7 +/- 16.4** | **11.7 +/- 24.9** | **3.2 +/- 4.4** |
| **0.3 +/- 0.2** | **0.2 +/- 0.2** | **0.3 +/- 0.2** | **0.3 +/- 0.2** | **0.3 +/- 0.4** | **0.3 +/- 0.4** | **0.2 +/- 0.2** | **0.1 +/- 0.2** | **0.2 +/- 0.2** | **0.3 +/- 0.4** | **0.3 +/- 0.4** | **0.3 +/- 0.2** |
| **1.6 +/- 2.4** | **1.0 +/- 0.8** | **8.1 +/- 27.6** | **0.2 +/- 0.2** | **1.8 +/- 2.8** | **2.6 +/- 13.8** | **7.1 +/- 19.9** | **1.6 +/- 2.5** | **1.4 +/- 1.9** | **4.0 +/- 17.3** | **8.1 +/- 27.0** | **1.4 +/- 2.2** |
| **0.3 +/- 0.3** | **0.4 +/- 0.3** | **0.3 +/- 0.2** | **0.3 +/- 0.3** | **0.3 +/- 0.3** | **0.3 +/- 0.3** | **0.4 +/- 0.3** | **0.3 +/- 0.3** | **0.4 +/- 0.3** | **0.3 +/- 0.3** | **0.3 +/- 0.3** | **0.3 +/- 0.3** |

*Women who has had more than one pregnancy resulting in viable offspring

**Discussion**

The prevalence of ToRCH infections varies significantly from region to region, depending upon various factors like climatic conditions, socio-economic status, including personal hygiene, cultural beliefs, dietary habits, and other anthropogenic factors [5,7]. Estimating regional seroprevalence of ToRCH agents from time to time is of immense help in formulating strategies for antenatal screening and guiding physicians in making screening decisions. It is even more important in countries like India that lack national screening programs for ToRCH infections in pregnant women. This prompted us to conduct the present study in the hilly state of Uttarakhand.

Our study observed a TG seroprevalence of 41.2%, among which 13.3% showed anti-TG IgM antibodies indicating active infection posing a threat to the developing fetus. The global prevalence of latent toxoplasmosis in pregnant women was estimated at 33.8%, with a significant association with countries of low income and low human development indices [11]. Singh and Pandit reported an overall Toxoplasma seroprevalence of 45%, which conforms with our finding. Another study from northeast India also reported a high TG seroprevalence of 48% [12]. However, a national serological survey of TG prevalence in India reported a lower seroprevalence of 9.4-19.7% in the north Indian population [13]. Similarly, another study from north India reported seropositivity of 21% in the general population [14]. This comparatively higher TG prevalence in the high-risk group of pregnant women prompts the need for antenatal screening and treatment. In the absence of vaccination against toxoplasmosis, antenatal monitoring and health education of the targeted population (pregnant women) regarding the handling of animals and avoiding consumption of undercooked meat products and raw fruits/vegetables can go a long way in reducing the burden of toxoplasmosis. Poor fetal outcomes and congenital anomalies can be avoided by prevention, timely...
hygiene for CMV, HSV, etc.), and public awareness about transmission and risk factors for controlling preventive approaches (like vaccination for RV, consumption of properly cooked food for TG, personal towards ToRCH infections. These observations call for an integrated approach of antenatal screening, prevalence of HSV infections in Muslim pregnant women, and predisposing role of multiparity and BOH months of January-March favoring RV and warmer months of April-June favoring TG infections, higher for serious fetal consequences. The findings of this study have provided baseline epidemiological data on the women gives an insight into the disease burden of ToRCH infections in this high-risk population responsible.

Conclusions

To conclude, estimating the serological status by assessing the IgM and IgG antibody levels in pregnant women gives an insight into the disease burden of ToRCH infections in this high-risk population responsible for serious fetal consequences. The findings of this study have provided baseline epidemiological data on the seroprevalence of ToRCH infections from this hilly state of Uttarakhand for future in-depth studies. We found an increased seroprevalence of TG and other infections with increasing age, the drier and windy months of January-March favoring RV and warmer months of April-June favoring TG infections, higher prevalence of HSV infections in Muslim pregnant women, and predisposing role of multiparity and BOH towards ToRCH infections. These observations call for an integrated approach of antenatal screening, preventive approaches (like vaccination for RV, consumption of properly cooked food for TG, personal hygiene for CMV, HSV, etc.), and public awareness about transmission and risk factors for controlling
ToRCH-related fetal complications.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee, All India Institute of Medical Sciences, Rishikesh issued approval (Letter No.: AIIMS/IEC/20/835, Date: 12/12/2020).

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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