Varicella in the fetus and newborn
Candice K. Smith*, Ann M. Arvin

Stanford University School of Medicine, 300 Pasteur Drive, G122, Stanford, CA 94305, USA

SUMMARY

Varicella (chickenpox) in pregnancy is unusual because most women of childbearing age are immune. It can, however, cause significant morbidity for the pregnant woman and in rare cases cause congenital varicella syndrome. The incidence of congenital varicella syndrome after maternal varicella during the first two trimesters is <1% across multiple cohort studies. Maternal infection in the third trimester is not associated with congenital varicella syndrome, but the infant may develop herpes zoster during the first one or two years. Maternal infection just before or after delivery presents a high risk for disseminated varicella in the infant. Serious infection can be prevented with passive antibody prophylaxis and antiviral therapy. Maternal herpes zoster does not result in adverse fetal or neonatal outcomes.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Varicella zoster virus (VZV) is a human alphaherpesvirus found throughout the world. As is characteristic of the alphaherpesviruses, VZV establishes latency in the cells of the sensory nerve ganglia after primary infection. It causes varicella (chickenpox) as the primary infection and herpes zoster when it reactivates. The clinical disease, which is usually self-limited, is a febrile illness with a pruritic vesicular rash. However, primary VZV infection can have severe consequences when it is acquired in pregnancy or the neonatal period.

VZV is highly infectious. Most adults in the USA are immune to varicella secondary to the high prevalence of transmission during childhood years. In addition, the varicella vaccine was licensed in 1995 and has significantly reduced the incidence of primary VZV infection in the population as a whole. For these reasons, varicella affecting women during pregnancy or neonates is rare. Pregnant women who contract varicella, particularly in the third trimester, are at higher risk for more severe disease, including pneumonia. The fetal outcomes include normal healthy infants in almost all cases, possible zoster in infancy, and, rarely, fetal death or congenital varicella syndrome (CVS). Perinatally acquired VZV can also cause significant morbidity and mortality in the newborn. Maternal herpes zoster is benign for both the pregnant woman and the fetus or newborn.

2. VZV epidemiology

VZV is a readily transmissible virus, with ~90% of susceptible household contacts becoming infected after exposure. Because of the widespread annual varicella epidemics, ~90% of adults born in the USA and Europe are immune to VZV. The introduction of universal varicella vaccination in the USA has modified the pattern of VZV transmission since 1995, but before then, the annual incidence of varicella was roughly equal to the birth cohort. Morbidity and mortality rates are higher in adults than in children, and pregnant women in particular are at risk, specifically for varicella pneumonia.

Although VZV infections occur in a worldwide distribution, there are notable variations in the incidence by latitude and climate. In the absence of varicella vaccination programs, varicella outbreaks follow a seasonal pattern of increasing numbers of cases in winter and spring in temperate climates. Through these epidemics, >90% of children become infected by age 15 years. By contrast, in tropical climates, VZV is acquired at less frequency and at older ages. These geographical differences in epidemic patterns are not understood, but may be secondary to viral strain differences, environmental conditions that limit survival of this heat-labile virus in the tropics, or host genetic factors.

Just before introduction of varicella vaccine in the USA, varicella had shifted from a peak incidence in children aged 5–9 years to 1–4 years. This shift was attributed primarily to earlier exposure through daycare attendance. VZV vaccine was licensed in 1995 and decreased the incidence of disease by 85–90% in the decade following licensure. In the USA, the national varicella vaccination program follows VZV with active surveillance, documenting a vaccine coverage rate of 80% within surveillance areas. Varicella incidence decreased most significantly in children aged 1–4 years, but decreases were shown in all age groups, including adults. Among adults, incidence of varicella declined 74% during 1995–2005, despite vaccination rates of only 3%. Herd immunity is the likely explanation for this decrease among adults.
Thus, the majority of adults who have lived since childhood in temperate climates are immune, as evidenced by the detection of VZV IgG antibodies in nearly 95% of adults in the USA.\textsuperscript{8,9} Therefore, only $\sim$5% of women of childbearing age remain susceptible to VZV.\textsuperscript{10} The incidence of primary VZV infection during pregnancy is correspondingly low. The rate was seven per 1000 in an early study of 30,000 pregnancies followed prospectively during the period 1958–1964.\textsuperscript{11} Introduction of universal childhood immunization against varicella has the potential to reduce the occurrence of varicella in pregnant women through herd immunity. Conversely, varicella vaccination programs must be comprehensive because of the risk that women will reach childbearing age without having either natural or vaccine-induced immunity.

3. Pathogenesis and clinical manifestations of primary VZV infection

Primary infection with VZV begins with mucosal inoculation of the virus through respiratory exposure or direct contact with fluid from varicella or herpes zoster skin lesions. The incubation period usually is 14–16 days but can vary from as few as 10 or as many as 21 days after contact. Based upon a poxvirus model, VZV had been presumed to replicate first in the regional lymphoid tissues, followed by primary viremia and viral replication in the liver and spleen; a secondary viremia was proposed to occur just before the appearance of skin or mucosal lesions in which infected mononuclear cells transported the virus to these sites.\textsuperscript{12} Recently, however, studies in the SCID-hu mouse model of VZV pathogenesis have shown that infected T-lymphocytes transport the virus to the skin xenografts within 24 h. A robust epidermal innate antiviral response with interferon-\alpha contributes to the delay in eruption of varicella skin lesions.\textsuperscript{13} From these studies, one may postulate that the 10–21 day incubation period is the interval required for VZV to overcome this innate immune response and create visible lesions at skin or mucosal surfaces. During the incubation period, the virus may spread as uninfected T-lymphocytes traffic into early stage lesions and transport progeny virus to new mucocutaneous sites; replication in reticuloendothelial tissue may also amplify the cell-associated viremia. By late incubation (24–48 h before the appearance of the rash), infectious VZV may be present in respiratory secretions, since respiratory transmission to susceptible contacts has been observed after exposures during this period.

Approximately half of individuals with primary VZV infection, more commonly older children and adults, experience a prodrome of fever, malaise, headache, and abdominal pain. The rash is initially manifested on the scalp, face, or trunk and consists of pruritic erythematosus macules that evolve to small fluid-filled vesicles. The vesicular fluid of skin lesions contains high concentrations of infectious virions, and the virus may be present in respiratory droplets or secretions. The period of contagiousness is one to two days before the onset of rash until all the lesions are crusted, usually five to seven days after the first lesions appear. Subclinical disease is rare — a difference between VZV and other herpes viruses that are typically asymptomatic during primary infection. Varicella is generally short in duration and mild in healthy hosts. The initial phase of illness may follow this apparently uncomplicated course in pregnant women and neonates. However, instead of resolving, it sometimes progresses rapidly to life-threatening disseminated infection involving the lungs, liver and central nervous system.

The clinical course of varicella in adults is more likely to be complicated, and this higher incidence of serious varicella in adults is magnified in pregnant women. Varicella pneumonia, which may progress to respiratory failure, constitutes the source of most morbidity and mortality in pregnant women, as it does in non-pregnant adults.\textsuperscript{14,15} The onset of varicella pneumonia is usually three to five days after the appearance of the rash. In a recent case series of 347 pregnant women with varicella, 18 (5.2%) had pneumonia, all were treated with acyclovir, and none died.\textsuperscript{4} The reduction in mortality compared with historical rates of 20–45% reflects both the availability of antiviral therapy and better respiratory management.\textsuperscript{16}

When primary VZV infection occurs in pregnancy, the virus can be transferred across the placenta to the developing fetus as a consequence of viremia. While transplacental transmission is assumed to be the most likely route, infection of the genital tract mucosa leading to an ascending infection with transfer across the amniotic membranes cannot be excluded. While viral transfer occurs and is evidenced by detection of VZV DNA in amniotic fluid, the rates of transplacental transmission do not correlate directly with fetal infection. The amniotic fluid may be positive for VZV by polymerase chain reaction (PCR) testing for viral DNA without causing fetal disease.\textsuperscript{17} Spontaneous abortion, fetal demise, and prematurity delivery have been reported after varicella in pregnancy, but the risk of these complications is low.\textsuperscript{18}

4. Intrauterine VZV infection

Primary VZV infection in the pregnant woman most often results in the birth of a normal newborn either because the virus was not transmitted to the fetus or fetal infection was controlled without consequences. Some of these infants may develop herpes zoster in infancy. However, the majority of infants with intrauterine infection evidenced by persistence of IgG at one to two years of age escape without signs or symptoms.\textsuperscript{19} Rarely, the outcome is congenital varicella syndrome (CVS) and/or fetal death. VZV may be transmitted across the placenta and cause intrauterine infection at any time during gestation. However, the spectrum of clinical disease that occurs correlates with the gestational age of the fetus. The highest risk for spontaneous abortion or CVS is in the first 20 weeks of gestation, but the overall risk of CVS in the first 20 weeks is <1%. There are a few case reports of infants with CVS whose mothers had varicella at 21–28 weeks gestation.\textsuperscript{16,19} If VZV transmission occurs as a consequence of maternal infection during the perinatal period, from approximately two days before delivery to five days after, the infant is at risk of severe life-threatening varicella disease.

4.1. Congenital varicella syndrome

CVS was first described in 1947, and >100 cases have been reported subsequently.\textsuperscript{16,20} A large prospective study of 1373 pregnancies complicated by maternal varicella performed in Germany and the UK confirmed several earlier studies with fewer such pregnancies that had suggested a low incidence of CVS. Nine cases of CVS were documented. All cases occurred during the first 20 weeks of gestation. The highest risk (2.0%) was observed between 13 and 20 weeks of gestation, with seven affected infants identified among 351 pregnancies. Only two cases of CVS were identified among 472 pregnancies in which maternal varicella occurred before 13 weeks (0.4%).\textsuperscript{21,22} Overall the incidence of CVS in nine reported cohort studies was 0.55% in the first trimester, 1.4% in the second trimester, and 0% in the third trimester.\textsuperscript{16}

The defects of CVS involve the skin, the limbs, the eyes, and the central and autonomic nervous systems (Table 1).\textsuperscript{22,23} The characteristic cicatricial skin lesions may be depressed and pigmented in a dermalaternal distribution or hypopigmented (Fig. 1). Ocular defects include cataracts, chorioretinitis, Horner syndrome, ptosis, microphthalmia and nystagmus. The typical limb and joint abnormalities are hypoplasia of the bones and muscle and/or absent or malformed digits (Figs. 2 and 3). Central nervous system abnormalities in CVS patients include cortical atrophy, seizures, and mental retardation. Many affected infants have microcephaly.
Dysfunction of the autonomic nervous system is evidenced by neurogenic bladder, hydroureter, esophageal dilation and reflux leading to aspiration pneumonia.24

The pathogenesis of CVS may reflect disseminated infection in utero or consequences of failure of virus–host interaction to result in establishment of latency, as normally occurs in postnatal VZV infection. Since VZV is a lymphotropic virus, it has the potential to spread to all fetal organs by the hematogenous route. A few reports that have examined fetuses infected after maternal varicella have shown that VZV is distributed throughout fetal tissue which supports the hypothesis of early viremia and with dissemination caused by a poor host immune response.24,25 Microcephaly can be attributed to VZV encephalitis and irreversible damage to growth of the developing brain. Of interest, the virus does not appear to cause intrauterine damage to the lungs or liver in infants with CVS, as it can in perinatal varicella or in other immunocompromised hosts. Fulminant infection involving these organs may result in fetal demise, rather than birth of an infant with CVS. VZV is also a neurotropic virus and many of the defects have been postulated to be a direct result of spinal cord and ganglia infection, causing destruction of the plexi during embryogenesis and leading to denervation of the limb bud and subsequent hypoplasia. Failure of muscle development has consequences for limb bone formation. The cutaneous defects are also likely to reflect VZV infection of sensory nerves. VZV infection of cells in developing optic tracts also explains the optic atrophy and chorioretinitis.26 In addition, VZV appears to destroy neural cells that comprise the autonomic nervous system in the affected fetus. Some skin lesions, which have the dermatomal distribution associated with herpes zoster, may be caused by VZV reactivation in utero. The short latency phase, if latency is established at all, can be explained by an inadequate cell-mediated immune response in the fetus.27

4.2. Herpes zoster in infancy

Maternal varicella during pregnancy can manifest as infant zoster in the first or second year.32–34 (Fig. 4). In one report, out of ten children who were asymptomatic at birth, but later presented with zoster, eight

---

**Table 1**

Clinical manifestations of congenital varicella syndrome.

<table>
<thead>
<tr>
<th>Skin</th>
<th>Nervous system</th>
<th>Eye</th>
<th>Musculoskeletal</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cicatricial lesions</td>
<td>Intrauterine encephalitis</td>
<td>Chorioretinitis</td>
<td>Intrauterine growth retardation</td>
<td>Cardiovascular defects</td>
</tr>
<tr>
<td>Cutaneous defects</td>
<td>Cortical atrophy/porencephaly</td>
<td>Cataracts</td>
<td>Developmental delay</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Seizures</td>
<td>Anisocoria</td>
<td>Gastrointestinal reflux</td>
<td>Urinary tract</td>
</tr>
<tr>
<td></td>
<td>Mental retardation</td>
<td>Musculoskeletal</td>
<td></td>
<td>Hydroureter</td>
</tr>
<tr>
<td></td>
<td>Autonomic instability</td>
<td></td>
<td></td>
<td>Hydronephrosis</td>
</tr>
</tbody>
</table>

---

**Fig. 1.** Classic cicatricial scarring is visualized in an infant with congenital varicella syndrome.
did so in the first year of life. The gestational age at the time of maternal varicella ranged from 14 to 33 weeks, with a median age of 25 weeks. The observed risk of zoster when maternal infection occurs before 24 weeks was 0.8%, compared to a 1.7% observed risk if maternal varicella was after 25 weeks. In another report, the risk of postnatal herpes zoster infection in infancy was 3.8% in cases when maternal amniotic fluid had been positive for VZV DNA by PCR.

5. Diagnosis of varicella and fetal complications in pregnancy

The diagnosis of varicella in pregnant women can often be made from the classic clinical presentation of a vesicular pruritic rash. In addition, there are often preceding or other secondary cases of varicella within the household. A case series of pregnant women with varicella identified 90% of index cases as one of the woman’s children. However, as the incidence of varicella decreases in countries with high vaccination rates, younger physicians will have less opportunity to see the characteristic skin lesions and may feel less confident with the clinical diagnosis. If the diagnosis is in question, laboratory testing can be performed. The base of a vesicular skin lesion can be scraped for culture, immunohistochemical staining, and/or PCR. VZV culture is highly specific, but takes seven to 10 days and is insensitive. Direct fluorescent antigen staining using monoclonal antibodies to detect VZV glycoproteins in cells from a skin lesion scraping can be performed within hours and has high sensitivity and specificity. If a qualified laboratory is available, rapid testing can also be done by VZV PCR. Serologic tests are of little or no value for the diagnosis of varicella as VZV IgG antibodies often only become detectable a few days after the onset of the illness, VZV IgG enzyme-linked immunosorbent assay (ELISA) methods have substantial false negative rates (15–20%), and seroconversion is a retrospective approach to diagnosis. Further, no validated serologic tests for VZV IgM are available to clinicians and VZV IgM antibodies can be detected in individuals who have had varicella at some time in the past. When standard ELISA methods are used to detect VZV IgM antibodies, the rate of false positives is high.

Evaluating the fetus for intrauterine infection after maternal varicella presents several challenges and developing validated
approaches is difficult because the incidence of both varicella in pregnancy and any associated fetal damage is fortunately quite low. Several studies have sought correlations between the detection of VZV IgM in fetal blood or the PCR detection of VZV DNA in fetal blood or amniotic fluid postnatal evidence of fetal infection. VZV IgM was positive in only 25% of infants born with clinical manifestations of disease. A study of 107 women who had varicella before the 24th week of pregnancy showed that negative PCR results in amniotic fluid correlated with favorable fetal outcome – good health, with normal psychomotor development. However, it is necessary to note that this sample size was not powered to evaluate for risk of fetal pathology when the risk of such sequelae is <1%. Additionally, VZV PCR has a poor positive predictive value for fetal disease or disease severity. One limitation of testing amniotic fluid for VZV by PCR is timing; an amniocentesis can only be performed after 16–18 weeks of gestation, so in some clinical situations the PCR could be obtained well after initial presentation of varicella in the mother. The risk of fetal demise from amniocentesis, which is low, must also be weighed against the low risk of VZV-related fetal damage. Importantly, VZV DNA in amniotic fluid does not indicate whether the fetus has been infected or, if infected, whether fetal damage will occur. In the study of 107 pregnant women with varicella, nine amniotic fluid specimens were VZV PCR positive (8.4%); of these, the pregnancy outcomes were five full-term normal infants, one infant with bilateral microphthalmia, two therapeutic abortions, of which one fetus showed limb hypoplasia, and one spontaneous abortion. Thus only two pregnancies were associated with signs of intrauterine varicella. Since varicella is a systemic infection, it should be assumed that the pregnant woman with varicella may have viral genomic DNA in many bodily fluids, including amniotic fluid, and the duration of persistence of VZV genomes, and whether it represents the presence of infectious virus is not known. The rate of detection of VZV DNA by PCR might be higher when the mother’s infection is more recent, but would not imply a higher risk of fetal sequelae. At this point, no conclusions can be drawn about the significance of a positive VZV PCR of amniotic fluid with regard to risk of VZV transmission to fetus or risk for fetal defects.

Serial evaluations of fetal development by prenatal ultrasound may be useful to identify severe manifestations of intrauterine VZV infection. Ultrasound is most definitive when the fetus has defects such as limb atrophy or evidence of microcephaly, but subtle findings such as liver calcifications on prenatal ultrasound were the only sign of damage in an infant who was severely affected. The role of prenatal magnetic resonance imaging for assessment of the fetus after maternal varicella is only beginning to be delineated, but it may provide improved specificity, particularly for central nervous system damage.

6. Antiviral treatment of varicella in pregnancy and intrauterine infection

Acyclovir is an analogue of guanosine that inhibits viral replication and is highly specific for cells infected with herpes simplex virus and VZV. Acyclovir is activated by the virus-encoded thymidine kinase. Acyclovir crosses the placenta and is excreted by the fetal kidney. Although it is concentrated in amniotic fluid, it does not appear to accumulate in the fetus. Valacyclovir is an orally administered prodrug of acyclovir that has improved oral bioavailability and improved pharmacokinetic properties. Acyclovir and valacyclovir are pregnancy category B and are not approved for any indication in pregnant women. However, a registry of neonates exposed to acyclovir during the first trimester showed that no teratogenic effects could be attributed to acyclovir. Therefore, in instances of serious disease or complication such as pneumonia in the mother, the Committee on Infectious Diseases of the American Academy of Pediatrics concluded that the benefit of treating with acyclovir in these cases outweighs risk. Valacyclovir achieves higher serum levels than oral acyclovir; there are no data regarding the risk to the fetus, but the risk can be considered low, based on outcomes when pregnant women have been given intravenous acyclovir.
Uncomplicated maternal varicella can be treated orally with acyclovir or valacyclovir and treatment should be considered, particularly later in gestation when risks of maternal complication from disease are increased and risks to the developing fetus can be considered minimal. This approach addresses the problem that VZV dissemination can occur very rapidly in a patient whose clinical course seems benign. The decision to treat must be based on clinical judgment despite the lack of an approved indication because the low frequency of maternal varicella means that sufficient data to establish risks and benefits cannot be obtained. Intravenous antiviral therapy is indicated for the pregnant woman who develops any signs of pneumonia including cough, dyspnea, hypoxia, or an abnormal chest X-ray.43 There is no information about whether giving acyclovir or valacyclovir to pregnant women with varicella reduces the already low risk for CVS.4

Because the manifestations of CVS result from intrauterine damage to the developing fetus, antiviral therapy in the newborn period cannot be expected to have substantial impact on the sequelae. However, a case-by-case evaluation of infants with CVS is necessary in making decisions about when or whether to treat with acyclovir. There is a paucity of evidence regarding the role of antiviral therapy in controlling any potential damage that might arise from the VZV replication postnatally. Nevertheless, if the infant has or develops clinical signs of active infection, it is prudent to treat. The acyclovir dose should be that established as safe for treating neonatal herpes simplex infections, which is 15 mg/kg per dose given intravenously every 8 h. The duration of therapy must be determined from evidence of control of active VZV replication, either by cessation of lesion formation or by using laboratory tests, e.g. VZV PCR or viral culture.

Herpes zoster in infants who acquired VZV in utero has been self-limited or responsive to treatment with acyclovir. If the zoster is extensive and painful, it is usually prudent to treat with intravenous acyclovir at least initially, followed by oral acyclovir. No antiviral regimen has been evaluated but treatment for seven to 10 days can be expected to be sufficient because these infants are not otherwise immunocompromised. Serious complications have been reported in only one case of a four-month-old infant of a mother who had had varicella at 17 weeks’ gestation. The infant was born full term without complications, developed herpes zoster at three months, then had generalized seizures, with VZV DNA in cerebrospinal fluid by PCR and findings consistent with central nervous system infection.44 This infant received intravenous acyclovir for 10 days, followed by oral acyclovir for three weeks; VZV PCR of the CSF became negative but whether resolution of the infection was accelerated or the outcome was improved cannot be judged from a single case report.

7. Management of pregnant women exposed to VZV

Passive antibody prophylaxis with immune globulin preparations that contain VZV IgG antibodies is indicated if a pregnant woman is susceptible to VZV, the exposure was a close contact and prophylaxis can be administered within 72–96 h after the exposure. Pregnant women who have a history of varicella are not considered at risk. Symptomatic re-infection with VZV is quite rare and pre-existing maternal immunity would be expected to protect the fetus. A clinical history of varicella is considered sufficient evidence of immunity. A recent study assessing the validity of a self-reported history of varicella showed that it is a strong predictor that the pregnant woman will have VZV IgG antibodies (≥98%).45 However, since 95% of adult women have VZV IgG antibodies, this correlation is not unexpected. Only a minority of women who had a negative or uncertain varicella disease history were actually seronegative, which is also consistent with the epidemiology of VZV infection in women of childbearing age from temperate climates. Because of the difference in epidemiology, concern about VZV susceptibility should be highest if the pregnant woman who has no varicella history is from a geographical area where epidemic varicella is less common. Cost-benefit analysis supports testing for serum VZV IgG titers if the mother with no history is from a high prevalence area because prophylaxis is likely to be necessary in <5% of cases. In practice, this approach requires access to a laboratory that can report the results on an urgent basis so that prophylaxis can be given within the 72–96 h, if required. Since VZV IgG assays have a significant false-negative rate, some women who are identified as susceptible will be immune to VZV. However, adverse reactions to prophylaxis are unusual in immune or susceptible individuals.

High titer varicella zoster immune globulin (VZIG) prepared from individuals with recent zoster or from donors screened for high VZV IgG titers (VariZIG) is preferred because of the intramuscular route of administration; intravenous immune globulin (IVIG) can be substituted if necessary at a dose of 400 mg/kg. The VariZIG can be obtained 24 h a day from the sole authorized US distributor (FFF Enterprises, Temecula, CA, USA; tel. 1-800-843-7477 or online at http://www.ffenterprises.com), and the recommended dose is 125 units/10 kg of body weight, up to a maximum of 625 units. The minimum dose is 125 units/10 kg. Refers VZG prevents varicella or reduces the severity of infection in most cases; however, patients should be monitored for breakthrough infection.46

Passive antibody prophylaxis is intended to protect the susceptible pregnant woman from severe varicella. Whether the fetus is protected from transplacental VZV transmission is not known, but it is reasonable to assume that preventing maternal viremia will reduce risk. In one prospective study, maternal breakthrough infection occurred despite VZIG prophylaxis in 97 cases. None of the infants had CVS, but this sample size is not sufficient to conclude that the fetus was protected, as the incidence of CVS is <1%.21 Acyclovir prophylaxis is not recommended because of the lack of information about its safety or efficacy compared to VZV immune globulin. Varicella vaccine can be given for post-exposure prophylaxis in non-pregnant individuals but the live attenuated vaccine is contraindicated in pregnancy.

As more women of childbearing age have vaccine-induced immunity to VZV, the assessment of immune status will shift to documenting that the exposed pregnant woman has received two doses of live attenuated varicella vaccine. If this history is documented, serologic testing is not recommended. Commercially available serologic assays for VZV IgG antibodies have even higher false negative rates in vaccine recipients than in naturally immune individuals. The correlation with protection against exposure is with the number of vaccine doses received. As the vaccine era progresses, it will be important to confirm immune status because some women may have not been vaccinated and are less likely to have natural infection as varicella epidemics are controlled.

8. Perinatal varicella

Varicella of the newborn is a life-threatening illness that may occur when maternal disease occurs within an approximate seven-day window that spans from five days before delivery until two days after delivery. These infants should be given VZIG if available or IVIG at birth or as soon as the maternal symptoms appear in the two days after delivery.47 IVIG contains high titers of VZV-specific IgG and VZV antibody titers have been shown to be equivalent after treatment with either VZIG or IVIG.48 Before the use of VZIG, an estimated 17–30% of the newborns contracted severe varicella because of the lack of maternal VZV IgG antibody transfer to protect the neonate and the relative immaturity of the neonatal immune system.49 Before VZV immunoglobulin was available, the risk of death among neonates born to mothers with the onset of rash up to
four days before delivery was 31%. The rate decreased to 7% when the use of VZIG was introduced and neonatal intensive care improved. Infants born to mothers with varicella within this high risk period are usually initially well-appearing. VZV presents with the classical skin lesions, but can disseminate with pneumonia, hepatitis, encephalitis and severe coagulopathy resulting from liver failure and thrombocytopenia (Fig. 5). Despite the administration of VZIG, infants exposed to maternal varicella in this high risk period should be monitored very closely and intravenous acyclovir should be given if there are any signs of illness. Acyclovir prophylaxis is not recommended because IVIG is readily available even if VZIG is not. A small uncontrolled trial of acyclovir and immunoglobulin in combination compared to immunoglobulin alone showed no clinical varicella in any of 10 infants given treatment with the combination versus two of four infants given immunoglobulin alone. The dosing of acyclovir in this trial was 5 mg/kg intravenously every 8 h for five days. The sample size is too small to determine whether the combination improved outcomes, and a standard prophylaxis dosage or duration has not been determined. Careful monitoring and early treatment of breakthrough varicella can be expected to be highly effective. Treatment of infants who develop breakthrough varicella with intravenous acyclovir should be continued for >48 h after the last new lesions have appeared; a duration of seven days is usually sufficient. There is no indication for additional therapy with oral acyclovir, but the infant should be monitored for new lesions and re-treated with intravenous acyclovir if necessary.

Infants who are born more than a week after the first appearance of the maternal rash are not at high risk of severe disease. They will likely have lesions at birth or within the first several days of life, but they are protected from severe disease secondary to maternal VZV antibodies having time to traverse the placenta. Again, despite the lower risk, if there are signs and symptoms of active VZV disease, treating with an antiviral is recommended. When the history of maternal varicella is in the few weeks preceding delivery, the infants may be asymptomatic or may have cutaneous lesions at birth or developing shortly thereafter, but are at low risk of dissemination of varicella disease or complications; nevertheless treatment is prudent.

9. Varicella vaccination

The early childhood varicella immunization program in the USA was recommended based on an analysis of the annual morbidity and mortality associated with varicella epidemics, most of which was associated with secondary Streptococcus pyogenes and Staphylococcus aureus infections or neurologic complications, including encephalitis and cerebellar ataxia in otherwise healthy individuals. Universal vaccination was implemented because of the almost universal prevalence of varicella disease, causing an estimated four million cases each year, and because those at risk for complications could not be predicted. The program of universal vaccination against varicella has decreased the varicella death rate in the USA across all age groups because of the impact on the annual epidemics.
When possible, maternal VZV immune status should be determined before pregnancy by reviewing the varicella history or documenting vaccination with two doses of varicella vaccine. If both are negative, then VZV IgG antibody testing should be done because the vaccine can be offered if the woman is not immune. Women of childbearing age without a history of chickenpox or vaccination and who are confirmed seronegative should be counseled about the risks of varicella during pregnancy and receive two doses of vaccine, given four to eight weeks apart. If more than eight weeks elapse after the first dose, the second dose can still be given without restarting the schedule.\(^5\) Vaccination can be given in the immediate postpartum period, and breastfeeding is not a contraindication for immunization.\(^5\) The US Advisory Committee on Immunization Practices recommends that postpartum women without evidence of immunity be given the first dose of vaccine before discharge from the hospital, and the second dose of vaccine at the follow-up postpartum visit (six to eight weeks after delivery).\(^5\) As the varicella vaccine was licensed in 1995, the cohort of infants immunized at 12–15 months is approaching childbearing age. It should be emphasized that each of these women should be screened for a history of two doses of vaccine to reduce the risk of varicella during pregnancy. While waning immunity following vaccination has been suggested from some epidemiological data, infection in vaccinated children may be due to failure to induce immunity associated with a single-dose vaccine regimen; a two-dose regimen has been introduced in response to these epidemiologic observations.\(^5\) The active surveillance sites for varicella are designed to identify changes in epidemiology that could indicate the need for booster doses of the vaccine. Changes in varicella epidemiology may occur because the continued circulation of VZV in the community may have provided a natural boosting of vaccine-induced immunity. As vaccine coverage rates improve and varicella outbreaks become increasingly rare, it may be necessary to give an adolescent/young adult dose of the vaccine as follow-up to the universal childhood vaccination program.

Because the effect on fetal development is not known, the varicella vaccine is contraindicated in pregnancy. The Advisory Committee on Immunization Practices recommends that pregnancy be avoided for one month after vaccination. However, there are cases of inadvertent vaccination of pregnant women, or vaccination within the few months prior to pregnancy. This is a low risk exposure as the vaccine strain of virus is attenuated and would be less virulent than wild type varicella. A registry has followed exposure as the vaccine strain of virus is attenuated and would be safe in immunocompromised patients and for making higher potency vaccines that could reduce the number of doses required, without increasing adverse events and risk of spread of the vaccine virus from the site of inoculation. A better understanding of the VZV proteins and the host response to these components of the virus may also lead to the design of protein/adjunct vaccines that would be valuable for high risk patients.

10. Future research directions

Research to evaluate the persistence of VZV immunity in vaccine recipients and to document the changing epidemiology of varicella will be important now that the universal varicella immunization program has been implemented. Such research has already led to the revision of the early childhood vaccine schedule to provide two doses. Further modification of the current varicella vaccine schedules could occur depending on observations about the rates of breakthrough varicella. Basic research about VZV remains a high priority in order to better understand the molecular mechanisms of pathogenesis and host control of this ubiquitous human pathogen. It is now possible to manipulate the VZV genome to reduce its capacity to infect human T-cells and sensory ganglia.\(^5\) This research is likely to reveal strategies for creating second generation genetically engineered live attenuated varicella vaccines that would be safe in immunocompromised patients and for making higher potency vaccines that could reduce the number of doses required, without increasing adverse events and risk of spread of the vaccine virus from the site of inoculation. A better understanding of the VZV proteins and the host response to these components of the virus may also lead to the design of protein/adjunct vaccines that would be valuable for high risk patients.

References


* The most important references are indicated with an asterisk.