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ORIGINAL ARTICLE

Seroprevalence of Varicella zoster virus antibody among young women before marriage in Sanandaj, Iran

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ABSTRACT

Background and Objectives: Varicella Zoster Virus (VZV) infection in pregnant women can cause complications for the mother and fetus. The aim of this study was to assess the immunity against VZV among young women before marriage.
Materials and Methods: In this cross-sectional study 250 women attending health centers in Sanandaj, Iran, for pre-marital medical check-up were randomly selected. The VZV IgG measured by ELISA and demographic characteristics of participants including their age, place of residence, number of siblings, occupation, education and history of chickenpox were also recorded. Data were analyzed using R statistical software. Association between VZV infection and participants' characteristics was assessed using Chi-square and Fisher's exact tests.
Results: Out of 250 participants, 178 individuals (71.2%) diagnosed as antibody positive and 72 (28.8%) negative. Our findings revealed that the immunity against VZV increased with individuals' age ($P<0.0001$) and their number of siblings ($P= 0.03$). Significant association was found between history of chickenpox and immunity ($P <0.001$). Positive and negative predictive values of self-reported history of chickenpox obtained by 94.60% and 49.25%, respectively.
Conclusion: A notable percentage of women were found to be susceptible to VZV, hence they are at risk of getting infected during pregnancy which in turn may result in fetus abnormalities. Screening the immunity and further studies on the need of vaccination before marriage are recommended.

Keywords: Varicella zoster virus, Chickenpox, Seroprevalence, Antibody, Sanandaj

INTRODUCTION

Varicella Zoster Virus (VZV), a human alphaherpesvirus, is the causative agent of varicella (chickenpox). The virus becomes latent in neurons and recurrent infection causing herpes zoster (shingles) in adults. Varicella is a highly contagious disease in which the virus enters the host through the mucous membranes of upper respiratory tract or conjunctiva (1). Although, varicella is a mild and self-limited disease, it may motive serious complications or even death in healthy adults, pregnant women and immunocompromised patients (2).

The primary infection of VZV in non-immune pregnant women may show itself with pneumonia and encephalitis in both mother and fetus. Maternal

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varicella infection in the early months of pregnancy may emerge as congenital varicella syndrome in neonates with symptoms such as low birth weight, limb hypoplasia, eye disorder, neurological abnormality and developmental delay. VZV infection during the third trimester or close to delivery can cause infection in newborn which may result in increasing the mortality rate of infants up to 20%. If the contact happens days before and after delivery the risk of developing neonatal chickenpox is about 17–30% (1-2).

The immunity against VZV has not been yet fully understood. After development of the rash in primary infection antibody is produced against VZV which remains for many years in blood. This may play a role in immunity to VZV. Maternal varicella-zoster immunoglobulin (VZIG) administration before rash development can modify the progression of the disease (1).

Vaccination against VZV can prevent the disease. The vaccine is made from the Oak strain of live attenuated VZV. Despite the public use of the varicella vaccine during childhood in developed countries, routine immunization against varicella has not been well established in developing countries such as Iran. In the absence of such an active immunization policy, the vulnerable populations including premarital women are at risk of developing the infection (3).

Epidemiology of chickenpox varies between temperate and tropical climates. Incidence of varicella varies with respect to population density and risk of exposure, social factors, humid conditions, and especially geographic locations of the world (3). The epidemiology of VZV infection has not been understood well in tropical areas where a relatively large proportion of adults are seronegative. In temperate climate countries like Iran, chickenpox occurs mostly during the childhood. Thus a large proportion of seroconversion occurs in early adolescence (1). In Iran, the level of immunity against VZV has been reported from 71.4% to 78.5% in general population (4-5) and 76.5% to 86.9% among women at childbearing age (6). It appears that antibodies increase with age (7).

In the event of physical contact between a non-immune pregnant woman and a chickenpox patient, the disease can be transmitted. Some studies have reported a significant association between a history of chickenpox and the immunity to VZV (2). In order to receive either VZIG or antiviral therapy, pregnant women should be screened for their immunity against VZV using either laboratory tests or the history of chickenpox (1). In most cases, chickenpox occurs in childhood and therefore the history of disease is not clear. Hence, some studies suggest counting only those cases with a positive history of chickenpox (2). Information about the immunity levels of VZV in young women is also important from administration perspective; it helps the health policy makers to assess the need for a vaccination program as well as the preparation for VZIG.

The main goals of this study were to estimate 1) the seroprevalence of IgG antibodies against VZV, 2) the positive predictive value (PPV), and 3) negative predictive value (NPV) of self-reported history of chickenpox in young women before marriage in the city of Sanandaj, Iran.

MATERIALS AND METHODS

Subjects: In this cross-sectional study, 250 young women attending the health centers in Sanandaj for premarital examinations were recruited and their informed consent for participation in the research was obtained. From every participant 5 ml blood was obtained. The blood samples were placed into a water bath at 37°C to form clots. They were centrifuged for 10 minutes at the 3000 rpm. Sera were aliquoted and placed in a freezer at -20°C.

Demographic information of participants including their age, education, occupation, number of siblings, location of residency (rural or urban), and the history of varicella infection were collected by interview.

For each specimen, the level of antibody against VZV IgG was assessed using ELISA kit (Captia™ VZV IgG, Trinity Biotech USA) and ELISA reader (Hiperion ,Germany). Antibody levels greater than 0.13 IU/mL considered as positive, 0.11 <equivocal< 0.13 IU/mL, and lower than 0.11 IU/mL as negative according to supplier instruction.

Statistical analysis: Data were managed in Microsoft Excel and analyzed using R statistical software version 3.1.3. The Chi-square test, Fisher's exact test, and Spearman correlation were used as appropriate in order to investigate the statistically significant association between the IgG antibodies against VZV and participants' characteristics in study.

Positive predictive value (PPV) and negative pre-

dictive value (NPV) of self-reported history of chickenpox were estimated using the following ratio:

$$PPV = \frac{\text{Women positive for both disease and tests}}{\text{women with disease}}$$

$$NPV = \frac{\text{Women negative for both disease and tests}}{\text{women with disease}}$$

RESULTS

Out of 250 young women in the study, 178 (71.2%) were diagnosed as antibody-positive and the rest (72 participants 28.8%) as antibody-negative against VZV. The maximum and minimum antibody levels were obtained 0.06 and 940.93 IU/mL, respectively. The mean level of individuals' antibody was 37.05 IU/mL. No borderline (equivocal) antibody level was observed; hence any need to rerun the test.

The age of participants ranged from 13 to 40 years with the mean of 22.39 (± 5.4, standard deviation). The association between antibody titer and age of participants was statistically significant (Spearman correlation ρ=0.29, P<0.0001). In addition, the level of antibodies to VZV increased with age. Fig. 1 displays seroprevalence pattern of subjects versus their age. The bars in the Figure represent 95% confidence intervals. Beginning with 40% and ending up with 100% at 31 years of age, seroprevalence showed clearly an increasing trend as individuals getting aged. The Figure also shows that all women older than 31 years were antibody positive whereas this was 40% for those in range of 13 to 14 years old.

In comparison of seroprevalence between women living in rural area with those living in urban areas, there was not any significant difference (Chi-squared, P = 0.56). Moreover, no statistically significant association between the level of immunity against VZV and participants' occupation (Fisher exact test, P = 0.987) and education (Chi-squared, P = 0.295) were observed.

Table 1 reports the seroprevalence of antibodies against VZV with respect to the number of siblings. As the number of sisters and brothers increased, a tendency toward more positive and less negative outcomes can be seen. In families with more than eight siblings, 83.3% of women showed positive test results. The Fisher exact test indicated a significant association between the immunity level of participants to VZV and their family sizes (P = 0.03).

Subjects were also asked about their history of chickenpox (Table 2). The total number of 111 individuals found with positive chickenpox history and 134 reported negative history.

The distribution of antibody levels showed highly positive skewed distribution hence to obtain sensible estimates, the median ± IQR (interquantile range) are reported. The median antibody level of women with positive history of chickenpox was 6.86 ± 20.63 IU/ml whereas it was 0.18 ± 5.69 for those with negative chickenpox history. Furthermore, out of 111 with positive varicella disease history, 105 subjects identified with positive varicella antibody.

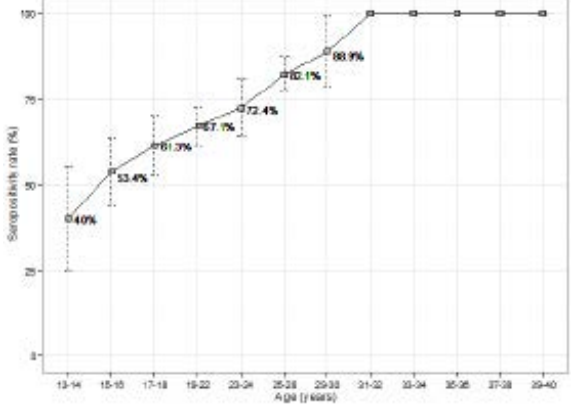

Fig 1: Varicella Zoster Virus IgG seroprevalence pattern of women versus the age (years). Bars represent 95% confidence intervals.

Table 1. The prevalence of antibodies to varicella-zoster virus according to the number of siblings

Siblings	Negative (antibody level < 0.11 IU/mL)	Equivocal (0.11 < antibody level< 0.13 IU/mL)	Positive (antibody level > 0.13 IU/mL)	Total
[1-2]	33 (39.29%)	0 (0%)	51 (60.71%)	84
[3-8]	38 (23.75%)	0 (0%)	122 (76.25%)	160
>8	1 (16.67%)	0 (0%)	5 (83.33%)	6
Total	**72 (28.8%)**	**0 (0%)**	**178 (71.2%)**	**250**

Table 2. The prevalence of antibodies to varicella-zoster virus according to history of chickenpox

History	Negative (antibody level < 0.11 IU/mL)	Equivocal (0.11 < antibody level < 0.13 IU/mL)	Positive (antibody level >0.13 IU/mL)	Total
Positive	6 (5.40%)	0(0%)	105 (94.60%)	111
Negative	66 (49.25%)	0(0%)	68 (50.75%)	134
Uncertain	0 (0%)	0(0%)	5 (100%)	5
Total	**72 (28.8%)**	**0(0%)**	**178 (71.2%)**	**250**

From 134 participants with negative varicella disease history, 68 were negative for varicella antibody. Positive predictive value (PPV) and negative predictive value (NPV) of self-reported history of chickenpox were calculated as 94.59% and 50.74%, respectively.

DISCUSSION

The severity of varicella in pregnant women requires regular screening strategies to identify susceptible individuals. The result of this study should provide the health policy makers and obstetricians the basic information about the potential transmission of the VZV in the studied population in order to implement necessary programs such as vaccination schedule, intervention with varicella-zoster immunoglobulin (VZIG), and antiviral therapy.

In this study, the level of immunity against VZV in pre-marital young women was obtained to be 71.2%. We also found a direct and significant association between the immunity level of participants, their age and number of siblings. We found 28.8% of women in the study were negative for varicella antibody and hence vulnerable to VZV. Thus, the potential of virus transmission and complications for mothers and their fetus should be considered with care.

Similar studies in Iranian population have reported the immunity against VZV from 72.9% (2) to 90.2% (8). Hosseininasab et al. found 89.35% of premarital women with serological varicella immunity in Kerman, south-east of Iran (9). This was 78.5% in another study conducted in Hamadan, the west of country (4). Furthermore, in Bushehr, the south of Iran, along the coastal region of the Persian Gulf, antibodies against VZV was estimated 74.5% among college females (10).

Studies in other countries reported higher rate of seroprevalence than what we observed in our study. In a study, UK, Bradford, the seroprevalence of VZV among pregnant women reported by 95% (11). In Korea, it has been reported by 89.6% among females fewer than 80 year of age (12). In spite of vaccination coverage the prevalence of VZV antibodies has found to be 92.8% among young adults in Madrid, Spain (13). The overall IgG seroprevalence was 84.3 % among Croatian women during their fertility period (14). All female daycare workers tested seropositive for VZV, compared to only 94% of the women not working in daycare in Amsterdam (15). Seroprevalence of VZV among pregnant women was 80.9% in Tunisia (16). In addition to other reasons, the vaccination against VZV in developed countries may explain in part the discrepancy between these results and our finding.

In agreement with our finding, some studies conducted in Iran and other countries also confirmed a direct association between immunity to chickenpox and age (2, 12, 14, 17-18). However, in a few studies conducted in Iran, no significant association between immunity and age was found (6, 8). In our study population, the seropositivity increased with age and hit 100% at ages over 31 or above. This is due to increasing the possibility of VZV transmission with age.

We found the mean marital age 22 years with a seronegative rate of 44.78% at 13-18 age group and 32.56% among19-23 years women. Thus, routine screen for VZV antibodies for women under 30 years who report no chickenpox history is recommended.

In agreement with our findings, increasing the immunity to chickenpox with the numbers of siblings has been reported in other studies in Iran (2, 8), Non-significant association between seroprevalence of VZV and education, palace of residence, as well as occupation have also been reported (4, 8-10, 14).

In some studies a significant association between history of chickenpox and immunity has been reported. By studying Iranian women with positive history

of pre-marital chickenpox, Hosseininasab et al. found that 94% were serological varicella immunity and 85% of them who were either uncertain or with negative history of chickenpox seropositive (9). Pourahmad et al. estimate the pre-marital PPV of participants with positive history of chickenpox 79.5% and the NPV 30.5% for those uncertain or with negative history of chickenpox (2). Koturoglu et al. studied the seroepidemiology of VZV and reliability of varicella history in Turkish adolescent population (19). They found the NPV about 57.8%decreased with age. Hannachi et al. reported PPV and NPV of chickenpox history 84.9% and 20.9% respectively in Tunisia population (16). In Hong Kong positive immunity was observed among 95.4% of pregnant women, and those with positive, negative, or uncertain history of infection reported similar high seroprevalence (96.4, 90.5, and 95.9% respectively) (20).

In our study, 94.59% of women with positive chickenpox history were identified as seropositive with mean level of antibody higher than those with negative history of infection. Significant association was observed between the history of chickenpox and immunity. These findings indicate that the positive history of chickenpox can be used alone as a good predictor of seropositivity. However, premarital serological test is recommended for negative cases.

In developed countries, vaccination coverage against VZV is well developed. Many countries are studying the possibility of mass vaccination against varicella (21). To develop vaccination programs and appropriate preventive health care measures against the disease, a good knowledge about the level of immunity is important. Hence, in Iranian society, population screening should be done across all provinces. However, since the coverage of varicella vaccination in Iran is not yet broadly available, to reduce the risk of varicella in women, vaccination before marriage and pregnancy is recommended for those who may have one or all of the following criteria; i) under 30 years old, ii) living in a household less than three siblings, and iii) with missing history of chickenpox and immunity.

In conclusions, our findings showed that there were a noticeable percentage of young women susceptible to varicella. This makes them vulnerable against the infection and possibility of the maternal and fetus abnormalities. Therefore, screening for immunity of young women and further studies on the need of vaccine administration before marriage or pregnancy is highly recommended.

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