SEROPREVALENCE OF RUBELLA ANTIBODIES AMONG TURKISH AND FOREIGN WOMEN IN TURKEY

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Abstract. The aims of this study were to determine seroprevalence of rubella antibodies among Turkish and foreign women living in Turkey and to estimate percent women susceptible to rubella infection. This retrospective study was conducted among 970 women (816 Turks) attending gynecology and obstetrics outpatient clinics. Serum samples were tested for anti-rubella IgG and IgM by chemiluminescent microparticle immunoassay. Eighty-eight percent of the subjects were positive only for anti-rubella IgG indicating immunity to rubella infection, none for only anti-rubella IgM and 1.5% for both anti-rubella IgM and IgG, the latter having a high avidity of anti-rubella IgG signifying a previous infection. Anti-rubella IgG seropositivity rate alone for Turkish women is 86.1%, significantly higher than that for foreign women. A significant association between age and seropositivity was found only for the age group of 15-20 years among both Turkish and foreign women. Anti-rubella IgG seropositivity rate of pregnant women increased with increasing age from 10.7% (at 15-20 years old) to 85.5% (at 36-40 years old). Among non-pregnant women, both anti-rubella IgM and IgG seronegativity rates were significantly higher in the age group of 31-35 years than the other age groups. Our results indicate that all pregnant women in Turkey should routinely be screened for anti-rubella IgM and IgG at antenatal period. Evaluation of susceptibility of women in reproductive age to rubella infection is important to setup a strategy for preventing antenatal rubella through vaccination of non-immune women throughout the country.

Keywords: rubella, antibody, seroprevalence, women, Turkey

INTRODUCTION

Rubella virus is an enveloped, positive-sense, RNA virus, genus *Rubivirus*, of the family Togaviridae, this virus causes German measles, a mild, self-limiting, febrile, exanthematous infection in children and adults (Gadallah *et al*, 2014; Ghorbanali *et al*, 2014; Gupta *et al*, 2015b). The most serious results of rubella infection occur in pregnant woman during the first trimester of gestation, resulting in abortion, still births and congenital rubella syndrome. Rubella virus is a biological teratogen of TORCH complex and transmissible in utero (Caidi *et al*, 2009; Agbede *et al*, 2011; Ghorbanali *et al*, 2014; Gupta

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et al, 2015a; Mounerou *et al*, 2015). Congenital rubella syndrome (CRS) causes heart defects, ocular abnormalities, deafness and mental retardation. Approximately 100,000 children are still born with CRS, even though rubella vaccination has strongly decreased such incidences (Caidi *et al*, 2009; Gadallah *et al*, 2014; Gupta *et al*, 2015).

Laboratory diagnosis of rubella is needed, as rubella infection is generally atypical and asymptomatic. Viral isolation by cell cultures can be used particularly during infections in pregnancy, but this is expensive, and as a result of the non-cytopathic effects of rubella virus, it is not usually recommended (Agbede *et al*, 2011; Jahromi *et al*, 2011; Gupta *et al*, 2015a). Detection of rubella virus nucleic acid by reverse transcriptase PCR of nasal, blood, throat, urine and cerebrospinal fluid specimens is another diagnostic method (Jahromi *et al*, 2011). However, common diagnostic methods of infection are based on serological tests, in particular the detection of specific IgM and IgG antibodies (Al-Jeboori Khalil, 2013). Enzyme-linked immunosorbent assay (ELISA) provides a sensitive, accurate and appropriate serological method to determine anti-rubella IgG and IgM levels (Ghorbanali *et al*, 2014). Anti-rubella IgM antibodies are first detected within the first 10 days of infection and peak at about 4 weeks post-infection, but may persist for over 7 months after an acute infection. On the other hand, a significant rise in anti-rubella IgG level through 3 weeks seroconversion is evidence of a developing rubella infection. Anti-rubella IgG can also be detected in sera of vaccinated or immune individuals after an infection (Agbede *et al*, 2011; Al-Jeboori Khalil, 2013; Mounerou *et al*, 2015).

This retrospective study determined seroprevalence of rubella antibodies among Turkish and foreign women living in Turkey and compared the findings with those reported in other studies. The results of this study will provide further information to estimate percent women susceptible to rubella virus infection and rubella immunity among women in the country.

MATERIALS AND METHODS

Study group

A total of 970 women attending hospital gynecology and obstetrics outpatient clinics located in Konya Dr Faruk Sukan Gynecology and Children Hospital between September 2015 and May 2016 were enrolled in the retrospective study.

The study was approved by the local institutional ethics committee of Konya Dr Faruk Sukan Gynecology and Children Hospital (Ref No. 24072050).

Laboratory analysis

Five ml of venous blood were taken from each participant and centrifuged at 4,000 rpm for 10 minutes at room temperature. Serum samples were analyzed on the same day or kept at -20°C until tested. Serum samples were analyzed using a chemiluminescent microparticle immunoassay (Architect® i2000SR; Abbott, Abbott Park, IL). Anti-rubella IgG concentration ≥10 IU/ml is classified as positive, ≤4.9 IU/ml as negative and 5-9.9 IU/ml as equivocal. Sample with concentration <1.20 index is considered as anti-rubella IgM negative, 1.20-1.60 index equivocal and ≥1.60 index positive. Equivocal samples were retested, and if the results were confirmed, the samples are classified as equivocal.

Avidity of anti-rubella IgG was measured using an enzyme-linked fluorescence assay technique (ELFA-Vidas, bioMérieux, Marcy l'Étoile, France). This

Table 1
Seroprevalence of anti-rubella IgG and IgM among Turkish and foreign women.

Nationality	IgG positive only *n* (%)	Both IgM and IgG positive *n* (%)	Both IgM and IgG negative *n* (%)	IgM positive only *n* (%)	*p*-value[a]
Turk	735 (86.1)	11 (78.6)	70 (68.6)	0 (0)	0.002
Foreigner	119 (13.9)	3 (21.4)	32 (31.4)	0 (0)	

[a]Chi-square Monte Carlo exact test.

technique employs a two-step sandwich immune enzymatic method yielding a quantitative output.

Statistical analysis

Data analyses were performed using Statistical Package for the Social Sciences (SPSS version 19.0; IBM, Armonk, NY). Relationship between test results and variables was evaluated by chi-square Monte Carlo exact test. Result is considered significant at p-value < 0.05.

RESULTS

Of the total of 970 women in this retrospective study, mean age was 26 ± 6 years (ranging 16 to 57 years old), among whom 816 (84.1%) were Turkish, 153 (15.8%) were pregnant and admitted to obstetrics outpatient clinics for antenatal screening and 817 (84.2%) admitted to gynecology outpatient clinics for other diagnosis.

Screening of serum samples for anti-rubella IgG and IgM antibodies showed that from 854 (88%) samples were positive for only anti-rubella IgG indicating an immune status and none positive for only anti-rubella IgM indicating susceptible status to rubella virus infection. Fourteen (1.5%) samples were positive for both anti-rubella IgM and IgG and 102 (10.5%) negative for both IgM and IgG indicating that no previous contact to rubella virus. Avidity tests performed on serum samples positive for both anti-rubella IgM and IgG demonstrated a high avidity signifying a previous infection.

Anti-rubella IgG seropositivity rate alone for Turkish women was 86.1%, higher than that of foreigners ($p < 0.05$) (Table 1). Susceptibility to rubella was higher in foreign than Turkish women. There is a statistically significant association of seropositivity between Turkish and foreign women.

There is a significant association between age and seropositivity in the age group of 15-20 years among both Turkish and foreign women ($p < 0.05$) (Table 2). Seropositivity rate of anti-rubella IgG alone was 22.1% for foreign women in the age group of 15-20 years, while that for Turkish women varied from 77.9% to 95.4% in the age group of 15-20 and 31-35 years, respectively. Despite the fluctuations, age-associated seropositivity to rubella decreased with increasing age especially after the age of 35 years (Table 2).

The proportion of pregnant women seropositive for anti-rubella IgG increased with age, from 10.7% to 85.5% (Table 3). The highest anti-rubella IgG seropositivity rate was in the age group of 36-40 years ($p > 0.05$). Among non-pregnant women, both anti-rubella IgM and IgG seronega-

Table 2
Seroprevalence of anti-rubella IgG and IgM among Turkish ($n = 816$) and foreign ($n = 154$) women according to age group.

Age (group)	IgG positive only *n* (%)	Both IgM and IgG positive *n* (%)	Both IgM and IgG negative *n* (%)	IgM positive only *n* (%)	*p*-value[a]
Turk					<0.001[a]
15-20[x]	116 (77.9)[y]	3 (75)[y]	3 (13.6)	0 (0)	
21-25	244 (87.1)	5 (83.3)	14 (66.7	0 (0)	
26-30	188 (85.1)	1 (50)	20 (90.9)	0 (0)	
31-35[x]	125 (95.4)[y]	2 (100)	20 (83.3)	0 (0)	
36-40[x]	52 (83.9)	0 (0)	12 (100)	0 (0)	
41-45	7 (100)	0 (0)	0 (0)	0 (0)	
≥ 46	3 (75)	0 (0)	1 (100)	0 (0)	
Foreigner					0.048[a]
15-20[x]	33 (22.1)[y]	1 (25)	19 (86.4)	0 (0)	
21-25	36 (12.9)	1 (16.7)	7 (33.3)	0 (0)	
26-30[x]	33 (14.9)[y]	1 (50)	2 (9.1)	0 (0)	
31-35	6 (4.6)	0 (0)	4 (16.7)	0 (0)	
36-40[x]	10 (16.1)	0 (0)	0 (0)	0 (0)	
41-45	0 (0)	0 (0)	0 (0)	0 (0)	
≥ 46	1 (25)	0 (0)	0 (0)	0 (0)	

[a]Chi-square Monte Carlo exact test.
[x,y]Different superscript letters denote the significant difference between proportions.

tivity rates are significantly higher in the age group of 31-35 years than in the other age groups (Table 3).

DISCUSSION

In recent years a large number of serological studies have been carried out to determine the epidemiology and seroprevalence of rubella infection in different countries (Karakoç *et al*, 2003; Gupta *et al*, 2015a). Serological screening of rubella is based on anti-rubella IgG and IgM antibodies detection by ELISA as it remains the most useful and reliable method (Agbede *et al*, 2011; Chopra and Mahajan, 2015). In our study, ELISA method was used for analyzing seroprevalence rates of rubella antibodies among women, similar to other studies (Corcoran and Hardie, 2005; Jahromi *et al*, 2011; Tahita *et al*, 2013; Gadallah *et al*, 2014; Gupta *et al*, 2015b).

In a study carried out in Egypt, seroprevalence rate of anti-rubella IgG among women is 88.2% (Gadallah *et al*, 2014), a similar rate to our study (88%). A previous study conducted in Algeria detected seroprevalence of rubella IgG antibodies of 68.6% in women who did not have rubella vaccination previously and emphasized the importance and need for a policy to immunize adolescent girls and females of childbearing age against rubella before conception (Ouyahia *et al*, 2013). In 2002, a study from Taiwan reported rubella seronegativity rate of 5.7% among women of childbearing age after initiating

Table 3
Seroprevalence of anti-rubella IgG and IgM among pregnant women and non-pregnant women according to age group.

Age group (years)	IgG positive only *n* (%)	Both IgM and IgG positive *n* (%)	Both IgM and IgG negative *n* (%)	IgM positive only *n* (%)	*p*-value[a]
Pregnant					0.076[a]
15-20	16 (10.7)	1 (25)	0 (0)	0 (0)	
21-25	51 (18.2)	2 (33.3)	3 (14.3)	0 (0)	
26-30	42 (19)	1 (50)	4 (18.2)	0 (0)	
31-35	19 (14.5)	1 (50)	1 (4.2)	0 (0)	
36-40[x]	53 (85.5)[y]	0 (0)	3 (25)[y]	0 (0)	
41-45	0 (0)	0 (0)	0 (0)	0 (0)	
≥ 46	0 (0)	0 (0)	0 (0)	0 (0)	
Non-pregnant					0.089[a]
15-20	133 (89.3)	3 (75)	22 (100)	0 (0)	
21-25	229 (81.8)	4 (66.7)	18 (85.7)	0 (0)	
26-30	179 (81)	1 (50)	18 (81.8)	0 (0)	
31-35[x]	112 (85.5)	1 (50)	23 (95.8)[y]	0 (0)	
36-40	9 (14.5)	0 (0)	9 (75)	0 (0)	
41-45	7 (100)	0 (0)	0 (0)	0 (0)	
≥ 46	4 (100)	0 (0)	1 (100)	0 (0)	

[a]Chi-square Monte Carlo exact test.
[x,y]Different superscript letters denote the significant difference between proportions.

nationwide rubella vaccination programs in 1986 and 1992 years to have all 15-year old schoolgirls and females of childbearing age vaccinated against rubella (Shih-Bin and How-Ran *et al*, 2002).

Studies investigating seroprevalence of rubella antibodies among pregnant women in Turkey in different years reported anti-rubella IgG seropositivity of 94.3% in 2008, 95.1% in 2011 and 86.5% in 2015 (Uyar *et al*, 2008; Karabulut *et al*, 2011; Parlak *et al*, 2015). High rates of rubella IgG seropositivity found in these studies among pregnant and non-pregnant women in Turkey were interpreted as an indicator of success of immunization practices, which were strictly carried out as a consequence of congenital rubella syndrome due to rubella outbreaks encountered in the past. In our study, some 86.1% of foreign women were susceptible to rubella. This might be explained by differences in characteristics, socio-economic level and vaccination status of the women studied. Vaccination status plays a significant role in response but this factor could not be determined due a lack of such information of the participants.

A study designed to determine age-specific rubella seroprevalence in women of childbearing age in Morocco reported a high proportion (16.6%) of women in childbearing age are susceptible to rubella and a significantly higher rate of susceptibility (29.3%) among women of 15-19 years compared to that (8.3%) of 35-39 years (Caidi *et al*, 2009). Similarly, our study indicated that despite fluctuations,

age-associated seropositivity to rubella decreased with increasing age especially after 35 years of age and a significant association between age and seropositivity in the age group of 15-20 years among both Turkish and foreign women.

In African countries such as Burkina Faso and Nigeria seroprevalence of anti-rubella IgG among pregnant women are 95% and 96.5%, respectively (Tahita *et al*, 2013; Mangga *et al*, 2014). These results were almost similar to another study conducted in Southern Iran (96%) (Honarvar *et al*, 2013). Seroprevalence of anti-rubella IgG among pregnant women obtained in a study carried out in Iraq is 86.7% (Hammod *et al*, 2012). In India, (Chopra and Mahajan (2015) found anti-rubella IgG seropositivity rate to be 53% among pregnant women while other studies reported higher rates, ranging from 84.3% to 95.2% (Désinor *et al*, 2004; Jubaida *et al*, 2011; Olajide *et al*, 2015). In a study from Sri Lanka (Palihawadana *et al*, 2003), there is a lower rubella seropositivity (76%), with seropositivity in pregnant women increasing with age in accordance with our study. Similarly, in Kenya seropositivity of anti-rubella IgG increases with age, from 86.7% for those less than 20 years old to 95.2% for women over 30 years of age, suggesting that women who remain susceptible are at a high risk of developing the disease during pregnancy (Kombich *et al*, 2012). This data is consistent with Agbede *et al* (2011) noted in Nigeria the highest prevalence of anti-rubella IgG (9.8%) among pregnant women aged 26-30 years compared to other age groups and that there is an initial increase followed by a decrease in the prevalence among the older age groups. Differences among the results might be attributed to that age-specific profiles of rubella seropositivity demonstrate significant variations, as rubella is a predominantly childhood disease in some countries but more prevalent in adults in other countries.

Seroprevalence of anti-rubella IgG was reported as 53% while IgM seropositivity is 10% in all IgG seropositive women in Nigeria (Onakewhor and Chiwuzie, 2011), higher than those in our study for both anti-rubella IgG and IgM. In our study population no participants had a recent rubella infection according to anti-rubella IgM and anti-rubella IgG aviditiy tests. We postulate that outbreaks which may have gone unrecognized due to the mild nature of the infection could be responsible for variations in prevalence of rubella IgG and IgM antibodies in various populations.

We found both anti-rubella IgM and IgG seronegativity are significantly higher in the age group of 31-35 years among non-pregnant women. These data indicate that rubella vaccination should target children under 15 years old and this would be a less costly strategy for preventing CRS than vaccinating large segments of the population including women of up to 45 years of age.

In conclusion, we recommend that in Turkey all pregnant women should routinely be screened for anti-rubella IgM and IgG antibodies at antenatal period, and females of childbearing age also should undergo such routine screening before marriage or conception, to vaccinate non-immune women as their immunity status will probably decrease over time. The results of our study should serve as a guide to health planners for possible intervention in preventing CRS through a program of mass vaccination of women of childbearing age, focusing on teenagers and non-immune adults. Even with the limitations of the data collected, our study constitutes an important step towards the determination of the seroprevalence of rubella virus

antibodies among women in Turkey and to overcome this public health problem.

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