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# Varicella Infection as a Congenital Health Threat: A Narrative Review

Khadije Rezaie Keikhaie [1], Fereshteh Javadian [2,*] and Aliyeh Sargazi [1]

[1]Department of Microbiology, Zabol University, Zabol, Iran
[2]Zabol University of Medical Sciences, Zabol, Iran

[*]*Corresponding author*: Zabol University of Medical Sciences, Zabol, Iran. Email: fereshteh.javadian@yahoo.com

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**Abstract**

Even though varicella is rare in pregnancy, if it occurs, it may be associated with a high rate of mortality and morbidity for both mother and newborn. Studies show that maternal infection causes congenital varicella syndrome, which could be presented with neonatal malformations such as limbs hypoplasia, skin scarring, and visual defects. This disease is more dangerous in the case of association with pneumonia, bacterial superimposed infections, and hemorrhage. Therefore, it is suggested that any varicella-exposed pregnant woman at any gestational age receives prophylactic varicella immunoglobulin. This paper deals with the clinical consequences and the available methods of prevention, diagnosis, and treatment of varicella-zoster virus infection during pregnancy.

*Keywords:* Health Threat, Varicella, Infection

## 1. Context

Varicella is an acute infectious disease caused by the Varicella-Zoster Virus (VZV). The recurrent infection, herpes zoster (also known as shingles), has been known since ancient times. The primary varicella infection (chickenpox) was not distinguished from smallpox until the end of the 19th century. In 1875, Steiner discovered that chickenpox is caused by an infectious agent when inoculating volunteers with the vesicular fluid from a patient with acute varicella. Clinical experiments on the relationship between varicella and herpes zoster were conducted in 1888 by von Bokay; in this study, children without evidence of varicella immunity were infected by varicella after contact with herpes zoster patients. VZV is an opportunistic pathogen that causes severe infection in immunocompromised patients. It also causes latent infection in these patients. Two main diseases are caused by this pathogen including common varicella, known as chickenpox, and herpes zoster (HZ) (1). It is also important in pregnancy because it influences the fetus and shows abnormalities as seen in 2% of pregnancies with VZ infection in the first 20 weeks of gestation. Moreover, any infection in the third trimester can cause severe infection in newborns (2). This disease could be prevented by live attenuated vaccines that were introduced in the 1970s. Many studies show that the vaccine is effective in creating a long-lasting immunity. The chickenpox vaccine is part of children routing vaccination program in many countries while there is no vaccination plan in Iran (3-7).

## 2. Epidemiology

The VZV is transmitted person-to-person via the respiratory system; therefore, close contact with varicella-infected individuals is one of the main ways of its spread. The infection risk is 10% - 35% in school exposure and 90% in home exposure (8). It is worldwide distributed with more prevalence in temperate climates and less frequency in tropical areas. The annual epidemics of this infection occur at the end of winter and spring (9). Almost all children are infected in temperate areas. For example, the varicella annual incidence is nearly equal to the birth rate in the United States. The susceptibility in adults is only 5% in temperate climates. However, half of the adults in tropical regions are susceptible because of no childhood exposure (10). Restriction endonuclease analysis is a technique used for providing evidence of epidemiological characteristics of varicella such as prevalence and virulence (11).

HZ appears in persons with a history of varicella. Unlike varicella-zoster, HZ does not exhibit any particular seasonal pattern. Studies show that the old age and the white race are the risk factors of HZ (12). The HZ incidence was reported 3.4 cases per 1,000 population on average; it was 10 per 1,000 in adults older than 75 years and rare in children (13, 14). HZ is seen in children under one-year-old

with a history of congenital varicella because of maternal infection in pregnancy (15, 16). HZ is more common among immunocompromised patients including immunodeficient patients and those receiving immunosuppressive medications (17). It is mostly seen in malignancies such as leukemia, Hodgkin's disease, non-Hodgkin's lymphoma disease, oat cell carcinoma of the lungs, and hematologic diseases such as systemic lupus erythematosus and rheumatoid arthritis (18). This infection has a close association with AIDS; therefore, HIV infection should be screened if HZ is positive.

Chickenpox (or primary VZV infection) is a routine childhood disease that usually causes a mild infection. Above 90% of people over 15 years of age in England and Wales were positive for VZV immunoglobulin G (IgG) antibody in their blood sera (19). Observations on pregnant women in Spain and France showed the immunity rate of 96.1% and 98.8% to varicella, respectively. Although the possibility of contact with varicella is common during pregnancy, especially in women who have children, primary VZV infection is rare in pregnancy. The probability of this infection is 3 per 1,000 pregnancies (20). Considering the high probability of negative titer of serum IgG in women living in tropical and temperate regions, they are more sensitive to chickenpox during pregnancy (21).

The presence of pneumonia complicates varicella in pregnancy and its rate has been recorded 10% - 14% (22) in small-scale studies. In a study on 347 cases of varicella infection in pregnancy, 5% of women were found with pneumonia (23). Generally, the mortality rate of varicella pneumonia in pregnancy in the English literature was 28/10 (36%) in the pre-antiviral period, which may reflect publication bias (24). Recent case-based studies reported that the mortality rate is 0% - 14%, which reflects the advancement of antiviral treatments and improved patient care (25, 26). In the UK, nine indirect deaths and one direct death were recorded due to the complications of varicella infection between 1985 and 1999 (27). These results indicate a low mortality rate. Mothers' deaths in confidential investigations have not been reported since then.

## 3. Zoster in Pregnancy

The uterine-related dermatomes are innervated in T10 - L1 spinal segments; therefore, it is expected that these dermatomes are at a higher risk of infection during pregnancy although this theory has not been proven clinically (28). Moreover, prospective studies showed that most neonates were born healthy to mothers with the experience of varicella at any gestational age. However, a few cases were reported with congenital varicella syndrome (16, 29). Therefore, all mothers exposed to varicella infection should receive prophylactic immunoglobulin.

## 4. Congenital Varicella Syndrome

The congenital varicella syndrome (CVS) is presented in neonates with malformations such as limb hypoplasia and skin scarring (30). The CVS would be associated with visual problems. The granulomatous tissue is seen to cover the face from forehead to eyes. Eyelashes, conjunctiva, and cornea are damaged, too. Cornea opacification and vascularization are particularly seen. On the other hand, varicella will cause limbs atrophy, limbs hypoplasia, and skin scarring.

There are studies demonstrating the association of maternal immunoglobulin with CVS (16, 31, 32). Moreover, a study by Orenstein et al. compared neonates whose mothers had contracted varicella at the gestational age of twentieth or thirteenth week and received or not received its immunoglobulin, showing that CVS was significantly less frequent in the former group (33). A similar study was conducted by Mouly et al. to assess the relationship between CVS and immunoglobulin injection in mothers who had contracted varicella in the first 24 weeks of pregnancy (34). In contrast, the study by Miller et al. showed that maternal varicella infection near delivery did not lead to neonatal varicella. Combining the data from the above-mentioned studies shows that out of 640 women with varicella experience during pregnancy, 142 received and 498 did not receive immunoglobulin. Among all newborns, only were 14 diagnosed with CVS, all of whom were born to mothers who had not received varicella-zoster immunoglobulin. In conclusion, the Fisher exact test showed a significant relationship between CVS and maternal immunoglobulin.

Varicella-zoster immunoglobulin (VZIG) prevents maternal infection but its role in fetal prevention has not been proven yet. In a study by Enders on pregnant women, the fetal infection was not seen in varicella-exposed mothers who had received VZIG (16). This finding was not statistically significant because of the small sample size of the study.

Although the preventive role of immunoglobulin is a matter of controversy, all exposed mothers at any gestational age should receive VZIG (35).

## 5. Neonatal Varicella

Chickenpox is an acute disease that manifests different symptoms from a mild febrile disease with skin vesicles to a complicated disease with pneumonia and hemorrhage.

In 30% of neonates, chickenpox is associated with complications and mortality, especially if the neonate did not acquire mother-to-child passive immunity (36). Pneumonia is more common among adults but if it happens in children, it will be associated with sepsis (37). A study on two chickenpox-infected neonates with pneumonia and bacterial superimposition showed that both cases were lethargic and had tachycardia, tachypnea, hyperthermia, and leukocytosis with high nucleated white cell count. Chickenpox was presented with papulovesicular rashes associated with pus discharge in the case with bacterial superimposition. The arterial blood gas analysis showed hypoxia in the neonate with pneumonia and metabolic acidosis in the case with bacterial superimposition. Chest X-ray showed consolidations in both cases but more severe wide-speared patchy consolidation appeared in the neonate with pneumonia. In the case with pneumonia, the mother showed chickenpox rashes four days following chickenpox presentation in her neonate while the mother of the neonate with superimposed infection had presented chickenpox one day before delivery.

## 6. Prevalence

Being aware of the epidemiology of varicella helps us in planning proper control and vaccination programs. Although a higher rate of varicella infection is reported among children, more susceptibility to VZ is seen at older ages. For example, studies show that 46%, 75%, 83%, and 94% of total VZV infected cases were five, five to nine, ten to fourteen, and ten-years-old in Switzerland, Spain, Italy, and Germany, respectively (38).

Seropositivity is directly correlated with age as its rate increases with age from 18.4% to 93.0% in patients aged 2 - 5 years and more than 75% in adults (39). In a study reported from Iran, this correlation was higher than what we mentioned before. The prevalence of VZ infection and complications is considerably high worldwide; therefore, VZ vaccination is proposed to decrease the varicella-related socioeconomic burden. For example, the vaccination program in the United States decreased by almost 85% of newly infected cases. In another study conducted in Iran, more than two-thirds of cases were seropositive and the VZ antibodies level was directly associated with age; therefore, susceptibility decreased in older patients. Approximately, 25%, 43%, 73%, and 87% were seropositive in 1 - 5, 6 - 10, 11 - 15, and 16 - 20 age groups (40, 41). This is in coordination with the results by Taghavi Ardakani et al. who conducted a study on serum antibodies in children aged 1 - 15 years. They showed that the IgG antibody prevalence increased by 17% with each year increase in age in this population. The seropositivity is almost two times more in families with more than four members than in smaller families; it is almost 40 times more in children with a history of chickenpox (42).

In different studies conducted in Iran, seropositivity was reported 42.5% in children aged 1 - 16 in Tehran in 2009 while it was 59.7% in children aged less than 10 years, 60.4% in children of 10 - 14 years old, and 87.5% in 15 - 19-year-old cases in Tehran in 2005 (43). A study conducted in Shiraz, located in a tropical area, showed that 35.2% of schoolchildren aged 6 - 10 years were seropositive while in another study conducted four years later in the same city, seropositivity was 25.3%, 43.1%, 73.5%, and 86% in children in age groups of 1 - 5, 6 - 10, 11 - 15, and 16 - 20, respectively (44).

Similar studies were conducted in Pakistan, Thailand, Singapore, and West India on serum immunoglobulin of children aged 1 - 15 years and reported that 37.4%, 52.3%, 20%, and 10% of their subjects were seropositive, respectively (21, 45, 46).

The seroprevalence was 93%, 45.8%, 94.2%, 85%, and 96.1% in children under five from the Netherland, under 10 from the United Arab Emirates, Germany, Turkey, and under 12 from Switzerland, respectively (38, 39, 47-49). Considering the high rate of VZV infection, the HZ infection rate is potentially high, as well. It is demonstrated that the incidence of hospitalization was 4.4 - 16.1 per 100,000 HZ-infected patients (50, 51). The wild type of HZ induces severe infection, neuralgia, and meningitis, particularly in immunocompromised patients (52). Accordingly, trials have been conducted to find the prevention methods. It has been shown that a high titer booster dose of VZV vaccine could be preventive at older ages (53, 54). Moreover, patients who had vaccinated against VZV showed less complicated HZ infection than the non-vaccinated group (55). Preventive varicella vaccination is cost-effective; therefore, it is suggested for children.

The data from past decades show that varicella was on the rias among adults while recent studies show the opposite trend (50, 56).

The pneumonia incidence is 0.32 - 1.36 per lakh in adult patients (57). The radiographic findings are presented in 5% - 50% of adults with varicella associated pneumonia (57). The most radiographic findings include interstitial and nodular infiltrations, which are more frequent among pregnant women (58, 59).

Immunocompromised patients and VZV-infected patients are at higher risk of pneumonia (60). Varicella-related pneumonia is presented one week after appearing first rashes along with fever, cough, chest pain, dyspnea, tachypnea, and hemoptysis (61, 62). Often when the symptoms are present, the radiologic findings are present, too (63). Even though there is a vast range of symptoms, they are not prognostic and may not be used for respiratory fail-

ure prediction (64).

Moreover, pneumonia itself is a cause of new respiratory diseases. In this case, smoking is considered a risk factor. Smoking makes patients more susceptible to viral infections, especially herpes infection (65). Skin spots appearance more than 100 in numbers is a prognostic factor for severe pneumonia and related viremia. Another factor that is associated with pneumonia is the history of contact. It is shown that children who acquire infection from their families develop more severe varicella. This could be related to the first inhaled infectious dose (8).

On the other hand, the high incidence of pneumonia and associated fever is observed in the third trimester of pregnancy. Many reasons explain this change such as fetus pressure on the thorax and Similar to pregnancy, the incidence of varicella- associated pneumonia is increaseds in other immunocompromised diseases. It also increases in chronic obstructive pulmonary disease (6).

## 7. Vaccination

Varicella vaccines are highly effective against the prevalence and pathogenicity of the disease (66). The vaccine is kept frozen. In 1984, the license was issued for the first commercial varicella vaccine. This vaccine was the first varicella vaccine that could be kept in a refrigerator. Its development began in 1991 and it has been licensed since 1994 (67). Although it is not universally accepted, the World Health Organization suggests that countries with high prevalence should place varicella vaccine in their vaccination program (66).

Most commonly, the first dose is given at 12 - 18 months of age; if approved, the second dose is scheduled at the age of 4 - 6 years. Alternatively, if the first dose (68, 69) lasts three months or longer, a second dose can be given in children under the age of 4, although a lower interval is assumed to be desirable in terms of epidemiological effect. Some countries need more time to get better in vaccination programs in childhood (68).

A single-dose vaccination program is effective for controlling severe diseases, but it is not enough as the progression of varicella may be observed (70, 71). Additionally, adding the second dose seems necessary to create more safety. The economic value of vaccination programs based on one or two doses has been widely discussed (72, 73), but national choices ultimately depend on priorities on vaginal exclusion or the prevention of severe illness. In addition, a modeling study in Italy showed that the coverage, effectiveness, dosage or dose interval, and high coverage were the main factors behind success (74). The World Health Organization recommends that vaccination coverage should be more than 80% to be successful (66).

There is no sufficient evidence of varicella-zoster immunoglobulin (VZIG) role in healthy individuals while trials on immunocompromised patients showed reductions in rates and disease complications (75). The associated risk between passive immunity and VZIG is low (76). Pregnant women are intensively at the risk of varicella-zoster infection. If the close contact happens, serum immunoglobulin (IG) should be measured without hesitation. If the IG level is low, undetermined, or unknown, VZIG should be injected in 96 hours. The exact timing is in controversy. Studies showed a reduced rate of fetal infection and maternal chickenpox (17). However, some studies showed that half of the mothers infected with varicella-zoster and receiving VZIG presented clinical varicella. Therefore, we can conclude the VZIG can reduce varicella complications but cannot eliminate it totally.

## 8. Chickenpox in Pregnancy

A first-trimester abortion is not associated with chickenpox (77, 78). Before 24 weeks of pregnancy, vertical transmission to the fetus has been observed by clinical/serological methods such as PCR; approximately, 24% and 8% of cases of with confirmed virologic maternal chickenpox respectively. Intrauterine growth restriction (IUGR) occurs in approximately 23% of cases (79) and low birth weight is universally spread (80). In a case-control study, non-exposed controls had a spontaneous preterm birth rate of 5.6% compared with 14.3% in cases of chickenpox in pregnancy (P = 0.05). The highest mortality and morbidity rates related to chickenpox in pregnancy are associated with the presence of CVS, maternal varicella pneumonia, and neonatal varicella.

## 9. Treatment of Varicella

Varicella disease is not serious in normal children and does not require treatment. However, the disease is very fatal in infants and people with immunodeficiency and some adults, necessitating treatment. Gamma globulin, which contains a high titer of varicella-zoster antiviral antibodies, can be used for treatment. Immunoglobulin can be used to prevent the development of disease in immunocompromised patients with a history of contact with chickenpox patients. If chickenpox starts, this product will be ineffective.

## 10. Varicella Diagnosis

Chickenpox is diagnosed with skin examination without the need for specific virus testing. In a classic way, the

virus can be removed from the surface of skin vesicles. The detection of virus DNA in vesicles is a very reliable method.

### 11. Clinical Manifestations of Disease in the Fetus

If a pregnant woman acquires chickenpox during the first half of pregnancy, her baby will be infected. In 1947, Lafart and Lynch first reported a pregnant woman suffering from chickenpox in the eighth week of pregnancy. The baby born to this woman had bone hypoplasia, eye atrophy, and hydrocephalus. If the mother's infection occurs in the first 20 weeks of pregnancy, almost 2% of this syndrome are observed and the use of varicella-zoster antiviral immunoglobulin does not reduce the risk of fetal infection. Shingles are very low in pregnant women and also is safe for the baby (81).

### 12. Conclusion

According to the study, most of the WikiLeaks virus, Zoster (VZV), is a neurotrophic Herpesvirus virus that infects most people. Host immunodeficiency even decades after the initial infection can cause the virus to re-activate itself, as a result, the ornament (zooster) is characterized by pain and rashes limited to lesions 1 to 3. This study summarized the current knowledge of the clinical and pathological complications of neurological diseases produced by the VZV reaction, latency, virology, and specific immunity, as well as the role of apoptosis in cell death caused by VZV, and the development of an animal model built by monkey varicella virus

### Footnotes

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