

# Varicella-zoster virus infection and pregnancy

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## ABSTRACT

Varicella-zoster virus is a herpes virus that causes mild to moderate disease when primary infection (chickenpox) is acquired in childhood, but leading to great morbidity and mortality in adults, with even more complications in pregnant women. As a physiologic adaptation in pregnancy that diminishes the possibility of fetal rejection, the altered maternal immune system is the reason why complications are more frequent in this segment of adult population. Moreover, a great concern is represented by the risk of vertical transmission to the fetus that can lead to congenital varicella syndrome (CVS) in the first 2 trimesters or to neonatal varicella if the mother develops the illness perinatally. Antiviral treatment reduces the gravity of the clinical manifestations, but the existent data shows that it doesn't influence the rate of fetal transmission. Immunoglobulin anti-VZV (VZIG) can be given as prophylaxis when there has been described contact with the virus. Vaccination should be offered to all non-immunized women at the prenatal visit to diminish the maternal and fetal risks in case of subsequent exposure. The purpose of this review is to update the current understanding regarding the best management of varicella infection in pregnancy, based on the latest data from literature and guidelines.

An electronic research for relevant reviews and articles published in the last 5 years was made, using PubMed, Medline, Cochrane Data Base, and also the current international guidelines promoted by the Obstetrics and Gynecology Societies in Canada, United States, Ireland and United Kingdom.

The importance of prenatal detection of non-immunized women by serologic testing for varicella antibodies should not be overlooked, and subsequent vaccination should be advised to lower the significant complications associated with developing the disease in pregnancy. In case of varicella infection in pregnancy, adequate treatment should be immediately initiated with immunoglobulin and antivirals. Careful follow-up with serial fetal echography should assess if there are abnormalities of fetal development consistent with congenital varicella syndrome. Future mothers need to be advised about the probability of vertical transmission and the associated fetal malformations. Future consideration must focus on identifying the woman at childbearing age at risk and facilitate the vaccination.

**Keywords:** varicella-zoster, infection, chickenpox, vaccination, pregnancy, TORCH

## INTRODUCTION

Varicella is a common infectious disease spread worldwide. Primary infection with the varicella-zoster virus is defined as chickenpox and represents one of the benign childhood infections, while reactivation of the dormant latent virus located in sensory ganglia is known as shingles or herpes zos-

ter. Varicella-zoster virus is a contagious DNA alpha herpes virus that is easily transmitted by droplets from the respiratory tract or direct contact with the fluid existent in the cutaneous vesicles of an infected person. The direct contact considered significant in order to determine the infection is of debate, and it is largely accepted that being in the same room for more than 15 minutes or having a face-to-face

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interaction for a period of minimum 5 minutes can lead to the transmission of the virus [1]. A person can be the vector for transmission 2 days before the rash erupts until the skin lesions crust over [1,2]. The primary infection (chickenpox) is characterized by fever and a generalized vesicular and pruritic exanthema, with high viremia. The time range of incubation is situated between 1 to 3 weeks and the infected person becomes contagious 48 hours before the onset of skin rash until the vesicles develop a crust and heal. The immunity after the primary infection usually is for life. Although children usually develop a mild form, adults are susceptible to develop varicella complications as bacterial infection of the cutaneous lesions, pneumonia, disorders of the central nervous system (meningitis, encephalitis with poor prognostic), hemorrhagic complications, Reye syndrome and rarely, can cause a multiorgan inflammatory response [2,3]. After the recovery, the varicella-zoster virus remains latent in the ganglia, respectively the sensory nerve root. It can be later in life reactivated having as clinical manifestation a painful vesicular eruption that affects only dermatomal regions of the body, defined as herpes zoster or shingles. Shingles is not related to high viremia and there are no risks of adverse fetal outcome if this pathology appears during pregnancy [2,4,5].

## METHODS

An electronic research for relevant reviews and articles published in the last 5 years was made, using Pub Med, Medline, Cochrane Data Base and also the current international guidelines promoted by the Obstetrics and Gynecology Societies in Canada, United States, Ireland and United Kingdom. The infection with varicella-zoster in pregnancy and its maternal and fetal impact were studied, with emphasis on the best health management and follow-up, in order to minimize the possible sequelae. Search words were “varicella-zoster“, “infection“, “chickenpox“, “vaccination“, “pregnancy“, “TORCH“. The publications used as source for creating this content are all mentioned in the section of references listed below.

## EPIDEMIOLOGY

Being a common childhood illness, chickenpox occurs rarely in the adult population. More than 90 % of the adult population is immunized and test seropositive for VZV IgG. Therefore, despite having contact with chickenpox, primary infection with VZV in pregnancy is rare. Among pregnant women, primary VZV infection can appear in about 2-3 cases of 1000 pregnancies [1]. The complications relat-

ed to primary infection increase direct proportional with the patient's age, the mortality rate growing 15 times when the disease appears in adulthood compared to childhood [6]. The pregnant woman develops more frequently varicella pneumonia than the general population, complicating 10-14% of the pregnancy infections, the severity of clinical manifestations increasing in the third trimester [1,7]. Less than 2% of women infected with varicella in the first and second trimester of pregnancy (especially before 20 weeks of gestation) develop an embryopathy, namely congenital varicella syndrome, as stated by the biggest prospective study ever published, the study of Enders et al., in 1994 [8].

## RISKS ASSOCIATED WITH VZV INFECTION IN PREGNANCY

### Maternal risk

The primary VZV infection comes with the replication of the virus in tonsils and in regional lymphatic nodes for a period of four to six days, being followed by extension to the other organs. After this first phase of replication, a secondary viremia is given by the release of the VZV in circulation, with subsequent invasion to the skin within 14 to 21 days that gives the clinical appearance of exanthema [2,9]. The diagnosis of chickenpox is made based mainly on the clinical aspect of vesicles distributed on any part of the body, but with a preponderance to the torso and the face. The most common complication related to primary infection with VZV is varicella pneumonia, which can affect 5-10% of the cases. The risk factors that can influence the onset and the then evolution of varicella pneumonia in pregnancy are smoking and a number of cutaneous lesions > 100. Moreover, the morbidity and mortality of pulmonary disease increase in the third trimester [10,11]. VZV infection, like any other virus, can put at risk for secondary bacterial or viral infections. Also hematologic, neurologic, pulmonary, or renal injuries can develop after catching chickenpox. Moreover, there are studies that relate late strokes as a consequence of varicella infection based on the inflammatory effect on the brain blood vessels [12]. The prognostic of varicella pneumonia has drastically improved after the discovery and use of the antiviral treatment with acyclovir. The pulmonary symptoms usually appear in maximum one week after the onset of the pruritic rash and include fever, coughing, pain in the chest, fever, which can be associated with shortness of breath and hypoxia. The mortality in pregnant women is related to a high incidence of respiratory failure and apart from the intravenous antiviral therapy that should be promptly initialized, intubation with mechanical ventilation is sometimes required [10].

## Fetal risk

The VZV infection in pregnancy can affect the fetus by transplacental transmission of the virus and can manifest as congenital varicella syndrome, if the mother develops the disease in the first two trimesters of pregnancy, or as neonatal varicella, if she becomes symptomatic in the interval between 5 days before delivery or 2 days postpartum [10]. Congenital varicella syndrome (CVS) was for the first time mentioned in 1947 and most frequently can develop if the mother gets infected with VZV in the first 20 weeks of pregnancy, although isolated cases have been described between 20 and 28 weeks of gestation [13,15]. The embryopathy is consistent with multisystem disorders that include chorioretinitis, cerebral malformation, malformation of the limbs (hypoplasia of the limbs), cutaneous lesions and can concern also the gastrointestinal tract, the cardiovascular and urinary systems [13].

CVS has a mortality rate approximated at about 30% in the first year of life and can develop herpes zoster in a proportion of 15% within 2 to 42 months of life. Moreover, maternal chickenpox is associated with a risk of low birth weight, intrauterine growth restriction and preterm birth. The neurological impairment in CVS can vary from cortical atrophy, micro- or hydrocephaly, to intellectual deficiency or retardation [14].

## HOW TO MANAGE THE VZV INFECTION IN PREGNANCY?

### Diagnosis

The diagnosis is, first of all, based on the clinical appearance of the vesicles, accompanied by fever and a general malaise in a pregnant woman with no history of chickenpox in childhood or vaccination. If there is doubt regarding the diagnosis, a PCR test from the vesicle fluid can be made. Also, the serologic detection for VZV IgM and IgG is important [7].

### Treatment

In a case of a non-immunized pregnant woman that describes being exposed to VZV, the management implies prompt administration of Varicella-Zoster Immune Globulin (VZIG), ideally in the first 96 hours for maximum effect. It can be given either intramuscular or intravenous, but the balance cost-benefit indicates that the intramuscular path is better. After the prophylactic treatment with VZIG, the exposed women should be carefully monitored and considered as potentially infected for a period of 1 to 4 weeks, which represents the incubation period of the virus [16,20].

The management of a confirmed pregnant patient with chickenpox should implicate immediate isolation and institution of antiviral treatment with

oral Acyclovir in high doses (800 mg x 5 per day, for a period of 7 days). Acyclovir is efficient in improving the disease manifestations if it is started in the day after the rash bursts. In complicated varicella, namely when the pregnant woman develops varicella pneumonia, intravenous therapy with acyclovir is necessary [10,16]. The safety of acyclovir in pregnancy hasn't been investigated in randomized trials, but the data available shows that there are no adverse effects associated with using it as a treatment for childbearing women [10].

### Prophylaxis

The vaccination program against VZV was introduced in 1995 and its implementation resulted in decreasing the morbidity and mortality of varicella by more than 94% in the United States only [4]. The vaccine contains a live and attenuated virus, and it implies 2 doses that must be administrated at 4-8 weeks distance. This scheme of treatment guarantees a seroconversion in more than 98 % of the people receiving the vaccine [3,9]. Being a live-virus vaccine, its use in pregnancy is contraindicated and careful advice should be offered to the woman at childbearing age receiving the vaccine about the necessity of contraception one month after the vaccination [17]. Taking into consideration the maternal and fetal complications that can result after being infected with VZV in pregnancy, all women need to be informed at the prenatal visit about the indication of vaccination against VZV if they have no history of varicella. Moreover, the vaccination is also indicated in the postpartum period, for diminishing the possibility of neonatal varicella if the woman is at risk [18]. If the mother develops chickenpox in the timeframe of 5 days before delivery and 2 days after birth, the baby needs to receive varicella immunoglobulin (VZIG) as prophylaxis of neonatal infection [18,19,20].

## CONCLUSIONS

Close consideration must be paid to primary varicella virus infection in pregnant women because of the important impact that has on the mother's health and fetus development. The immune status to VZV must be established from the first prenatal visit and vaccination offered to all women that are at risk to develop the disease in the future pregnancy. If a non-immunized woman has contact with the virus during pregnancy, prompt administration of VZ immunoglobulin could reduce the risk of developing the disease. Once typical symptoms consistent with chickenpox appear, antiviral therapy should be administrated in the first 24 h for decreasing the gravity of the clinical manifestations. After a primary VZV infection in pregnancy, routine

ultrasound screening until the delivery should be made to detect fetal abnormalities that complicate the congenital varicella syndrome. The importance

of prenatal vaccination should not be overlooked, and the future mother has to receive appropriate counseling.

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