

Seroprevalence of VZV and HSV-2 Antibodies among Women of Childbearing Age Referring to Health Centres of Mashhad, Iran: The Need for Consideration of VZV Vaccination Program

Abstract

Background: Infections with herpes simplex virus type 2 (HSV-2) and varicella-zoster virus (VZV) are associated with serious maternal and neonatal health consequences. The literature review reveals a research gap regarding the seroprevalence of HSV-2 and VZV among women of reproductive age in Mashhad, Northeast of Iran. The present study aims to evaluate the seroprevalence of these viruses among a group of women in Mashhad, Iran. **Methods:** Sera were collected by health center personnel using a cluster sampling method from healthy women with specific age characteristics residing in three distinct socioeconomic regions of the city. The participants, aged 20–35, were divided into three groups (20–25, 26–30, and 31–35 years). The levels of VZV and HSV-2 IgG antibodies were evaluated using commercial ELISA kits. Subsequently, the results were analyzed using SPSS software. **Results:** A total of 93 women were included in the study. Anti-HSV-2 IgG antibody was detected in 3 out of 93 participants (7.5%), while anti-VZV IgG antibody was found positive in 80 out of 93 individuals (83.3%). The HSV-2 positive cases were concurrently positive for the VZV antibody. There was no significant difference in the positivity of anti-HSV-2 and anti-VZV antibody positivity within age groups or socioeconomic status ($P > 0.05$). **Conclusions:** The high seroprevalence of VZV among nonvaccinated participants indicates a widespread presence of the virus and underscores its potentially serious impact on community health. Therefore, it is recommended that a VZV vaccination program be considered by the health system. Furthermore, the reactivation of latent HSV-2, whether symptomatic or asymptomatic, during pregnancy should not be disregarded as a life-threatening threat.

Keywords: *Herpes simplex type 2, Iran, Mashhad, varicella-Zoster virus*

Introduction

Numerous viral pathogens, including herpesviruses such as Herpes simplex virus (HSV), Cytomegalovirus (CMV), and varicella-zoster virus (VZV), can cause serious complications during pregnancy.^[1] Herpesviruses are characterized by lifelong latent infection in nerve cells and the potential for viral reactivation.^[2] Reactivation of HSV in pregnant women can lead to life-threatening infections in newborns.^[3] HSV-2 can be vertically transmitted during vaginal delivery, particularly in cases of Preterm Rupture of Membranes (PROM). In 80% of cases, neonatal Herpes is caused by HSV-2. Intrauterine infections present with Herpes lesions at birth or within the first 24 hours, while neonatal acquired infections develop vesicles in 6–13 days

after birth. Neonatal Herpes caused by HSV-1 can occur through direct contact with labial HSV-1 or accidental exposure to contaminated hands.^[4] Clinically, neonatal Herpes infection is always symptomatic, and in untreated cases, the mortality rate reaches 50%.^[5] In addition to skin lesions, encephalitis and disseminated multiorgan involvement are serious manifestations of the infection.^[6,7] It is noteworthy that delayed diagnosis of neonatal HSV infections increases the risk of mortality, and clinical diagnosis at the right time is lifesaving. The issue becomes important when the maternal reactivated infection is asymptomatic. In this regard, studies have shown that only 40% of new cases of HSV-2 cause clinical symptoms in patients.^[8] In addition to the high mortality rate, neonatal infection may be associated with permanent neurological complications.

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Therefore, maternal screening for type-specific antibodies against Herpes viruses has been proposed in healthcare protocols.^[9]

The other Herpes virus, VZV, causes potentially severe complications in pregnancy.^[10] Primary VZV causes a wide range of severe outcomes such as secondary bacterial infections, encephalitis, pneumonia, hepatitis and multiorgan involvement in immunodeficient patients, and even stroke.^[11,12] In addition, a latent virus may cause different types of shingles presentations.^[13] Primary infection with VZV during pregnancy has significant implications for maternal and fetal health. Therefore, pregnant women are among the high-risk group for VZV infections.^[14] First, in primary infections, maternal pneumonia^[15] results in a noticeable mortality rate, and the patients should be hospitalized and receive antiviral medication.^[16] Second, symptomatic or subclinical primary maternal infection may cause congenital varicella syndrome.^[17] Third, in addition to congenital varicella syndrome, perinatal transmission of maternal primary infection results in serious and potentially fatal neonatal varicella infection.^[18] On the other hand, it seems that transmission of secondary (reactivated) VZV infection during pregnancy is generally accompanied by rather fewer effects on the fetus due to the spontaneous transmission of maternal neutralizing antibodies to the fetus.^[18] In general, due to the risk of primary VZV infection or possible VZV reactivation in immunocompromised cases, monitoring of VZV during pregnancy is of high clinical importance,^[19] and protocols have been developed to prevent and manage VZV involvement during pregnancy.^[20]

Little is known and recorded regarding HSV-2 and VZV seroprevalence among women of childbearing age in Mashhad, Iran, and meta-analysis studies have indicated that their estimations have been done without data from the Northeast part of Iran. Therefore, the present study was performed to provide epidemiological data regarding these clinical important viruses.

Materials and Methods

Study groups

Sampling was performed based on a stratified sampling method. The Mashhad city area was divided into three distinct regions based on socioeconomic status (SES). In each cluster, selected mother and child health centers were recruited to perform sera collection. In these centers, remaining sera of routine laboratory tests were stored frozen at -20°C to be used for serosurvey analysis. Among the available samples, 93 were finally selected. Age groups consisted of an equal number of cases aged 20–25, 26–30, and 31–35 years. Participants stated no history of diagnosed clinical conditions.

ELISA for IgG against HSV-2

An indirect immunoenzyme assay was used to evaluate Immunoglobulin G (IgG) antibodies against VZV and HSV-2 in serum samples. The commercial kits were purchased from Vircell, S.L., Santa Fé, Granada, Spain. The assay was performed based on the manufacturer's instructions. Briefly, samples were added to each well and incubated for 60 min at 37°C . The plates were then washed three times. Thereafter, conjugated enzyme solution was added to each well and incubated for another 30 minutes at 37°C . After careful washing steps, a substrate–dye solution was added and incubated for 15 minutes at room temperature in the dark. Afterward, a stopper solution was added to all wells to stop enzymatic reactions. Then, the optical density (OD) values were measured spectrophotometrically with a microplate reader at 450/620 nm.

Statistical analysis method and sample size

Data analysis was performed using software SPSS version 18. The Kolmogorov–Smirnov test was used to determine the normal distribution of quantitative data. A comparison of age in various socioeconomic groups was performed with the Analysis of Variance (ANOVA) test or its nonparametric equivalent, i.e., the Kruskal–Wallis test. In this study, a significance level of less than 0.05 was considered statistically significant in all calculations.

Ethical considerations

The study was performed in accordance with the universal ethical principles stated in the Declaration of Helsinki on human research. Study results were anonymous, and samples were coded to ensure research confidentiality. All individuals freely agreed to participate in the study. Additional sampling was not performed, and sera were provided from the remaining samples of routine blood tests conducted in maternal healthcare centers. The study proposal was reviewed and approved by the ethical committee of Mashhad University of Medical Sciences (Ethical approval code: IRMUMS.fmREC.1396.377).

Results

Demographic variables

The samples were equally selected in each cluster ($P > 0.05$). Among the 93 participants, 31 (33.3%) were from the high SES cluster, 30 (32.3%) were from the middle SES cluster, and 32 women (34.4%) were from the lower SES part of the city. The mean age of the studied participants was 29.45 ± 4.68 years. Participants were divided into three equal age groups ($P > 0.05$).

Measurement of anti-HSV2 and anti-VZV IgG antibodies

Based on standard curves of OD values, the anti-VZV IgG antibody was positive in 80 out of 93 women (83.3%).

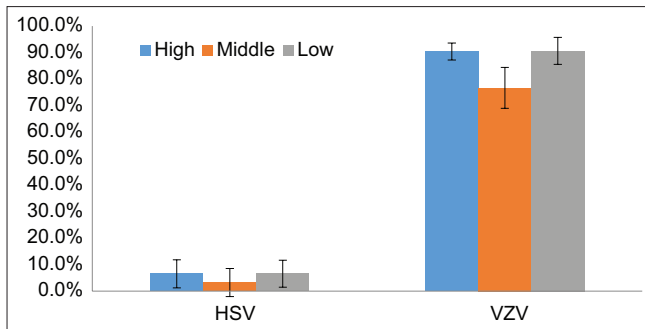


Figure 1: The percentage of positive cases for HSV2 and VZV antibodies among different socioeconomic clusters (error bar = one standard error; no statistical difference was observed in each socioeconomic group)

Among the study participants, the anti-HSV2 IgG antibody was positive in seven individuals (7.5%).

As shown in Figure 1, there was no significant difference among socioeconomic clusters in terms of VZV IgG positivity ($P = 0.199$). Similarly, Figure 2 demonstrates that VZV IgG was positive and approximately identical in the study groups ($P = 0.535$).

Regarding HSV 2, the seven cases were distributed in the three socioeconomic clusters as follows: 6.5% in the low SES cluster, 3.2% in the middle SES cluster, and 6.5% in the high SES cluster ($P = 0.570$) [Figure 1]. Regarding age groups, 6.2% of the age group of 20–25 years, 3.4% of the age group of 26–30 years, and 6.2% of the age group of 31–35 years were positive for HSV-2 IgG ($P = 0.539$) [Figure 2].

Discussion

Based on our best knowledge, the present study is one of the first reports addressing two main Herpes viruses among a sample of selected women in Mashhad, Iran.^[21] The global prevalence of HSV-2 varies among different countries^[22] and among different population groups. Importantly, specific attention has been drawn to childbearing-aged women.^[23] The global prevalence of HSV-2 among people aged 15–49 years has been estimated to be 11.3% with an annual incidence of 0.5% of new cases.^[24] Specific geographic areas, female gender, number of partners, poor SES, and the age of onset of sexual activity are associated with increased HSV-2 prevalence. Therefore, the estimated global prevalence should not be generalized to all distinct societies and various demographic groups. A global meta-analysis pooling data from all around the world reported a wide range of HSV-2 seroprevalence, from of <1% in Europe to >80% in some African areas.^[25]

In Iran, reported HSV-2 seroprevalence ranges from 2.7% in Kerman to 23.3 and 28.19% in Kazeroun and Shiraz, respectively.^[26-28] Only one study conducted in Isfahan reported a high seropositivity of HSV-2 (43.7%) among 96 pregnant women, which seems unlikely and might be due to technical issues.^[29] One meta-analysis conducted

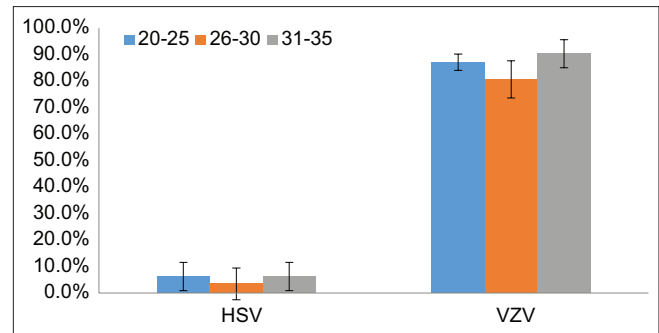


Figure 2: The percentage of positive cases for HSV2 and VZV antibodies among different age groups (error bar = one standard error; no statistical difference was observed in each age group)

by Mina Malary and colleagues in 2016 included 33 studies (11 seroprevalence reports) except Mashhad. The authors stated that based on data from 7,762 evaluated samples, the prevalence of HSV-2 in Iran is about 6.5% (95% CI: 4.7–8.2).^[30] The frequency of HSV-2 in the current study is consistent with the estimated HSV-2 prevalence reported in Malary *et al.*'s study.

There is a consensus that VZV infection is a common global human disease,^[31] although vaccination programs in many countries have changed the natural course of the infection. Therefore, new upcoming seroepidemiological data focus on the efficacy of immunization with the VZV vaccine to elicit anti-VZV IgG antibodies.^[32,33]

In Iran, one meta-analysis including 22 studies with a total sample size of 7,876 samples reported general VZV IgG seropositivity of about 78.50% (95% CI of 77.74–79.25%), although the study indicated a high heterogeneity among included studies and highlighted a lack of data from various parts of Iran, including northeastern Iran.^[34] Another meta-analysis in the country reported a seroprevalence of 59.7% among children under 11 years, and 87% among adults over 40 years.^[35] The findings of these meta-analyses are consistent with the results of the present study, although they lacked data from Mashhad.

The virus is highly prevalent in the community, and most individuals become infected before reproductive ages. However, VZV risk during pregnancy is still serious for the percentage of women who remain unimmune until reproductive age, as well as cases of reduced immunity. As mentioned previously, the clinical significance of transmission of reactivated VZV from mother to fetus in case of declined maternal neutralizing antibodies remains to be further explored.^[36] In addition, primary VZV infection in the pregnant mother can be a serious threat to neonatal health. The risk is even worse in the case of neglected asymptomatic primary VZV infection. Therefore, due to high prevalence of VZV, it seems logical to consider VZV vaccination program in national health system. Global vaccination strategies vary among different countries, with most of these strategies based on benefit-to-risk studies in each country. Childhood

general vaccination or vaccination of specific groups has been considered in different societies.^[37,38]

Taken together, here we report the results of HSV-2 and VZV from a group of women in Mashhad.

The main limitation of the present study was the small sample size. Periodical seroprevalence studies are recommended to follow possible decreasing or increasing trends and to assess the achievements of implemented health interventions.

Conclusions

The study indicated that HSV-2 reactivation and ultimate risks may occur in almost 7.5% of women of childbearing age. In addition, a high rate of VZV antibody (83.3%) was observed among the studied individuals, which is of great health importance. Therefore, it is recommended to implement a vaccination program to reduce the circulating wild-type VZV. This program would contribute to health promotion and improve health indicators.

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Code of Ethics

The study proposal was reviewed and approved by the ethical committee of Mashhad University of Medical Sciences (Ethical approval code: IRMUMS.fmrEC.1396.377).

Authors' Contributions

Study design: MY, FZA, MKR Data gathering: MY, HGh Data Analysis: MKR Drafting the manuscript: MY, FZA, HGh, MKR Revising the Manuscript: MY, FZA, MKR Final Approval: MY, FZA, HGh, MKR.

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Conflicts of interest

There are no conflicts of interest.

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