

Review

Chickenpox in pregnancy: Revisited

Michael Paul Tan, Gideon Koren*

*The Motherisk Program, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children,
University of Toronto, 555 University Avenue, Toronto, Ont., Canada M5G 1X8*

Received 22 October 2004; accepted 14 April 2005

Available online 23 June 2005

Abstract

Varicella infection during the first and second trimester of pregnancy may increase the risk for congenital varicella syndrome 0.5–1.5% above the baseline risk for major malformation. Third trimester infection may lead to maternal pneumonia which can be life threatening if not treated appropriately. Varicella-zoster immune globulin (VZIG) should be administered as soon as possible preferably within 96 h from exposure to prevent maternal infection or subsequent complications. Later than 96 h, the effectiveness of VZIG has not been evaluated. Neonatal varicella is more severe if maternal rash appears 5 days prior to or 2 days after delivery. The newborn should be given VZIG immediately. Intravenous acyclovir is recommended for maternal pneumonia and severely affected neonate. No controlled study has yet evaluated the effectiveness of acyclovir or valacyclovir for postexposure prophylaxis to pregnant women or neonates. Unlike primary varicella infection in pregnancy, herpes zoster has not been documented to cause complications unless in the disseminated form. The advent of advanced imaging techniques and molecular biotechniques has improved prenatal diagnosis. With increase use of vaccination, the incidence of chickenpox in pregnancy is expected to decline in the future.

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Keywords: Varicella; VZIG; Herpes zoster; Pregnancy; Congenital Varicella Syndrome

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* Corresponding author. Tel.: +1 416 813 5778; fax: +1 416 813 7562.
E-mail address: mkoren@sickkids.ca (G. Koren).

1. Introduction

In 1947, two fourth year medical students, LaForet and Lynch [1], reported a case of multiple congenital defects following maternal varicella at 8 weeks of gestation. During that time, it was still in doubt whether the varicella virus was the etiologic cause or whether the congenital anomalies were just coincidental. This initial report prompted more physicians and medical researchers to report similar findings, which led to the confirmation of congenital varicella syndrome (CVS) [2]. From 1947 to 2000, there have been more than 110 cases of CVS reported in the literature [3]. Although uncommon in women of child-bearing age, varicella infection during pregnancy may lead to teratogenic effects to the fetus with potential serious sequelae to both the mother and the newborn.

2. Epidemiology

The epidemiology of varicella-zoster virus (VZV) infection differs between temperate and tropical climates. In the temperate region, varicella infection peaks during winter and early spring. In countries such as North America, Japan and Europe, more than 90% of the population have the primary infection by 15 years of age [4–9], while in the tropical countries it ranges between 25 and 85% [10–16]. Therefore, for child-bearing age women in tropical countries, one would expect a higher incidence of primary VZV infection.

The true incidence of varicella infection in pregnancy is not known. The current estimates are based on the proportion of child-bearing age women who are susceptible to infection and their risk for exposure during pregnancy [6]. In the UK, the estimated infection risk from surveillance of adults aged 15–44 years is 2–3 per 1000 [17]. In the US, the National Health Interview Survey estimated an annual rate between 1.6 and 4.6 per 1000 [6].

In the 1990s, there have been reports of upward shift of varicella morbidity towards women aged 15–44 years in the US and the UK [18–20]. The reason for the shift remains unknown. However, with the increasing administration of varicella vaccine to susceptible pregnant women and to children of pre-school age, the rate of seronegativity among women of reproductive age is expected to gradually decline [21].

3. Pathogenesis

VZV is a highly contagious infectious agent. Humans are the only known source. The virus is easily cultured from skin lesions of patients. However, it has been quite difficult to isolate the virus from nasopharyngeal secretions, casting doubt on whether transmission through respiratory secretions does occur. However, with the advent of the polymerase chain reaction (PCR) method, the VZV DNA has been documented in the nasopharynx. Hence, it is now evident that the disease is transmitted from person to person by direct

contact with the vesicular fluid of the skin lesions and/or by secretions from the respiratory tract [22]. The virus enters the host through the conjunctiva and/or mucosa of the nose and mouth either through contact with contaminated hand or through airborne spread. The usual incubation period is 13–17 days. The mechanism of infection with VZV in utero is not known. It has been hypothesized [23,24] that during incubation two viremic phases occur over the 2 weeks. It is during the viremic periods, days 4–6 and 10–14, when there may be transplacental transmission of the virus. The second viremic period is thought to play a major role in fetal transmission. Grose [23] suggested that since prophylaxis with varicella-zoster immunoglobulin would only be effective when given prior to the primary viremia, perhaps acyclovir should be considered for prevention or amelioration of secondary viremia. Whether this will prevent in utero fetal transmission of the virus from the mother remains to be proven.

At the end of the second viremia, pruritic maculopapular rash erupts. The most infectious period is usually 2 days before the onset of rash and contagiousness occurs till the vesicles crust over, 5 days after the onset of rash.

Although primary varicella infection is thought to confer life long immunity, there have been case reports of clinical reinfections [25]. In a survey by Hall et al. [26], reports of recurrence of symptomatic varicella infection ranged from 4.5 to 13%. Subclinical reinfection has also been documented immunologically [27]. Possible risk factors for the occurrence of clinical varicella reinfections are first infection at a young age (especially <12 months), mild initial infection, genetic factor (such as one sibling has had reinfection) and if the index contact is a household member or a close friend during second exposure [26]. Hypotheses for reinfection include failure to develop or maintain immune memory cells after the initial infection, failure to activate memory cells upon reinfection or viral loads being too high and hence overwhelming for the immune defense of the host [28].

4. First and second trimester infection

Chickenpox in the pregnant women during the first and second trimester is of concern because of the small possibility of embryopathy. Congenital Varicella Syndrome (CVS) is also known as fetal varicella syndrome, congenital varicella-zoster syndrome, varicella embryo-fetopathy, varicella embryopathy, varicella fetopathy and fetal herpes-zoster syndrome [29]. The pathogenesis of CVS is hypothesized to be due to subsequent herpes-zoster reactivation in utero rather than from the initial fetal varicella infection. The short latent period between primary fetal infection and reactivation to herpes zoster is probably due to the lack of or immature cell-mediated immunity in the first and second trimesters. Evidence of this would be the skin lesion that showed a peculiar dermatomal distribution similar to herpes-zoster infection, segmental maldevelopments of the

Table 1
Clinical features of congenital varicella syndrome

Clinical features	Reports			
	Sauerbrei and Wutzler [3]		Enders and Miller [6]	
	n = 112	%	n = 25	%
Skin lesions	79	73	18	72
Neurologic defects or diseases	67	62	12	48
Eye diseases	56	52	11	44
Limb hypoplasia	50	46	18	72
Intrauterine retardation	25	23		
Muscle hypoplasia	22	20	6	24
Gastrointestinal abnormalities ^a	20	19	5	20
Genitourinary abnormalities	13	12	–	–
Affections of internal organs	14	13	–	–
Developmental delay	13	12	–	–
Defects of cardiovascular system	9	8	–	–
Defects of other organs	9	7	–	–

^a Enders combined genitourinary and gastrointestinal abnormalities.

musculoskeletal systems and the segmental dysfunction of the somatic and/or autonomic nervous system [30].

Congenital varicella syndrome is usually characterized by cicatricial scars in dermatomal distribution, neurological defects, unilateral limb-shortening defects with muscular hypoplasia, eye disease, gastrointestinal abnormalities and genitourinary abnormalities. Details of the defects can be found in the review by Birthistle and Carrington [31]. Table 1 lists the clinical features collated by Sauerbrei and Wutzler [3] and Enders and Miller [6]. It is not certain whether the higher number of reported cases for neurological defects and eye disease in Sauerbrei and Wutzler study is true as it may be due to publication bias or increase awareness among physicians of isolated neurological and ophthalmologic problems associated with CVS [32–39]. Sauerbrei and

Table 3
Incidence of congenital varicella syndrome in first 20 weeks

Study	No. of CVS ^a /No. of LB (%)
Paryani and Arvin [27]	1/~22 ^b (4.55)
Balducci et al. [40]	0/35 (0)
Pastuszak et al. [41]	1/86 (1.16)
Enders et al. [42]	7/816 (0.86)
Jones et al. [43]	2/146 (1.37)
Dufour et al. [44]	0/17 (0)
Figueroa-Damian and Arredondo-Garcia [45]	0/22 (0)
Mouly et al. [46]	2/89
Harger et al. [47]	0/190 ^c
Mean (%)	13/1423 (0.91%)

^a Only infants with CVS that were born live were considered. Spontaneous abortions, intrauterine death and termination of fetus due to suspected CVS were not included.

^b Total LB in first and second trimester.

^c Number with inadequate follow-up not given.

Wutzler collated published cases found in the literature, whereas Enders and Miller collected cases referred for laboratory confirmation of intrauterine varicella infection through their laboratory service.

Between 1986 and 2002, nine [27,40–47] cohort studies calculated the overall incidence of CVS among mother–child pairs (Table 2). The rate was 4/725 (0.55%) for first trimester, 9/642 (1.4%) for second trimester and 0/385 (0%) for third trimester. The overall rate of CVS was 14/2000 (0.70%) with a trend towards more cases during the second trimester. None of the newborn from third trimester maternal infection had CVS. Maternal varicella infection occurred prior to 20 weeks of gestation in 11 out of 12 cases of CVS in these cohort studies. The overall rate for CVS in the first 20 weeks of gestation was 13/1423 (0.91%) as shown in Table 3. The recent pooled risk rate is much less than what was previously estimated at 2.2% [48].

Table 2
Incidence of congenital varicella syndrome in cohort studies

Study	No. of CVS ^a /No. of LB (%)			Overall (%)
	First trimester (2–12 weeks)	Second trimester (12–28 weeks)	Third trimester (28–42 weeks)	
Paryani and Arvin [27]	1/11 (9)	0/11 (0)	0/16 ^b (0)	1/38 (2.63)
Balducci et al. [40]	0/35 (0)	–	–	0/35 (0)
Pastuszak et al. [41]	1/58 (1.72)	0/34 (0)	0/8 (0)	1/100 (1.0)
Enders et al. [42]	1/469 (0.21)	6/~477 ^c (1.26)	0/~345 ^d (0)	7/1291 (0.54)
Jones et al. [43]	1/110 (0.91)	1/46 (2.17)	0/13 (0)	2/169 (1.18)
Dufour et al. [44]	n/a ^e	n/a ^e	0/3 (0)	0/20 (0)
Figueroa-Damian and Arredondo-Garcia [45]	0/9 (0)	0/13 (0)	–	0/22 (0)
Mouly et al. [46]	0/33 (0)	2/61 (3.28)	–	2/94 (2.13)
Harger et al. ^f [47]	n/a	n/a	n/a	1/231 (0.43)
Mean (%)	4/725 (0.55%)	9/642 (1.4%)	0/385 (0%)	14/2000 ^g (0.70)

^a Only infants with CVS that were born live were considered. Spontaneous abortions, intrauterine death and termination of fetus due to suspected CVS were not included.

^b Excluded three cases due to maternal rash @ <10 days before delivery.

^c Twelve to twenty-four weeks of gestation = 477.

^d Twenty-four to thirty-six weeks of gestation = 345.

^e Fail to define number of LB per trimester.

^f Failed to exclude herpes-zoster patients and did not define the number of LB per trimester that had satisfactory follow-up.

^g Not all studies classified data by trimester. Thus, the sum of all the trimester is lower than the “overall” number.

Table 4
Estimated incidence of CVS in USA, Canada, UK and Germany per year^a

	USA	Canada	UK	Germany
Birth rate (2004)	4140090	354660	654976	696280
Annual estimated varicella infection risk in pregnancy (2:1000)	8280	710	1310	1390
In 1–20 weeks of gestation	4140	355	655	695
CVS cases per year (1%)	41	4	7	7

^a Modified from Enders and Miller [6].

Based on the estimated risk of 1% in the first 20th weeks, together with the estimated varicella infection risk during pregnancy of 2:1000 and the annual birth rate, the number of expected CVS cases per year would be 41 in US, 4 in Canada, 7 in UK and 7 in Germany (Table 4).

In cohort studies [49,43,41], no significant differences in spontaneous abortion rates or intrauterine death between maternal varicella group and control group were noted.

Likewise, there was no increase risk for major malformation noted due to the very small number of fetus/newborn with CVS. Although, theoretically, one does expect an overall less than 1% increase risk above the baseline of 1–3% for major malformation. One study suggested that maternal varicella infection may increase the risk for preterm delivery [41]. Low birth weight was an almost consensual finding with CVS [31]. Mouly et al. [46] and Enders and Miller [6] both separately reported vertical transmission rate of 8% when infection occurred before 24 weeks of pregnancy by PCR method, whereas Paryani and Arvin [27] reported rates of 24% through clinical and serological criteria. There was no relationship between the age of gestation at which maternal varicella infection occurred during the first or second trimester and the severity of clinical features of CVS [42]. There were substantially more female fetuses reported with CVS, at 66–85% [29,42,30,50]. Alkalay et al. [50] proposed that it could be due to a higher affected male fetal mortality rate. Unpublished data presented by Enders and

Table 5
Case reports of CVS fetus with maternal varicella infection after 20 weeks of gestation

Maternal varicella at weeks of gestation	AOG at delivery	Abnormalities	Confirmation test	Case report
21	40 (ER CS)	Female, weak hoarse cry, intrahepatic, intracranial and splenic calcification, inactive L chorioretinal scarring near the macular region, mild R ptosis and L hemiplegia, esophageal dysmotility	(–) For TORCH including Herpes 1 and 2	Kerkering [53]
22	36 (vaginal)	R Lower limb hypoplasia and equinovarus, neuropathic ulcer, bilateral chorioretinitis, microcephaly, global developmental delay with severe learning difficulties, epilepsy	(–) For TORCH including Herpes	Deasy et al. [54]
23	29	Male, calcified skin cicatrices, a large head, focal necrosis with calcification in the skin, liver, spleen, myocardium and cerebral cortex, particularly large in the lungs. Died at 21 h in respiratory failure	DNA–DNA in situ hybridisation was (+) in all tissues. (+) IgM	Michie et al. [55]
24	FT	Female, multiple cicatricial skin scars on trunk and legs, chorioretinal scar L eye, psychomotor retardation and learning difficulties, esotropic L eye	IgG (+) @ 5 yrs of age with no previous hx of exposure	Lambert et al. [56]
24	39	Skin scars, a macular chorioretinal scar of the L eye with retinal atrophy temporal to the macula	(+) IgM	Harger et al. [47]
25 1/2	34 (induced vaginal)	IUGR, microcephaly, bilateral cataracts, large R subarachnoid cyst, bilateral porencephaly, seizure, bilateral ventricular myocardial hypertrophy with focal hemorrhage and necrosis and a small pericardial effusion	(–) IgM	Salzman, Sood [57]
25 1/2	>35 1/2	Microcephaly, healed R chorioretinitis, R occipital porencephalic cyst	(+) Serological test	Ong and Daniel [58]
26	NG	Skin scars, chorioretinitis	NG	Forrest et al. [59]
28	38 (CS)	Cicatricial scars, hypopigmented areas, multiple bleeding ulcers over both lower extremities, equinovarus of R foot	None	Bai et al. [52]

NG, not given.

Miller [6] did not show a significant difference between genders (F/M = 13/12). Sauerbrei and Wutzler [29] noted that among infants with CVS, 15% suffered from zoster within 2nd–41st month of life. About 0.8% of infants had zoster if maternal varicella occurred in the second trimester and in 1.7% if in the third trimester. Nearly 30% of infants born with severe CVS died during the first months of life. Recently, Schulze-Oechtering et al. [51] detected VZV DNA in the cerebrospinal fluid as well as in fluid samples from skin lesions of a baby born with typical CVS. This led to the suspicion that the newborn with CVS may be infectious and isolation after birth may be warranted.

Most CVS cases reported in the literature had documented maternal varicella infection occurring in the first 20 weeks of gestation [3,42]. Thus, it is commonly believed that after this period, there is virtually no risk for fetus to develop CVS. However, this may not necessarily be true as maternal varicella infection as early as 3 weeks of gestation to as late as 28th weeks was associated with CVS [42,47,52–59] (see Table 5).

5. Third trimester infection

5.1. Neonatal varicella

To our knowledge, only one case of CVS had been reported with maternal varicella rash appearing at the third trimester [52]. Though there were no serological tests done, maternal history was present.

In the third trimester, the concern is that maternal varicella near term or immediately postpartum may lead to severe neonatal varicella. Infection may occur by transplacental viremia, ascending infection from the birth canal or through direct contact with infectious lesions during and after delivery.

Data from Miller et al. [60] revealed that if maternal infection occurs 1–4 weeks before delivery, up to 50% of babies may be infected. Approximately 23% of these develop clinical varicella despite high titers of passively acquired maternal antibodies. Antibodies were present in all of 66 babies when the mother's rash appeared more than 7 days before delivery. When the mother's rash appeared 7–3 days before delivery, progressively fewer infants had antibodies. No antibody was detected in any of the 60 babies born less than 3 days after the onset of the mother's rash. The clinical attack rate was highest (62%) in infants born within 7 days after the onset of rash. Among the 19 infants who had severe symptoms, 16 were among the 118 whose mothers had the rash between 4 days before and 2 days after delivery (13.55%). These infants have not had time to receive passively maternal varicella-specific antibodies. Thus, there appears to be an increase in neonatal varicella severity around $-7/+7$ days. If rash appears in the mother from $-4/+2$ days from delivery, the estimated fatality rate to neonates has been reported at 30% [61–63]. This may be an overestimate since there was a selection bias plus the fact that neonatal intensive care units

Table 6

Risk factors associated with varicella pneumonia

Cigarette smoking
≥100 Skin lesions
Advanced gestational age (decreased cell mediated immunity?)
History of chronic obstructive airway disease
Immunosuppression
History of household contact

were not available during the 1970s. There was no death among patients who were given varicella-zoster immune globulin promptly. Sauerbrei and Wutzler [64] reported a case of fatality despite VZIG being administered after birth.

5.2. Maternal varicella pneumonia

VZV pneumonia is the most common complication in adults with varicella [65]. The incidence of varicella pneumonia does not appear to be increased in pregnancy, 10–14% [27,64,66,67]. If it does occur, it is well established that the morbidity and mortality from this infection in pregnancy is higher than in non-pregnant adults. The early symptoms are fever, dry cough, exertional dyspnea and mild hypoxemia, which usually appear during the first week after onset of rash. In severe conditions, where mechanical support is needed, mortality from varicella complicating pregnancy was reported to be between 20 and 45% before the antiviral therapy era [64,66,68] and 3–14% with antiviral therapy [63–65]. The difference may also be attributed to better respiratory management. The mortality is highest if infection occurs in the third trimester. This is postulated to be due to more pronounced immunosuppression during late pregnancy [63]. Pregnancy, however, does not result in clinically significant immunodeficiency as there is little evidence that communicable infections increase during this stage. It is more plausible to relate this complication to the mechanical effect of an enlarged uterus to the movement of the diaphragm [69]. Smoking remains to be a significant risk factor for the development of pneumonia (see Table 6) [65,70,71].

6. Herpes zoster

VZV remains in a latent state in human nerve tissue and reactivates in approximately 15% of infected subjects. It has not been documented that zoster is acquired from contact with a patient with zoster or chickenpox [25]. Herpes-zoster infection presents as a vesicular rash with pain and itching in a dermatomal distribution. The prevalence of herpes zoster during pregnancy is estimated to be 1.5 per 10,000 [72] in US and 2:1000 in UK [6]. In two reports [6,27] involving 480 women with herpes zoster occurring during pregnancy, including 301 in first and second trimester, no cases of CVS was documented. Theoretically, intrauterine infection may

still occur if the dermatomes involved were T10-L1, which innervate the uterus. However, no case report of CVS from localized herpes-zoster infection in pregnancy has been documented. Among cases of congenital malformation from maternal herpes zoster described by Higa et al. [30], only one infant with typical CVS was identified. The mother in that case had disseminated zoster at 12 weeks of gestation, which highlight the possibility of infection caused by maternal viremia. Miller et al. [60] and Enders and Miller [6] found no clinical or serological evidence of VZV infection in infants whose mother developed perinatal zoster. Therefore, VZIG is not indicated for the neonates born to mother with herpes zoster.

7. Diagnosis

Serologic tests have verified that 97–99% of adults, who reported a positive history of varicella are seropositive [73]. Varicella infection is routinely diagnosed based on clinical presentation and/or serological changes.

For diagnosis of CVS, Alkalay et al. [50] proposed the following criteria:

1. appearance of maternal varicella during pregnancy;
2. presence of congenital skin lesions in dermatomal distribution and/or neurologic defects, eye disease, limb hypoplasia.
3. proof of intrauterine VZV infection by:
 - detection of viral DNA in the infant;
 - presence of specific IgM;
 - persistence of IgG beyond 7 months of age;
 - appearance of zoster during early infancy.

Serological testing of IgM and IgG in fetal blood samples is often unreliable due to low sensitivity [42] for CVS, though proved useful in confirming evidence of intrauterine infection. Viral isolation by culture is also often proved to be unsuccessful. Serologic cross-reactions between HSV and VZV have been described [25] since both share common antigens with similar polypeptides and glycoproteins, yet cross-protection has not been documented. Thus, rises in heterologous antibody titers in apparent HSV or VZV infections may be due to cross-reactions of the viruses but also may indicate simultaneous infection by both viruses. Both Coxsackie B virus and Herpes Simplex type 2 (HS2) virus have been reported to cause congenital lesions similar to CVS. Recently, an infant born with cutaneous scar and limb hypoplasia wherein serological test and PCR revealed HS2 infection as the etiologic agent rather than VZV has been reported [74]. Therefore, defects in infants born to mother with varicella in pregnancy should not be automatically considered to have been caused by VZV in all instances.

Both PCR methods and in situ hybridization have been found to be sensitive and accurate [6,25,46,75]. PCR of amniotic fluid samples, fetal blood samples and

Table 7
Incidence of CVS after maternal herpes zoster

Reports	No. of CVS/No. of LB Overall (%)
Enders and Miller [6]	0/466
Paryani and arvin [27]	0/14
Mean (%)	0/480 (0)

serology testing will only confirm the presence of infection, but does not reflect whether the fetus is affected. In most cases, wherein the results were positive, the fetus was often found to have normal morphology at birth [46] (Table 7).

Prenatal diagnosis is most often done by detailed ultrasound searching for limb deformity, microcephaly, hydrocephalus, polyhydramnios, soft tissue calcification and IUGR [6,53,76,77]. One has to keep in mind that ultrasonography will not be able to detect all defects. At least 5 weeks interval between imaging and maternal onset of rash is advised since sonograms taken less than 4 weeks apart have been reported to fail in the detection of the deformities [78]. Magnetic resonance imaging and cranial tomography for further delineation of morphologic abnormalities have also been found useful [53,54,79]. Table 8 shows the prognostic value of prenatal diagnosis using ultrasound and PCR as described by Enders and Miller [6]. On initial examination at 17–21 weeks of gestation, if a detailed ultrasound is normal and VZV-specific PCR is positive in amniotic fluid, the risk is questionable. If repeated ultrasound done at 23–24 weeks of gestation is normal, the risk for CVS is remote but cannot be totally excluded. A positive PCR result in amniotic fluid is not predictive for fetal abnormalities if a repeat ultrasound is normal. It would suggest the presence of intrauterine infection. The risk is high if ultrasound results are showing features compatible with CVS together with positive PCR results from either or both blood and amniotic fluid samples after 22 weeks of gestation. MRI may be warranted to confirm morphologic abnormalities. A normal ultrasound at 23 weeks of gestation or later and a negative one round PCR or nested PCR in amniotic fluid at 19–22 weeks of gestation suggest a low risk of intrauterine infection or of severe malformations (Table 9).

Table 8
Prenatal diagnosis using ultrasound and PCR for risk of CVS [6]

Weeks of gestation	PCR	High level ultrasound	Risk for CVS with severe malformation
Initial			
17–21	(+) Amniocentesis	Normal	Uncertain
Repeat			
23–24	(+) Amniocentesis	Normal	Unlikely
22–24	(+) Amniocentesis (±) cord blood	Abnormal	High
18–22/>23	(–) Amniocentesis	Normal	Low

Table 9
Counselling advice for pregnant women at risk

Maternal rash appears	Risk for varicella embryopathy	Counselling advice
First 20 weeks	<1% above the baseline risk	VZIG within 96 h after contact if pregnant patient is seronegative or cannot recall ever having had varicella Level II ultrasound at 18–20 wks to detect defects If >14 weeks of gestation when rash appeared, level II ultrasound 5 weeks after maternal rash appears to detect defects Ophthalmologic examination after birth
21–28 Weeks	Rare	VZIG within 96 h after contact if pregnant patient is seronegative or cannot recall ever having had varicella. Level II ultrasound 5 weeks after maternal rash appears to detect defects Ophthalmologic examination after birth
After week 28	None	VZIG within 96 h after contact if patient is seronegative or cannot recall ever having had varicella to prevent varicella complication Explain baseline risk
5 Days before to 2 days after	None	If possible, delay delivery until 5–7 days after onset of maternal rash to allow transfer of IgG from mother to fetus Administer VZIG to neonate if exposed IV Acyclovir is warranted for severe cases
Maternal varicella pneumonia		IV Acyclovir 10–15mg/kg every 8 h for 5–10 days and antibacterial Blood gas, mechanical ventilation if needed Supportive therapy

8. Management

8.1. Prevention

8.1.1. VARIVAX (OKA strain)

VARIVAX, a varicella vaccine, was licensed in the US in March 1995 and was introduced in Canada on May 1999. Consequently, the incidence of varicella infection and hospitalizations have declined by approximately 70–80% in the US from 1995 to 2000. During this period, administration of varicella vaccine among children aged 19–35 months has risen to 74–84% with evidence of catch-up vaccination among older children [80]. The findings in this report suggest that there would be a steady decline in varicella incidence during pregnancy as well.

Studies in Japan have shown that antibodies to VZV were present in 97% of children 7–10 years after vaccination. Titers using Fluorescent Antibody Membrane Antigen (FAMA) were comparable to those in children who had natural varicella infection 7–10 years earlier [81]. Subsequently, a 20-year follow-up study revealed higher antibody levels than those observed 10 years earlier. One explanation for this would be that asymptomatic boosting of vaccine-induced immunity from exposure to wild-type VZV has occurred [82]. Similarly, prelicensure clinical trials in the US revealed protection for at least 11 years [83].

As a live vaccine, women who receive the vaccination are advised to avoid pregnancy for at least 1 month [73,84]. In the event of pregnancy prior to the 1-month waiting period, pregnancy registry [85] reveals that out of 498 reported cases of exposure in pregnancy, no birth defect compatible with CVS has been documented. Birth defect rates among women who received the vaccine were not higher than

what is expected in the general population. In 23 cases, inadvertent administration of VARIVAX in place of VZIG occurred. Varivax should not be given to pregnant women as a postexposure vaccination.

Transmission of varicella vaccine virus from a recently immunized 1-year-old child to his VZV-susceptible pregnant mother has been described by Salzman et al. [86]. Transmission was ascertained by VZV-specific PCR. After the mother developed chickenpox at 5–6 weeks of gestation, she elected to have an abortion but no virus was detected in fetal tissue.

Women who have received Varivax postpartum can be rest assured that they can continue to breastfeed. A study involving 12 women who received the vaccine revealed no evidence of VZV DNA in their breast milk samples with a total of 217 postvaccination breast milk specimens collected [87]. A similar pilot study was conducted by Dolbear [88] and no varicella gene sequences could be detected from the postvaccination breast milk samples obtained.

8.1.2. Varicella-zoster immunoglobulin

Susceptible pregnant women who have significant chickenpox exposure are candidates for VZIG therapy. Significant exposure is defined as household contact, face-to-face contact with an index case for at least 5 min, playing indoors with an index case for more than 1 h or sharing the same hospital room with a contagious patient [89]. Ideally, a serological test should be conducted prior to administration since 70–80% of adults who recalls no history of chickenpox are actually immune [90–92]. In the clinical setting, the results usually will not be available soon enough to alter management.

VZIG should be given within 72–96 h (and up to 10 days in UK probably due to a more concentrated immunoglobulin formulation [23]) following varicella exposure. When

given within 96 h, VZIG may prevent or significantly modify the course of the disease [93]. Since it takes some time for VZIG to be absorbed from the injection site and achieve an immunoprotective level in the blood, it should be given as soon as possible. The effectiveness of VZIG when given beyond the 96 h after initial exposure has not been evaluated [73]. Enders and Miller [6] reported on 108 pregnant women who received VZIG prophylaxis after exposure and before the onset of rash. None of the 108 delivered had infant with congenital varicella syndrome nor zoster postpartum. However, no statistical inference of whether there is actual decrease in maternal–fetal transmission can be drawn from these observations since the number was too small to document statistical significance. Pastuszak et al. [41] reported a case of CVS despite the mother receiving VZIG 4 days postexposure. It is not known whether VZIG prevents fetal viremia or CVS. Due to the rarity of CVS, it is unlikely that a randomized controlled prospective study will have sufficient power to show a favorable effect of VZIG. Furthermore, with VZIG being labeled for varicella infection in pregnancy, it is unlikely that ethics board will approve such a study. At present, VZIG is used to prevent severe maternal complications in pregnancy.

The duration of action of VZIG is not known, but protection should last at least one half-life of the immune globulin, which is approximately 3 weeks. Subsequent exposures later than 3 weeks after a dose of VZIG may require additional doses [73].

VZIG was recommended for neonates whose mothers developed chickenpox rash up to and including 5 days before delivery or up to 2 days after delivery [94]. The current guidelines are that VZIG should be considered also if newborns are exposed to varicella and born to susceptible mothers, <28 weeks AOG, or weighing <1000 g at birth who are exposed to varicella regardless of maternal history because they may not have acquired maternal antibodies. The recommended dosage is 125 U/10 kg or 0.5 ml/kg IM (0.5 ml/kg IV) to a maximum of 625 U. Increasing the dose given to neonates may not prevent infection but may reduce the severity of neonatal chickenpox [60]. In a pregnant woman weighing >50 kg, 625 U may be too small to ameliorate chickenpox [23]. However, the optimal dose for adults is unclear. VZIG may prolong the incubation period of the virus to 28 days. Thus, exposed neonates who have been given VZIG may need to be isolated for a longer period of time.

A new intravenously administered VZIG has been evaluated and found to reach a higher level of serum concentration than the intramuscular VZIG in a shorter amount of time [95]. This result offers a rational alternative towards using the intravenous form for prevention.

8.2. Antiviral therapy

Acyclovir is a synthetic nucleoside analog of guanine. When phosphorylated by enzymes produced by the cells infected with VZV, it inhibits viral DNA polymerase

stopping replication of human herpes viruses. When administered within 24 h of onset of rash, it has been shown to be effective in reducing the morbidity and mortality associated with varicella [73].

Intravenous acyclovir is preferred for initial treatment since the oral form has poor bioavailability. It has been considered in severe complications in pregnancy such as varicella pneumonia especially during the second half of pregnancy. The therapy has been clinically accepted to be effective in ameliorating the condition reducing mortality [69,71,96,97]. The dose is usually 10–15 mg/kg of BW or 500 mg/m² IV every 8 h for 5–10 days for varicella pneumonia and should be started within 24–72 h of the onset of rash.

Though there has been no sufficient evidence that treating pregnant women with acyclovir affects the course of fetal infection or reduces embryopathy, when given in children as postexposure prophylaxis after family contact, it showed significantly less with clinical infection [98,99]. Acyclovir crosses the placenta readily and can be found in fetal tissues, cord blood as well as in the amniotic fluid [31]. It may inhibit intrauterine viral replication during maternal viremia, limiting transplacental passage of the VZV [93,100]. Prospective pregnancy registry [101] as well as population-based observational study [102] revealed no increase risk for malformations with acyclovir. Grose [23] suggested a possible benefit of postexposure prophylaxis with acyclovir in pregnant women. Oral acyclovir is best given on the seventh day postexposure to prevent secondary viremia. Given too early, there were more cases with clinical infection. [103]. Since valacyclovir has a better oral absorption than acyclovir and is a prodrug of acyclovir, it would be a better choice for oral use. Drug safety information for valacyclovir is still limited for pregnancy exposure but combined with the acyclovir data, suggests that exposure during pregnancy does not increase the risk of major malformation [104].

Intravenous acyclovir is commonly given to neonates showing signs of infection to prevent severe sequelae [64,94]. Neonates with varicella complicated by neurological or ophthalmologic sequelae have been anecdotally reported to benefit from this treatment as well [64,105].

There is no well-controlled study for prophylactic use of acyclovir for maternal varicella exposure near term or in exposed neonates to prevent neonatal varicella. However, there have been several anecdotal reports of benefit from such therapy usually in combination with immunoglobulin [106,107]. Prophylaxis dosage for acyclovir has not yet been established.

Duvic and Grossman [108] reported two cases where acyclovir given during the first 24 h after rash, altered the immune status of the children leading to early zoster or reinfection symptoms.

Acknowledgement

GK holds the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation (Toronto), and the

Ivey Chair in Molecular Toxicology, The University of Western Ontario (London, ON).

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