Varicella in the Peripartum Period

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Epidemiology

VZV is a highly communicable virus that was extremely common in the United States and Europe prior to the introduction of widespread varicella vaccination in 1995 [1]. Due to either vaccination or childhood history of chickenpox, more than >95% of adults in the United States are immune to varicella [2]. Correspondingly, the incidence of varicella in pregnant women is very low.

For regions of the world that do not have effective universal vaccination, there are distinct geographical differences and seasonal patterns to varicella outbreaks. Temperate regions have increased incidence during the winter and spring seasons, leading to periodic outbreaks affecting young children. In contrast, tropical regions have a lower incidence of outbreaks; as a result, adults in these regions are more likely to remain susceptible to infection [3, 4].

Pathogenesis

VZV is a member of the Herpesviridae family. VZV is transmitted by airborne respiratory droplets (during primary varicella) or by direct contact with skin lesions (during episodes of varicella or zoster) [5]. Airborne transmission of VZV is highly efficient, with attack rates exceeding 80%. VZV can also be acquired by transplacental transmission from a viremic mother to her fetus [6–9]. VZV rapidly reaches all fetal tissues but is particularly tropic for the central nervous system, eyes, and skin [10, 11]. Congenital and perinatal varicella are caused by hematogenous spread

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J. B. Cantey (ed.), *Neonatal Infections*, https://doi.org/10.1007/978-3-319-90038-4_23

of VZV across the placenta to the fetus during the initial viremia; in contrast, postnatal VZV infection results from airborne or contact transmission to the newborn.

After infection, VZV incubates for approximately 2 weeks (range, 1–3), followed by viremia and ultimately the appearance of the rash [12]. The infected are considered contagious from 1 to 2 days preceding the rash until all lesions are crusted over. After primary varicella infection, the virus becomes latent in the dorsal root ganglion and may reactivate later in the form of herpes zoster (i.e., shingles). Infants with either congenital or postnatal VZV are also at risk for zoster during infancy and later life [13].

Clinical Findings

The spectrum of disease caused by varicella correlates with the timing of primary infection during pregnancy. The majority of infants born to mothers with primary varicella infection have uneventful deliveries [14]. Spontaneous abortion, preterm delivery, and fetal death do not seem to be increased among pregnancies complicated by varicella. However, complications of varicella infection in pregnancy do include congenital varicella syndrome, perinatal varicella, and postnatal varicella. In addition, pregnant women are at increased risk for varicella pneumonia due to attenuation of cellular immunity during pregnancy (see chapter "Varicella in the Peripartum Period") [15].

Congenital varicella syndrome. Congenital varicella syndrome occurs in approximately 1–2% of pregnancies complicated by varicella infection before 20 weeks gestation [16]. Characteristic scattered scarred skin lesions or "cicatrices" are the most common finding, occurring in 70% of cases [17]. Cicatrices may be dermatomal, clustered, or scattered. Ocular lesions (e.g., chorioretinitis, microphthalmia, cataracts), neurologic injury (e.g., microcephaly, seizures, cortical destruction), and limb abnormalities (e.g., hypoplasia, atrophy) are also present in >50% of cases. These signs are apparent at birth, but some infants are not diagnosed until later in infancy, especially if the skin lesions go unnoticed initially. Infants with congenital varicella syndrome, particularly those with neurologic impairment, may have developmental delay and increased risk for mortality [18].

Perinatal varicella. Perinatal varicella is defined as onset of rash within 10 days of delivery and is caused by transplacental transmission of VZV [19]. Maternal infection from 5 days antepartum to 2 days postpartum is associated with severe neonatal infection in approximately 25–50% of infants. The severity of perinatal varicella is presumably because when maternal infection is late, there is no opportunity for the development or transfer of passive maternal antibody to the infant. In addition, neonates have decreased T cell activity relative to older infants [13]. As a result, the case-fatality rate of perinatal varicella approaches 30%. In contrast, the attack rate of perinatal varicella when maternal infection is >5 days before delivery is 5–15%, and no neonatal deaths have been reported, presumably due to development of passive immunity from the mother [20, 21].

Postnatal varicella. Varicella acquired postnatally generally presents after age 10 days (median 15 days, range 10–28). As opposed to perinatal varicella, postnatal varicella is usually mild, although some neonatal deaths have been reported [20].

Maternal varicella pneumonia. Varicella pneumonia complicates 10–20% cases of varicella infection during pregnancy and can be severe; mortality due to varicella pneumonia is approximately 20% in pregnant women [15]. In areas where varicella is still endemic, varicella pneumonia represents a significant cause of morbidity and mortality in pregnant women. Onset of varicella pneumonia is 3–5 days after onset of rash; patients present with bilateral interstitial pneumonitis. *Streptococcus pyogenes* (group A *Streptococcus*) is associated with superinfection of varicella pneumonia or skin lesions and can markedly worsen prognosis [22].

Diagnosis

Diagnosis of maternal varicella in pregnancy can be made based on clinical findings of the classic vesicular pruritic rash or confirmatory laboratory testing. The following techniques can be used to confirm a varicella diagnosis.

Polymerase chain reaction (*PCR*). PCR amplifies the number of copies of VZV DNA, if any is present in a clinical sample. PCR is extremely sensitive and rapid and can be used on blood, cerebrospinal fluid, vesicular scrapings, amniotic fluid, and tissue, to name a few [23].

Viral culture. Viral culture may be used to diagnose varicella in mothers or infants. The base of the vesicles should be scraped, as the virus is present in epithelial cells but may not be in vesicular fluid. The culture is highly specific for varicella but less sensitive than PCR, and it may take up to a week for culture to yield results [24].

Direct fluorescent antigen staining. This laboratory test directly identifies the presence of VZV antigens (glycoproteins) in scrapings from a vesicle base by using tagged monoclonal antibodies. Direct fluorescent antigen staining is highly sensitive and specific and takes only a few hours to perform [24].

Serology. VZV IgG antibody usually appears ~5–7 days after the onset of rash (see perinatal and postnatal varicella, above). Therefore, serology is not particularly useful for diagnosing acute infection. However, serology is the gold standard for determining varicella immunity; patients with detectable IgG are considered immune to varicella. Of note, varicella immune globulin (VZIG, see Prevention, below) can persist for several months after administration and may complicate serologic evaluation.

Treatment

Antiviral treatment for varicella is generally accomplished with acyclovir or valacyclovir [25–27]. Both antivirals are pregnancy category B and can be used in pregnancy; the risk to the fetus is presumed to be low. The use of antiviral

Table 1 Clinical features and treatment of varicella in pregnant women and newborns

Condition	Clinical signs	Onset	Treatment	Mortality
Maternal varicella, uncomplicated	Pruritic vesicular lesions on erythematous base, in successive crops	Variable	Acyclovir, 800 mg PO q6 h until all lesions crusted	None
Maternal varicella, pneumonia	Interstitial pneumonitis	3–5 days after appearance of rash	Acyclovir, 10 mg/kg/dose IV q8 h	~20%
Congenital varicella syndrome	• Cicatrices (skin scarring) • Ocular lesions • Neurologic lesions • Limb lesions	Usually occurs before 20 weeks gestation following maternal varicella but rarely identified before birth	None unless active vesicles	~25%
Perinatal varicella	Pruritic vesicular lesions on erythematous base, in successive crops	≤10 days after delivery	Acyclovir, 10 mg/kg/dose IV q8 h, *OR* acyclovir, 500 mg/m^2/dose (1500/day) IV q8 h	~30%
Postnatal varicella		>10 days after delivery		<5%

therapy depends on the timing and severity of infection (Table 1). In general, pregnant women with primary varicella infection should be treated orally, although severe infections—including pneumonia—may prompt intravenous treatment. Infants with congenital varicella, for whom the actual infection is over by the time the infant is born and comes to clinical attention, do not require antiviral therapy unless they have reactivation (zoster) later in infancy. In contrast, perinatal or postnatal varicella disease should be treated with antiviral therapy.

Zoster in pregnant women or infants has not been as extensively studied, but oral therapy is generally recommended to speed resolution.

Prevention

Preexposure prophylaxis. VZV vaccine was introduced in 1995, and since 2007, a two-dose schedule is recommended as part of routine childhood immunization (at age 1 and 4 years) [28]. Women of childbearing age should be screened for a history of chickenpox or documentation of two doses of varicella vaccination to reduce risk of varicella infection during pregnancy [26, 27]. If a woman is seronegative, then two doses of the varicella vaccine should be administered 4–8 weeks apart. VZV vaccine is a live-attenuated vaccine and therefore contraindicated during pregnancy. Childbearing-age women who receive the vaccination should be counseled to avoid pregnancy for the following month. However, clinical registries have not identified congenital varicella syndrome or VZV-related adverse pregnancy outcomes among

Table 2 Recommendations for postexposure prophylaxis with varicella immune globulin (VZIG) following varicella exposure in nonimmune, high-risk patients [30]

Patient	VZIG dose
Pregnant woman	625 units IM
Infant whose mother has varicella 5 days before to 2 days after delivery	<2 kg: 62.5 units IM >2 kg: 125 units IM
Infant <28 weeks gestation regardless of maternal immunity to varicella	
Infant >28 weeks gestation only if mother is nonimmune	

VZIG should be given as soon as possible after exposure, but no more than 10 days later
Patients who develop varicella despite VZIG should be treated with antiviral therapy as per Table 1

women inadvertently vaccinated during pregnancy [29]. VZV vaccine can safely be administered to a breastfeeding mother.

Postexposure prophylaxis. Immune individuals exposed to varicella do not require any additional management. However, for nonimmune pregnant women or for infants at high risk of perinatal varicella, passive immunoprophylaxis can be accomplished with VZIG (Table 2) [30, 31]. The only available VZIG product in the United States currently is Varizig® (Cangene Corporation, Winnipeg, Canada). The only distributor of Varizig in the United States is FFF Enterprises (Temecula, California, 1-800-843-7477). VZIG is highly effective at reducing both attack rates and case-fatality rates of varicella infection in high-risk individuals.

References

1. Stagno S, Whitley RJ. Herpesvirus infections of pregnancy – herpes simplex virus and varicella-zoster virus infections. N Engl J Med. 1985;313:1327–30.
2. Lebo EJ, Kruszon-Moran DM, Marin M, et al. Seroprevalence of measles, mumps, rubella and varicella antibodies in the United States population, 2009-2010. Open Forum Infect Dis. 2015;20:ofv006.
3. Chen B, Sumi A, Wang L, Zhou W, Kobayashi N. Role of meteorological conditions in reported chickenpox cases in Wuhan and Hong Kong, China. BMC Infect Dis. 2017;17:538.
4. Mahmud AS, Metcalf CJ, Grenfell BT. Comparative dynamics, seasonality in transmission, and predictability of childhood infections in Mexico. Epidemiol Infect. 2017;145:607–25.
5. Asano Y. Clinicopathologic understanding and control of varicella-zoster virus infection. Vaccine. 2008;26(50):6487.
6. Hartung J, Enders G, Chaoui R, et al. Prenatal diagnosis of congenital varicella syndrome and detection of varicella-zoster virus in the fetus: a case report. Prenat Diagn. 1999;19:163–6.
7. Kawana K, Yoshikawa H, Sata T. Postpartum detection of varicella-zoster virus DNA in the placenta. Int J Gynaecol Obstet. 1996;55:165–6.
8. Sauerbrei A, Muller D, Eichhorn U, Wutzler P. Detection of varicella-zoster virus in congenital varicella syndrome: a case report. Obstet Gynecol. 1996;88:687–9.
9. Greenspoon JS, Masaki DI. Fetal varicella syndrome. J Pediatr. 1988;112:505–6.
10. Nikkels AF, Delbecque K, Pierard GE, et al. Distribution of varicella-zoster virus DNA and gene products in the tissues of a first-trimester varicella-infected fetus. J Infect Dis. 2005;191:540–5.
11. Arvin AM, Moffat JF, Sommer M, et al. Varicella-zoster virus T cell tropism and the pathogenesis of skin infection. Curr Top Microbiol Immunol. 2010;342:189–209.
12. Heininger U, Seward JF. Varicella. Lancet. 2006;368:1365–76.

13. Terada K, Kawano S, Yoshihiro K, et al. Varicella-zoster virus (VZV) reactivation is related to the low response of VZV-specific immunity after chickenpox in infancy. J Infect Dis. 1994;169:650–2.
14. Harger JH, Ernest JM, Thurnau GR, et al. Frequency of congenital varicella syndrome in a prospective cohort of 347 pregnant women. Obstet Gynecol. 2002;100:260–5.
15. Lamont RF, Sobel JD, Carrington D, et al. Varicella-zoster virus (chickenpox) in pregnancy. BJOG. 2011;118:1155–62.
16. Ahn KH, Park YJ, Hong SC, et al. Congenital varicella syndrome: a systemic review. J Obstet Gynaecol. 2016;36:563–6.
17. Borzyskowski M, Harris RF, Jones RW. The congenital varicella syndrome. Eur J Pediatr. 1981;137:335–8.
18. Gershon AA, Marin M, Seward JF. Varicella, measles, and mumps. In: Wilson CB, Nizet V, Maldonado YA, et al., editors. Remington and Klein's infectious diseases of the fetus and newborn infant. 8th ed. Philadelphia: Elsevier; 2016.
19. Berkoff MC, Brown WD. Varicella after the perinatal period. Pediatr Rev. 2013;34:537–8.
20. Meyers JD. Congenital varicella in term infants: risk reconsidered. J Infect Dis. 1974;129:215–7.
21. Gershon A. Commentary on VZIG in infants. Pediatr Infect Dis J. 1987;6:469.
22. Allard R, Pilon PA. Streptococcal infections and varicella. Clin Infect Dis. 2016;62:1056.
23. Mouly F, Mirlesse V, Meritet JF, et al. Prenatal diagnosis of fetal varicella-zoster virus infection with polymerase chain reaction of amniotic fluid in 107 cases. Am J Obstet Gynecol. 1997;177:894–8.
24. Coffin SE, Hodinka RL. Utility of direct immunofluorescence and virus culture for detection of varicella-zoster virus in skin lesions. J Clin Microbiol. 1995;33:2792–5.
25. Chiodo F, Manfredi R, Antonelli P, et al. Varicella in immunocompetent children in the first two years of life: role of treatment with oral acyclovir. Italian Acyclovir-Chickenpox study group. J Chemother. 1995;7:62–6.
26. Shrim A, Koren G, Yudin MH, et al. Management of varicella infection (chickenpox) in pregnancy. J Obstet Gynaecol Can. 2012;34:287–92.
27. American College of Obstetricians and Gynecologists. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015;125:1510–25.
28. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56:1–40.
29. Marin M, Willis ED, Marko A, et al. Closure of varicella-zoster virus-containing vaccines pregnancy registry – United States, 2013. MMWR Morb Mortal Wkly Rep. 2014;63:732–3.
30. Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG – United States, 2013. MMWR Morb Mortal Wkly Rep. 2013;62:574–6.
31. Huang YC, Lin TY, Lin YJ, Lien RI, Chou YH. Prophylaxis of intravenous immunoglobulin and acyclovir in perinatal varicella. Eur J Pediatr. 2001;160:91–4.