World Journal of Virology

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DOI: 10.5501/wjv.v5.i3.97

World J Virol 2016 August 12; 5(3): 97-124
ISSN 2220-3249 (online)

REVIEW

Microbiology laboratory and the management of mother-child varicella-zoster virus infection

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Author contributions: Both authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Manuscript source: Invited manuscript

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Received: April 22, 2016
Peer-review started: April 23, 2016
First decision: July 5, 2016
Revised: July 8, 2016
Accepted: July 20, 2016
Article in press: July 22, 2016
Published online: August 12, 2016

Abstract

Varicella-zoster virus, which is responsible for varicella (chickenpox) and herpes zoster (shingles), is ubiquitous and causes an acute infection among children, especially those aged less than six years. As 90% of adults have had varicella in childhood, it is unusual to encounter an infected pregnant woman but, if the disease does appear, it can lead to complications for both the mother and fetus or newborn. The major maternal complications include pneumonia, which can lead to death if not treated. If the virus passes to the fetus, congenital varicella syndrome, neonatal varicella (particularly serious if maternal rash appears in the days immediately before or after childbirth) or herpes zoster in the early years of life may occur depending on the time of infection. A Microbiology laboratory can help in the diagnosis and management of mother-child infection at four main times: (1) when a pregnant woman has been exposed to varicella or herpes zoster, a prompt search for specific antibodies can determine whether she is susceptible to, or protected against infection; (2) when a pregnant woman develops clinical symptoms consistent with varicella, the diagnosis is usually clinical, but a laboratory can be crucial if the symptoms are doubtful or otherwise unclear (atypical patterns in immunocompromised subjects, patients with post-vaccination varicella, or subjects who have received immunoglobulins), or if there is a need for a differential diagnosis between varicella and other types of dermatoses with vesicle formation; (3) when a prenatal diagnosis of uterine infection is required in order to detect cases of congenital varicella syndrome after the onset of varicella in the mother; and (4) when the baby is born and it is necessary to confirm a diagnosis of varicella (and its complications), make a differential diagnosis between varicella and other diseases with similar symptoms, or confirm a causal relationship between maternal varicella and malformations in a newborn.

Key words: Mother-child infection; Congenital varicella syndrome; Varicella-zoster virus; Neonatal varicella; Microbiology laboratory

Core tip: Although varicella during pregnancy is infrequent and congenital varicella syndrome (CVS) is rare, every available means should be used to prevent and diagnose them. Microbiology laboratories can be crucial in these situations: Evaluating a mother's immune status with sensitive and specific tests for the detection of antibodies; allowing a rapid diagnosis with molecular biology tests when a clinical manifestation may be due to different etiologies; following pregnant women with varicella for the prenatal diagnosis of CVS with close collaboration between molecular biology investigators and specialists in imaging diagnostics.

De Paschale M, Clerici P. Microbiology laboratory and the management of mother-child varicella-zoster virus infection. *World J Virol* 2016; 5(3): 97-124 Available from: URL: http://www.wjgnet.com/2220-3249/full/v5/i3/97.htm DOI: http://dx.doi.org/10.5501/wjv.v5.i3.97

INTRODUCTION

Clinical features of varicella-zoster virus

Varicella-zoster virus (VZV) is responsible for varicella (chickenpox) and herpes zoster (shingles). Varicella is typically a childhood disease. Children experience a slight fever, fatigue and the appearance of typical vesicles on the skin[1]. Except in children aged < 1 year, complications are rare (2%-6%), but include *Staphylococcus* and *Streptococcus* super-infections of the lower and upper respiratory tract (pneumonia is more frequent in children aged < 1 year), conjunctivitis, corneal infections, meningo-encephalitis and occasionally death[2-5]. The disease is infrequent in immunocompetent children and adults, but complications are 25-40 times more frequent than in infants, probably because of a lower cell-mediated immune response than children[5-9]. These complications include a high fever, hepatitis, encephalitis, and especially viral or bacterial pneumonia (the latter in 10%-20% of cases), and the mortality rate without treatment may be as high as 20%-45%[10-12]. In general, adult varicella accounts for only 5%-7% of the total number of reported cases, but the mortality rate is about 35%[5]. Furthermore, 36% of immunocompromised subjects may experience serious and deadly disease with visceral dissemination and other complications (pneumonia, meningo-encephalitis)[5,13-15].

The infection may be transmitted by air (inhalation of the virus from respiratory tract secretions or vesicular fluid), fomites (*e.g.*, skin cells, hair, clothing, and bedding), or direct contact[16-18]. The incubation period is usually 14-16 d (range 10-21 d), but may be up to 28 d in subjects treated with immunoglobulins, and even longer in immunocompromised subjects[5,9,19]. The virus enters the body through various mucous membranes (the nasopharynx, conjunctiva) and passes into regional lymph nodes where it replicates[9,20]. Primary viremia occurs 4-6 d after infection, with dissemination to, and replication in other organs (liver, spleen, the sensory ganglia); secondary viremia appears after about 14 d (range 10-21 d) and is expressed in the form of a skin infection and the characteristic rash[5,21,22]. The macules quickly progress to papules and vesicles, and then to scabs. The lesions appear at various stages of development at the same time, and have a central distribution, mainly on the trunk and face, and less on the limbs[5,7]. The vesicles contain many viruses, and may therefore be the most important route of transmission[23-25]. Patients are usually infectious from two days before the rash until the formation of scabs generally five days after[26,27].

Herpes zoster (shingles) is caused by virus reactivation years after the first infection, during which the virus migrates to the sensory nerve ganglia of the dorsal root and establishes latent infection in neuronal cells[13,28]. Its reactivation years or decades later causes the reappearance of the lytic infection in up to 15%-30% of the population[29-33]. The virus spreads unilaterally along the dermatomes and produces vesicles confined to a single dermatome of the skin, giving rise to a particularly painful rash[34-36]. Post-herpetic neuralgia usually lasts 2-3 wk but, in some cases, it can last for months or even years after the rash has disappeared[9,37].

Reactivation is caused by a decline in cell-mediated immunity (CMI) (particularly in specific T lymphocytes), or immunosuppression due to diseases, transplantations or medical therapies[9,18,38], although other possible predisposing factors may be considered as gender, seasonality, race, stress, exposure to immunotoxic substances, trauma and genetic susceptibility[39,40]. It is more frequent in the elderly (50% of people aged > 85 years of age experience episodes of herpes), and in subjects with CMI disorders (lymphoproliferative cancers, organ transplantation, AIDS, *etc.*)[18,41,42].

The virus

VZV or human herpesvirus 3 is a DNA virus belonging to the order *Herpesvirales*, family *Herpesviridae*, subfamily *Alphaherpesvirinae*, genera *Varicellovirus*[43]. It is exclusively human, and has a diameter of about 175 nm[9,44]. Of the seven known genotypes (E1, E2, J, M1, M2, M3, M4), five are phylogenetically circulating groups, and two (M1 and M2) are probably recombinants of E1 and J[30].

The genome consists of a unique long region of 107836 bp flanked by inverted repeat regions (the long terminal repeat and internal repeat long and a unique short region flanked by repeated internal regions (the short terminal repeat and inverted repeat short)[45].

The DNA contains 70 genes that are expressed sequentially during the lytic cycle with the production of immediate early non-structural and late structural proteins[45,46]. The structural proteins form an icosahedral capsid (162 capsomeres) containing the DNA, linked to the outer lipoprotein envelope by a tegument (amor-

phous-protein structure)[9,47]. The envelope is made up of glycoproteins (gB, gE, gH, gI, gK) and is important in virion attachment, entry, envelopment, cell-to-cell spread and egress[48]. After entering a cell, the virus replicates in the nucleus where the pre-formed DNA is incorporated into capsids that leave the nucleus through the nuclear membrane. After passing the inner nuclear membrane, a first enveloped virus is formed in the perinuclear space and, by means of the fusion of this envelope with the outer leaflet of the nuclear membrane, the nucleocapsid is released into the cytoplasm. The nucleocapsids are re-wrapped in the Golgi complex, and the mature virions are released into the outer space after the fusion of the vesicle membranes with the cell membrane[49]. Unenveloped virions can also pass from cell to cell, thus contributing to the spread of the virus, for example in the skin[9,40]. The latency phase is characterised by the expression of only a small number of proteins, and the resumption of the lytic cycle after latency leads to the manifestation of herpes zoster[40,50].

Natural immunity

Natural infection induces a long-lasting immunity that is maintained and enhanced by internal reactivation and/or external boosting after exposure to VZV[9,34,51,52]. A person who has had varicella is usually protected against the disease unless he or she is immunosuppressed[5,9,53,54]. People with a history of varicella who are re-exposed to the virus may develop a new infection but it is usually asymptomatic and can only be detected on the basis of an increase in antibody titres[5,55,56], but it may sometimes be mildly symptomatic in the case of a failure to develop or maintain cell memory (leading to a reduction in specific T lymphocytes), or if the viral load is too high[57,58]. Some studies have reported 4.5%-13% of symptomatic cases in children with a reported previous history of varicella, and there have also been cases of varicella during pregnancy in the presence of weak antibody positivity[58-63].

Humoral immunity does not prevent latent viral infection or subsequent reactivation in the form of herpes zoster, but CMI is important to contain the virus because the virus spreads through the human body intracellularly[9,64-67]. If CMI is working correctly, the absence of antibodies after infection does not automatically imply susceptibility to re-infection, but a poor or absent response increases incidence of herpes zoster even in the presence of antibodies as has been reported in the elderly[9,34,68,69]. Finally, in addition to antibody-dependent cellular cytotoxicity, natural killer cell cytotoxicity is also important[70].

Humoral immunity is expressed as the production of antibodies against components of the capsomere and surface glycoproteins[71-78]. The antibodies against the surface glycoprotein components (anti-gE, anti-gB, anti-gI and anti-gH) are particularly neutralising[79-81].

In the acute phase, IgM antibodies appear 1-7 d after the rash, peak after 14 d (range 7-30), and generally disappear during convalescence, although they may persist for several months[82-84]. They may also be found during re-infection and reactivation, appearing 8-10 d after the rash and peaking after 18-19 d in 50% of herpes zoster cases[30,82,85]. However, IgM is not always found in cases of full-blown varicella and so their absence does not indicate the absence of infection[30].

IgA antibodies have the same trend as IgM and, in the case of re-exposure or reactivation, reappear (or increase) in 50%-99% of cases of herpes zoster[83,85,86].

IgG antibodies appear about 9-10 d after the beginning of the rash, peak after about 60-70 d, and then decrease to lower levels for the rest of the infected subject's lifetime[82,87]. External boosters (contacts with exogenous virus) or internal reactivation can increase their titres over time[9,34,51,52].

Epidemiology

Varicella is a ubiquitous disease: In countries with a temperate climate such as North America, European countries, more than 90% of the population contract the infection before the age of 15 years[54,88-93]. It mainly affects children with especially winter/spring seasonality: It is estimated that 52%-78% of all reported cases of varicella occur in children aged < 6 years, and 89%-96% of cases in children aged < 14 years; only 5%-7% of cases occur in adults[5,94,95]. The population incidence is about 1300-1600 cases per 100000 inhabitants per year[87], but varies with geographical location: It is 300-1291 cases per 100000 in Western Europe[96-98], 164-1240 cases per 100000 in Southern Europe[99-111], 350 cases per 100000 in Eastern Europe[112,113], and 1500-1600 cases per 100000 in the United States (pre-vaccine era)[114]. The reported mortality rate is 0.04-0.06 per 100000 inhabitants, and 2-4 per 100000 cases of varicella, including 35% of adult cases[5,30,115-121].

Epidemiology is different in tropical countries, where there is no marked seasonality[5]. The infection is acquired in childhood less than in temperate countries, with only 25%-85% of subjects contracting primary infection before the age of 15 years[122-131]. Various hypotheses have been postulated to explain this difference, including viral inactivation due to high ambient temperatures, race, interference from other more prevalent viruses and a lack of exposure due to the rural living conditions in the tropics, where VZV does not circulate very much[123,132-134]. Advanced age of infection and the severity of adult disease may be responsible for the increased morbidity and mortality due to varicella and complications in these areas[59,135-137].

However, epidemiology in industrialised countries is changing because of the increase in immigration and/or greater vaccination coverage insofar as the incidence of infection has decreased by 57%-95% in all age groups in the places in which vaccination is widespread[5,138-140].

As regards the herpes zoster, the reported annual incidence is 120-480 per 100000 inhabitants (all ages), and 720-1180 per 100000/year in people aged > 60 years[18,27,141,142].

Consequences of an infection contracted during pregnancy

As varicella is a widespread disease, especially among children, the global risk of exposure during pregnancy has been estimated to be 12%-24%[54,56,143]. Fortunately, as most adults in temperate countries are already protected, the possibility of contracting varicella during pregnancy among susceptible women is much lower, and the estimated incidence of varicella is 0.1-3 per 1000 pregnancies[8,26,90,117,144-150].

Contracting varicella during pregnancy can be very serious for a mother, especially if it is contracted in the third trimester[10,151]. In fact varicella can be more severe in all adults than in children as it may lead to complications such as meningoencephalitis, hepatitis and, especially, pneumonia[16,152]. The incidence of pneumonia during pregnancy does not seem to be higher than in non-pregnant adults, but it is more severe in pregnant than in non-pregnant women especially if it appears in the third trimester of pregnancy[6,10,19,26,56,121,144,153-157]. Pneumonia can appear in 5%-20% of pregnant women[54,121,152,158] and leads to death in 20%-45% of cases unless appropriate treatment is started, but with appropriate treatment and better breathing management, the mortality rate drops to 0%-14%[10,16,152-154,157,159-163].

During pregnancy, the infection can also be transmitted to the fetus and, depending on the time of transmission, may cause congenital varicella syndrome (CVS), neonatal varicella, or childhood herpes zoster. It has been estimated that transmission from mother to fetus occurs in 8%-24% of cases[56,90,145,164]. Early studies using IgM in the newborn as a sign of infection (now considered a very insensitive marker) indicated transmission rates of 5% in the first trimester, 10% in the second, and 25% in the third[145].

The crossing of the placental barrier seems to occur both viremic phases of incubation, but secondary viremia seems to play a greater role in fetal transmission[21,22,26]. Furthermore, infection arising from a lesioned birth canal can cause intrauterine infection[165].

CVS: The characteristic defects include skin scarring with a dermatomeric distribution; eye defects (microphthalmia, chorioretinitis, corneal alterations, cataracts); limb hypoplasia with muscle hypoplasia; neurological abnormalities (microcephaly, cortical atrophy, mental retardation or bowel and bladder sphincter dysfunction, cerebral calcifications); and (less frequently) ear, cardiac, gastrointestinal and genitourinary abnormalities, slow fetal growth and a pre-term delivery[26,145,166-168].

It has been reported that the mortality rate during the first month of life is 30%, but infants who survive this period can have a good long-term outcome even though there is a 15% risk of developing herpes zoster between the fourth and forty-first month of life[26,53,145,147,159,169,170].

CVS is probably due to herpes zoster-like reactivation *in utero* rather than initial varicella, and this view is supported by the fact that the skin lesions have a dermatomal distribution similar to that of herpes zoster[26,167,171]. The short period between primary infection and reactivation may be due to an immature VZV-specific cell-mediated immune response in the fetus[172]. As 65%-85% of the infants born with CVS are female, it has been hypothesised that there is a higher rate of fetal death among males[26,145,147,168,171].

It has been estimated that 8%-25% of the cases of viral transmission to the fetus occur during the first two trimesters of pregnancy, but only 12% of these cases actually develop CVS, and so the incidence of CVS in different studies ranges from 0% to 2.63%[53,56,145,152,164,166,173-178]. A meta-analysis of studies published between 1986 and 2002 calculated a total incidence of 0.70% (0.55% in the first trimester, 1.4% in the second, and 0% in the third)[26]. The most important period of transmission is between the fifth and twenty-eighth week of pregnancy, particularly up to the twentieth week, when the incidence of 0.91%[26,145,168,179]. Cases of CVS are rare between the twenty-first and twenty-eighth week, and are mainly described in individual case reports[152,179-186]. The probability of observing cases before 3-5 wk and after 28 wk of gestation is practically zero (in the latter case because of fetal maturation)[26,145,159]. Considering an average risk of two cases per 1000 pregnancies, the number if expected cases per year was estimated to be 41 in the United States, four in Canada, 2-10 in the United Kingdom, and seven in Germany[26,54,90,187,188].

The risk of a miscarriage is debated in the literature: Some authors have indicated a 3% risk during the first trimester, and an 8% risk during the second, whereas others have found that the risk does not seem to be any greater than the risk in uninfected pregnant women[16,145,159,166,173,176,189,190].

Neonatal varicella: In the case of mothers who contract varicella in the four weeks before birth, there is a 50% possibility of infection in the newborns, 20%-30% of whom will actually develop the disease[16,191]. If the maternal varicella appears 20-7 d before the birth, the varicella in the newborn (if it develops) generally has a benign and non-fatal course because newly born infants have their mothers' antibodies and the risk of complications is low[5,26,131,165,191-193].

In the case of maternal varicella between seven days before and seven after delivery, 2/3 of the infants become infected and 50% have severe symptoms because they do not have maternal antibodies and their cell-mediated response is insufficiently mature[26,145,169,191,194,195]. During this period, the most dangerous situation is when maternal varicella appears between five days before and two days after delivery because, in the absence of adequate therapy, the neonatal mortality rate may be as high as 20%-30% and, even with therapy, may still be 7%[5,153,157,159,165,191,196-198].

Maternal varicella may be transmitted transplacentally, or by means of ascending infection during birth, or by means of respiratory droplets or direct contact with infectious lesions after birth, and neonatal disease may manifest itself with skin lesions, ulcerated

necrotic or hemorrhagic lesions, and/or systemic disease (pneumonia, liver failure, encephalitis or coagulopathy)[16,26,53,159,165]. As the incubation period of varicella transmitted *in utero* from the initial maternal rash is 10-12 d (but may be as short as four days), the varicella observed in infants in the first 10-12 d of life is considered of intra-uterine origin, and that appearing later as probably post-natal[53,90,145,159,165].

In conclusion, if the newborn has passively acquired maternal antibodies, post-natal varicella contracted from the mother or from people other than the mother is rare and more benign[193]. However, if the baby is premature (< 28 wk or < 1000 g), he or she is still at high risk in the first six weeks of life because of the non-acquisition of maternal antibodies as a result of the reduced period of gestation[131,192,199]. Consequently, in the case of planned childbirth, it is advisable to avoid delivery during the 5-7 d after the onset of the rash in order to allow the passive transmission of antibodies[16,200,201].

Herpes zoster in the first years of life: Maternal varicella occurring after the twenty-fourth week of gestation leads to asymptomatic fetal seroconversion and the birth of an asymptomatic newborn; however, herpes zoster may develop in the first years of life (especially in the first or second year) because of viral reactivation[202]. The short latency period is due to the infant's immature cell-mediated response[203]. The course of the disease is normally uncomplicated, but it is recommended to check children with herpes zoster for other clinical signs of intra-uterine infection especially at ophthalmological signs[147,203].

The incidence of herpes zoster is 4%-20% in the case of documented *in utero* infection but, if this is not the case and the mother had varicella during the pregnancy, the incidence decreases to 0.8%-1.7% depending on whether the maternal varicella appeared in the second or third trimester[145,159,164,165,203].

Herpes zoster may also occur after 2-41 mo of life in 15% of newborns with CVS if the onset of maternal varicella was between the eighth and twenty-fourth week of gestation[147].

Prevention and treatment

Vaccination: The first live attenuated vaccine contained wild-type OKA VZV cultivated human embryonic lung fibroblasts (WI-38) and propagated embryonic guinea pig fibroblasts[204,205], and has been used in the United States since March 1995. Commercial versions all use the OKA strain but differ in terms of the number of passages in guinea pig and human cells (with additional passages in MRC5 cells), the viral load in each dose, excipients and other patented aspects[9]. It is currently available as a vaccine to be administered alone, or in a quadrivalent vaccine against measles, mumps, rubella and varicella (MMRV)[5,206].

It has been shown that a single dose is effective in preventing varicella in 80%-85% of cases and severe forms in 95%-100%, especially in children aged < 10 years of age, but also in 74% of adults[5,30,206-209]; vaccinated subjects are also at lower risk of developing herpes zoster[115,210]. The vaccination was initially administered as a single dose and, as it was not 100% effective, failed to protect about 15% of treated subjects[211-214]. There have been reports of cases of breakthrough varicella (BV) in 10% of vaccinated healthcare workers and 15%-20% of vaccinated children after one dose due to primary (no take) or secondary vaccine failure (immune response decreasing over time), and that 30% of vaccinated subjects gradually lose antibodies after the first dose[5,9,30,215,216].

BV occurs more than 42 d after vaccination and is due to wild-type virus[217]. Its symptoms are milder than those of classic varicella as there is no fever and < 50 skin lesions, which take the form of papules and tend not to progress to vesicles[5,218-220]. Classic varicella is associated with 250-500 lesions, but one study found that 56% of the patients with BV had < 50 lesions, 33% had 50-300 lesions, and only 11% had > 300 lesions[5,221]. These occurrences of BV led to the indication to administer two doses but, although the second dose has minimised primary vaccination failure, BV may still occur[5,206,222,223].

Vaccination induces a humoral immune response with the production of antibodies that appear after 3-5 wk, a cell-mediated response that appears after four days in 50% of vaccinated subjects[224]. The immunity persists for at least 20 years, thus providing long-term protection, and the subjects who remain seronegative after vaccination still have the chance of acquiring CMI[9,30,165,225-228].

The rate of seroconversion in healthy children is about 87%-100% after the first dose and 97%-100% after two doses[5,9] and consequently, antibody testing is not considered necessary after two doses[5]. Vaccination is generally stronger in children[229,230]: In adults, 78% respond after the first dose and 94%-99% after the second[5]. As it is a live attenuated vaccine, vaccination is not recommended in immunocompromised patients, but may be considered in some categories of patients (patients with human immunodeficiency virus infection and normal CD4 cell counts, patients with leukemia, candidates for transplantation, *etc*.)[5,88,231].

Antibody titres gradually decline after the initial peak, but can be restored by an external booster[30,226]. Like the wild-type virus, the vaccine virus may also become latent and then be reactivated to cause herpes zoster in both healthy and immunosuppressed subjects[30]. However, the risk is lower and the symptoms are milder and without complications[5,232], probably because the attenuated vaccine virus is less likely to be reactivated and cause a rash that allows the virus to travel to the dorsal root and establish latency[25]. Nevertheless, herpes zoster is more frequent if there is a post-vaccination rash[233], which may occur in 5% of the subjects receiving the first dose, and in 1% after the second[5]. It must also be borne in mind that herpes zoster in vaccinated subjects may be due to the vaccine virus or

the wild-type virus, and there also the possibility of their recombination[5,30,221,234,235].

The vaccine may also be useful in preventing varicella if administered within 3-5 d of exposure to infection due to contact, even if not entirely prevents it[5,236-238]. However, as it is a live attenuated vaccine, it is not recommended for pregnant women exposed to infection[19]. Furthermore, pregnancy should be avoided for at least one month[199,206,239,240], although it may be offered to susceptible women before conception or *post partum*, and it is not contraindicated during breast-feeding[5,169,241].

Finally, a vaccine against herpes zoster that contains a higher titre of the OKA strain used in the MMRV vaccine has been approved for subjects aged > 50 years, and is recommended for those aged > 60 years[5,242].

Immunoglobulins: It has been found that, in order to prevent the most serious consequences of infection in susceptible pregnant women, immunoglobulins (VZIGs) can be administered within 72-96 h of exposure (within 10 d according to the United Kingdom guidelines)[16,145,188,199,206,243-249]. The difference in the timing has been attributed to the different formulation of the VZIGs[21]. The protection lasts for about three weeks, and any further exposure requires additional administrations[16,19,199,250].

The rationale underlying the administration of VZIGs is that it can prevent or mitigate varicella by as much as 75%, although some authors insist that it mitigates rather than prevents varicella[16,145,159,165,206,245,251-253]. It has been reported that 50% of the mothers treated with VZIGs present an uncomplicated or mildly evolving form of varicella, and 5%-25% a sub-clinical form[8,54,90,253]. Fetal transmission also seems to be reduced[254]. As the virus crosses the placenta during the two viremic phases of incubation, it has been suggested that passive prophylaxis may be effective if administered before the first[21,22,26]. It has been reported that ZVIGs can reduce intra-uterine transmission from 12.3% to 1.1%, and reduce or practically eliminate the risk of developing CVS[16,54,90,145,164,254]. There are in fact very few published cases of CVS[166], but it is unclear whether VZIGs prevent CVS because they prevent fetal viremia or prevent CVS even in the presence of fetal viremia, and so there is still some uncertainty concerning their real effectiveness in this regard[26,159]. It has also been pointed out that, as CVS is a rare disease, it is numerically and ethically difficult to carry out studies[54]. In any case, the guidelines indicate the administration of VZIGs after exposure at any time during pregnancy, and after childbirth if the delivery takes place within 10 d of exposure, but not after the appearance of the rash[188,199,255-257].

The administration of VZIGs to newborns is indicated if the mother had varicella symptoms between seven days before and seven days after childbirth, and especially between five days before and two days afterwards, but is probably not necessary if maternal varicella appeared before or after this period[5,16,165,174,247,258-260]. In general, the combined neonatal administration of VZIGs (and antiviral agents) alters the clinical course of the disease, but does not completely prevent it, and 50% of the infants may still experience clinical symptoms[87,191]; however, mortality is reduced (even if not entirely eliminated)[16,153,191,261,262].

VZIGs are also recommended in premature infants (born after 28 wk or later) who have been exposed in the neonatal period and have mothers without any evidence of immunity (*i.e.*, there has been no passive transmission of antibodies from the mother), and in those born before 28 wk (or weighing $\geqslant$ 1000 g) who have been exposed neonatally regardless of the immune status of the mother (because the reduced gestational period means that they cannot have acquired maternal antibodies)[5,26,165,199,263,264].

However, once again, infant administration is not indicated if varicella has already appeared[261,262].

Therapy: The most widely used drug, acyclovir (and its precursor valacyclovir) is a synthetic nucleoside analogue of guanine that is highly specific for cells infected by herpesvirus and does not interfere with human DNA[169]. When phosphorylated by cellular enzymes (thymidine kinases), acyclovir triphosphate inhibits viral DNA synthesis by competing with deoxyguanosine triphosphate as a substrate for viral DNA polymerase. Incorporation of acyclovir triphosphate into viral DNA results in obligate chain termination. Viral DNA polymerase is tightly associated with the terminated DNA chain and is functionally inactivated[53]. Acyclovir crosses the placental barrier, and can be found in fetal tissues, cord blood and amniotic fluid[19].

It has been suggested that viral treatment after exposure is a means of preventing or mitigating the infection because, if administered within 24 h of the appearance of the rash, its use in immunocompromised children and immunocompetent adults reduces the symptoms[21,26,252,256,265,266]. Consequently, it has been suggested as prophylaxis in pregnant women (especially if VZIGs are not available)[169], particularly if administered within seven days of exposure and within 24 h of the onset of the rash[26,54,252,265,266]. The use of acyclovir during pregnancy has been widely debated in the literature: There is general consensus concerning its use when the mother's life is in danger and as a means of reducing the severity of complications occurring in late pregnancy[19,53,151,156,256,267], but its therapeutic and CVS prophylactic use before the twentieth week of gestation is more controversial; some authors favour its administration always, and others only after 20 wk[10,16,19,53,54,151,156,169,252,256,267-271].

As the virus crosses the placenta during both viremic phases of incubation, the second of which seems to play a greater role in fetal transmission, it has been suggested that secondary viremia can be prevented or minimised by acyclovir provided that it is not given too early[21,22,26,265]. However, there are still doubts as to whether inhibiting maternal viral replication can inhibit or limit trans-placental transmission, thus reducing fetal

mortality and morbidity[26,53,154,199,245,272,273]. It is important to note that the use of acyclovir during pregnancy does not seem to increase the risk of fetal malformations, and that international registries show that the incidence of embryopathies in women treated during the first trimester of pregnancy is equal to that in the general population[16,269,274-277].

Finally the use of acyclovir in infants with varicella can reduce the severity of the disease and the complications[153,259,278,279]. The are also a few case reports indicating that it can block the ophthalmic and neurological progression CVS in newborns[279,280].

THE ROLE OF THE MICROBIOLOGY LABORATORY

Microbiology laboratories play an essential role in relation to the general management of four aspects of maternal/infantile VZV infection: Determining immune status after VZV exposure; diagnosing varicella in pregnant women; prenatally diagnosing intrauterine VZV infection and/or CVS; and diagnosing neonatal infection.

Anamnesis

In the case that a pregnant woman comes into contact with someone (usually a child) affected by varicella, the first step is to record her medical history as this may be important to establish the risk that she will contract the infection. The main points to consider are the risk of transmission, which depends on the source of infection and the immune status of the pregnant woman.

Risk of transmission: This depends on whether the source of exposure is someone with varicella, someone with herpes zoster, someone with BV (due to wild-type virus), or someone with post-vaccination rash (due to the OKA strain).

In subjects with varicella, the horizontal transmission rate is 61%-100% of susceptible contacts[5,34,281]. Infection can occur 1-2 d before the appearance of vesicles, lasts for 5-7 d after the onset of the rash, and continues to be infectious until the vesicles are crusted over[1,26,282]. The virus is transmitted by means of direct contact or through the air (respiratory tract secretions or the inhalation of aerosols from the vesicular fluid of the skin lesions)[5]. Infection normally occurs as a result of close face-to-face contact or simultaneous presence in the same room for 15-60 min[16,19]: Most authors believe 15 min are sufficient, whereas others specify 5 min of face-to-face contact and 15 min in the same room[16,159,165]. The risk of congenital varicella in a mother who develops varicella during pregnancy has been described above. Transmission due to asymptomatic infection or re-infection has been hypothesised, but not convincingly documented[169,283].

In subjects with herpes zoster, the horizontal transmission rate is 16% of susceptible contacts[284]. Transmission primarily arises from the exposed skin lesions of immunocompromised subjects or subjects with disseminated zoster, and is rare if the lesions are not exposed[16,17,285-289]. The risk of fetal infection is virtually zero: Localised maternal zoster (the few published data estimate 0.15-2 cases of herpes/1000 pregnancies[90,147,290,291]) does not seem to be associated with fetal or *in utero* infection, nor with post-natal infection because newborns are protected by passively transmitted maternal antibodies[56,90,145,147,166,173,191]. There are published case reports of fetal malformations in mothers affected by localised zoster during pregnancy but without any laboratory evidence of intra-uterine infection[159,290,292]. Instead one case of a confirmed VZV-infected newborn with CVS, whose mother had disseminated herpes zoster after 12 wk of pregnancy, was reported[171].

In subjects with BV, the disease is milder, fever free, and with fewer skin lesions, which are generally atypical with papules that tend not to progress to vesicles, and so the subjects are not considered infectious until new lesions appear[30,218]. Transmission affects 12%-37% of susceptible contacts but, if the number of lesions is > 50, the wild virus transmission rate is the same as that of classic varicella in unvaccinated subjects[293,294]. In the case of BV, the risk of fetal varicella is considered to lower than that in unvaccinated subjects, but the only data come from reports of cases without fetal consequences[159,295]. In any case, the prophylactic and therapeutic measures are the same as those for unvaccinated women[159,165].

In subjects with post-vaccination rash (OKA strain) as a complication of vaccination, the rash appears in 4%-6% of the subjects vaccinated with one dose, and 1% of those receiving the second dose[5]. Horizontal transmission is rare[16,206]: There are very few reported cases, and it only occurs in the presence of rash[5,206]. The contacts have asymptomatic infections (seroconversion) or only mild symptoms[5], but it is, important to check whether the varicella, that develops within 42 d of vaccination is due to the wild-type or vaccine virus. Anti-VZV vaccinations should be avoided in pregnant women because they involve a live attenuated vaccine, and vaccinated women should avoid pregnancy for at least one month, but no cases of fetal malformations have been reported in inadvertently vaccinated pregnant women[16,54,156,199,206,239,240,296,297]. There is one case of transmission from a vaccinated child to a pregnant woman without subsequent fetal infection[298]. Furthermore, no viral genome has been found in breast milk after vaccination, and there have been no reports of transmission through the breast milk of women vaccinated after giving birth, who can therefore continue to breastfeed[16,241,299].

Finally, no cases of transmission from patients vaccinated with zoster vaccine have been reported[5].

Immune status: An anamnesis can provide important information about a subject's immune status because a history of varicella is 90%-99% predictive of the presence

Table 1 Anti-varicella-zoster virus seroprevalence rates in women in some countries with a temperate climate

Country	Population	Age	Anti-VZV seroprevalence (%)	Ref.
United Kingdom	Pregnant women	Mean 28 yr	95.8	[301]
United Kingdom	Pregnant women	Mean 28 yr	94.8	[308]
Spain	Women	19-39 yr	92.3	[309]
Spain	Women	Not reported	95.3	[313]
Holland	Women	Mean 47 yr	93	[311]
Holland	Women	Mean 29 yr	100	[312]
Slovenia	Women of childbearing age	15-49 yr	97.2	[314]
Croatia	Women (12% pregnant)	Not reported	84.3	[315]
France	Women	Mean 30.4 yr	98.8	[316]
Germany	Pregnant women	Mean 28 yr	96.7	[317]
Finland	Pregnant women	Mean 30 yr	95	[318]
Italy	Women	15-39 yr	87.4	[321]
Italy	Pregnant women	15-49 yr	89.4	[310]

VZV: Varicella-zoster virus.

Table 2 Seroprevalence rates in some tropical countries

Country	Population	Seroprevalence (%)	Ref.
St.Lucia (Caribbean)	40-year-old	> 70	[123]
Tropical islands	Pregnant women	84	[131]
Bolivia	Women of child-bearing age	88.4	[322]
Singapore	15-24 yr	40	[95]
	25-34 yr	> 80	
India	17-20 yr	30	[130]
India	Adults (rural areas)	68.9	[134]
	Adults (urban areas)	96.6	
Iran	Pregnant women	78.5	[323]
Saudi Arabia	Pregnant women	74.4	[324]
Singapore	15-24 yr	40	[515]
	25-34 yr	> 80	

of antibodies, although the time between vaccination and exposure should be carefully considered as the antibodies appear 3-5 wk after vaccination[54,199,224,300-334].

If there is no reported history of varicella, antibodies are in any case present in 70%-90% of cases[54,302-306]. The seroprevalence rate is high in industrialised and/or temperate climate countries[99,150,301,307-321] (Table 1). However, a reported history of varicella is rather less predictive in women from tropical countries where the seroprevalence rate is lower[123,129-132,134,150,300,322-324] (Table 2).

The intense population movements of recent times should encourage a careful evaluation of the epidemiology of a woman's region of origin. Furthermore, a previous vaccination (preferably formally documented by a vaccination certificate) may be important for evaluating antibody protective: As 78% of adults respond to the first dose and 99% to the second, women who have received two doses are considered protected, an antibody search is not necessary, and immunoglobulins are not indicated[5,159]. Vaccination policies vary from country to country, and so it is necessary to consider a woman's country of origin in the case of recent immigration[325,326].

It has been estimated that at least 80% of women can be reassured after a careful history has been taken; the others need to be referred for laboratory tests[304].

Labotoristic determination of immune status

In the case of women of foreign origin or those with a negative history of varicella, as well as if there are doubts any kind, it is necessary to search for specific antibodies in order to determine immune status[8,16,139,151,159,247]. This should be done as soon as possible because the results of serological tests should be expected before 24-48 h and, if they are negative, VZIGs must be administered within 96 h[16,54,244,327]. The antibodies detected within 7-10 d of a contact with someone who is infected are considered as having been acquired before exposure[328].

It is possible to investigate both cell-mediated and humoral immunity. The tests that have been used to detect cell-mediated responses are ELISPOT[329-332], flow cytometry[333,334], hypersensitivity skin tests[306,335-337], and T cell cytokine response tests[338], but these have mainly been used to test the response to vaccination[294,339-341]. For example, a positive response to ELISPOT has been found in 90% of subjects one year after vaccination, and in 87% after five years[338]; the response is greater after two doses than after one dose[294,339,340]. A positive response to a hypersensitivity skin test has been found in 100% of subjects 5-7 wk after vaccination[337]. However, CMI tests cannot usually be used for routine purposes as they require special instruments and the time necessary is not compatible with a rapid response.

It is much quicker and easier to analyse antibody responses, and many tests have been used to predict disease susceptibility and the immune response to vaccination. These include complement fixation (CF), anti-complement immunofluorescence (ACIF), immune adherence hemagglutination (IAHA), passive hemagglutination (PHA), radioimmunoassays (RIAs), neutralisation tests (Nt), latex agglutination (LA), indirect fluorescent antibody tests (IFA), fluorescent antibody to membrane antigen (FAMA), time-resolved fluorescent immunoassays (TRFIAs), immunoblotting (IB), enzyme-

linked immunosorbent assays (ELISAs) or enzyme immunoassays (EIAs), glycoprotein ELISAs (gpELISAs), chemiluminescence immunoassays (CLIAs), and enzyme-linked fluorescent assays.

CF: One of the first tests was CF, but it is not very sensitive, difficult to automate, and can only be used to diagnose recent infection[342-349].

ACIF, IAHA, PHA, RIA: The sensitivity and specificity of tests such as ACIF[350], IAHA[351-356], PHA[357-359], and RIAs[344,360-363] have been compared with other methods with varying results[364], but they are generally impractical and difficult to use for routine testing. Although RIAs are more practical and sensitive[344,346,361], they are no longer usable because of the need for radioisotopes.

Nt: Nt measure the antibodies against virus glycoproteins, and can therefore highlight the ability to neutralise the infectiousness of the virus[342,343,365-375]. A preparation of free virus from cells is incubated with dilutions of the examined serum in order allow a virus/antibody interaction. Inoculation of the mixture in a cell indicator (MRC-5) allows the cytotoxic effect to develop (in the absence of neutralising antibodies) or not (in their presence). Sensitivity has been improved by adding guinea pig complement (C-enhanced neutralisation test) and/or anti-immunoglobulins (Ig-enhanced neutralisation test), although some prozone effect has been observed[366,369,372,376]. A titre of 1:2-1:16 (conventional test) or 1:4 (enhanced test) is considered protective against varicella, but not against re-infection, which leads to a rise in antibody titre in the absence of clinical symptoms[343,365,376]. Nt (primarily the C-enhanced tests) have been found to be as sensitive as FAMA in some studies, but they cannot be automated and, as they are laborious and take a long time, they are difficult to use in routine practice and are therefore only used in reference centres[348, 366,367,376,377].

LA: LA is simple, cheap and rapid[377-380]. The sensitivity of some commercial tests is comparable with that of ELISAs in subjects with natural infection, but they may give false positive reports and may not be sufficiently sensitive in vaccinated subjects[5]. Furthermore, they cannot be automated easily.

IFA: Indirect immunofluorescence antibody tests allow the detection of IgG or IgM antibodies which binds to a spot of virus infected cells on a slide by a fluorescent-labled secondary antibody and can be detected using a fluorescence microscope[348,381-383]. They are sensitive and rapid tests, but manual and difficult to automate, subjectively read, and unsuitable for large numbers[348,384].

FAMA: FAMA is considered the gold standard[347, 376,379,385-388]. It is highly sensitive because the preservation of the structure of the surface glycoproteins on infected cells allows neutralising antibodies to be detected[389]. It has been used to assess protection against varicella as a value of $\geqslant$ 4 correlates with protection[215,347,376,390-392]. Its limitations are that it is semi-quantitative, cannot be automated, and requires specialised personnel and specific equipment; reading is subjective and subject to inter-laboratory variability[30]. It is generally only used in specialised centres[54].

TRFIA: TRFIA is a quantitative test that has been well standardised using an international calibrator and allows the results to be expressed mIU/mL[30,253,380]. Some Authors have indicated a cut-off value 150 mIU/mL as the threshold of protection (positive > 150 mIU/mL, doubtful 100-150 mIU/mL and negative < 100 mIU/mL)[380], and others have reported that a cut-off value of 130 mIU/mL is capable of discriminating infection-naive subjective (those that have never come into contact with the virus) from those who have previously had the infection among vaccinated subjects[393]. It is more sensitive and specific than many commercial ELISAs but requires special equipment and is only used in a few specialised centres[54,380,394].

IB: Some studies have used IB, particularly Western blotting, which has been used to study difference in the presence and intensity of the bands in patients with varicella or herpes zoster, but its usefulness in discriminating primary infection from an anamnestic response is a matter of controversy[75,82,362,395].

ELISAs and EIAs: ELISAs or EIAs, which use antigens of the complete virus, are widely used because of their simplicity and the possibility of automation[328,364,396-401]. However there is considerable variation in the sensitivity of the different tests[380,394]. They are generally sufficiently sensitive in subjects with a history of natural infection, but not sufficiently sensitive to detect seroconversion after vaccination as the antibody titres induced by vaccination are a logarithm lower than in the case of natural infection[5,30,54,380,393,397]. In vaccinated subjects, the tests are less sensitive than FAMA as studies have found that 58%-88% of the subjects who were negative or borderline at ELISA were positive to FAMA, which uses surface antigens[91,96,402,403].

GpELISA: The gpELISAs are ELISAs that use the external glycoproteins (typically gE, gB, gH) as antigens of the solid phase[219,339,371,404-412]. They are sensitive enough to detect low antibody levels after vaccination, and have been used to evaluate the level of protection[407]: In one study, 95% of the vaccinated subjects had a gpELISA value of $\geqslant$ 5 U/ mL six weeks after immunisation, whereas those with values of < 5 were at three times greater risk of developing BV[413]. However, these tests were not easy to find[30].

Quantitative CLIAs: The need for more sensitive and

standardised tests has led to the production of CLIAs against international standards. The proposed cut-off values are 150 mIU/mL[414] or 100 mIU/mL (negative < 50 mIU/mL; doubtful 50-100 mIU/mL; positive > 100 mIU/mL)[327,403]. Their ability to give a quantitative result makes it easier to distinguish protected and unprotected subjects: For example, when they were used before VZIG administration to test women exposed to VZV during pregnancy, it was found that the women with CLIA (or TRFIA) values of < 100 mIU/mL were more likely to develop varicella than those with values of > 100 mIU/mL[253]. A value of 100 mIU/mL may therefore differentiate women susceptible to infection from those protected against exposure[253]. However, some of the international guidelines, while stressing the importance of this value, point out that this cut-off value may vary depending on vaccinations, ethnicity or age[54].

Microarrays: Finally, there are also some serological microarray tests for the simultaneous screening of antibodies against VZV and viruses such as herpes simplex virus (HSV-1 and HSV-2), cytomegalovirus, mumps, rubella or measles[415-419].

Diagnosing varicella in pregnant women

Varicella can still occur during pregnancy because the woman may not realise she has been exposed or may have consulted a doctor too late, or because the administration of VZIG does not provide 100% protection[159].

Classic varicella is usually diagnosed clinically, but a laboratory diagnosis may be crucial in doubtful cases such as BV, in immunocompromised women, or varicella in women who have received VZIG, or when it is important to make a differential diagnosis with other exanthematic diseases (especially HSV or enterovirus), arthropod bites or stings, allergic reactions (Stevens-Johnson syndrome), pityriasis lichenoides et varioliformis acuta, and guttate psoriasis[5,30,87].

Technological advances over the years have led to the development of increasing sensitive and specific tests for the diagnosis of varicella.

Tzanck smear tests: Cytology (the Tzanck test) was initially important as it can detect the cytopathic effect of herpesvirus infection morphologically[420-426]. Cells taken by scraping the base of the vesicles or pustules of skin lesions during the rash are placed on slides and, after Giemsa-Wright, hematoxylin-eosin or Papanicolaou staining, are examined by means of light microscopy for the cytopathic alterations typical of herpesvirus (multinucleated giant cells, syncytia and ballooning cell degeneration). Although this test is easy to perform, rapid and cheap, its sensitivity is limited (only 40%-50% in comparison with cell cultures)[422,427]. It is also influenced by the stage of the lesion as it is more sensitive to material taken from fresh vesicles rather than from pustules or scabs[421,428] and, above all, cannot distinguish the lesions caused by HSV and those caused by VZV[429].

Electron microscopy: Electron microscopy has been used, but it is laborious and does not distinguish HSV and VZV[332,424,430,431]. It is more specific when using antibodies conjugated with colloidal gold, although there may still be cross-reactivity with other alphaherpesviruses[430,432]. It is therefore impractical for routine screening.

Virus isolation: Virus isolation in tissue cultures was long considered the gold standard, and was used to evaluate the sensitivity and specificity of other tests[423,425,432-435]. It uses permissive cell lines in which material is deposited from skin or mucocutaneous lesions, or other biological fluids. The various cell lines include human diploid lung fibroblasts (MRC-5, WI-38), human lung carcinoma cells (A549) and primary rhesus monkey kidney cells, which have different yields in terms of viral replication[434,436,437]. However, the method suffers from the need to particular sampling techniques, and special sample transport and storage conditions as the material must be obtained from the base of fresh vesicles during the first 3-4 d, and immediately transported to the laboratory because the virus is labile[429]. In general, viral culture sensitivity is good if specific, fluorescein - conjugated monoclonal antibodies are added, but is still less than that of the latest molecular biology tests[423,434,438,439]. Viral cultures are also laborious, require trained personnel and specially equipped laboratories, and the results are subject to subjective interpretation. They also take a very long time[434]: Tube viral cultures (the standard culture) require seven days to two weeks, but this can be shortened 16-18 times by using shell vial cultures as a centrifuge facilitates virus adherence to the monolayer on round cover-slips, although there are different opinions concerning the sensitivity[348,440]. Viral isolation can be confirmed using immunofluorescence and anti-VZV monoclonal antibodies[348]. Viral cultures may still be useful in determining the antiviral activity of anti-VZV drugs[441,442].

Direct fluorescent antibody assay: The direct fluorescent antibody (DFA) assay uses specific fluorescein-conjugated, polyclonal or monoclonal VZV antibodies to detect VZV antigens on slides with cells scraped from identified skin lesions[235,423,425,433,434,438,443-447], and there is also an immunoperoxidase version[348]. The monoclonal antibodies of choice are those against cell membrane-associated viral antigens[446]. The assay is highly specific and more sensitive than Tzanck smears or viral cultures[423,434,448], and as specific as but less sensitive (73.6%-86%) than molecular biology tests[348,428], although it can be used if molecular biology tests are not available[5]. It is also rapid (about two hours), but it needs special equipment that mean it can only be used in limited areas[348,349], and requires material collected from the skin lesions, which have to be swabbed in order to avoid any bleeding (any antibodies present in the blood can stop the reaction and lead to false negative results)[30].

Molecular biology tests: Molecular biology tests based on in vitro nucleic acid amplification (PCR) are now considered the new platinum tests[20,30,429,449,450]. Various types of PCR are used to diagnose varicella and herpes zoster[13,421,422,450-456], including nested PCR, which is particularly sensitive, but susceptible to contamination leading to false positive results[348]. However, the latest real-time PCR tests are not only rapid, easy to perform, and as sensitive as nested PCR, but have also reduced the risk of contamination[348]. Furthermore, they can be automated tests and used on a wide variety of materials. They are more sensitive than viral cultures, DFA and Tzanck smears particularly when primers for genes 28 and 29 are used[30,428,429,440,449,450,457]. Molecular biology tests are also useful in the case of varicella appearing 7-42 d after vaccination, in the case of herpes zoster appearing 42 d after vaccination and, in the case of the suspected transmission of the vaccine virus, can distinguish virus vaccine, wild-type virus and potential recombinants of vaccine and wild-type viruses[30,451,452,454,455,458-463], although some tests have proved to be less appropriate over time for these purposes[30].

There are also some multiplex assays that can differentiate HSV-1, HSV-2 and VZV in cutaneous and mucocutaneous samples, making them very useful in the case of skin lesions of unclear etiology or immunosuppressed patients[429,464,465]. Multiplex tests are rapid, need only a small volume of sample, and can simultaneously detect different viral agents at the same time in a single, closed-tube reaction[466-468]. They are also robust enough to avoid the need for an extraction step, thus reducing the time of execution at the expense of only small decrease in sensitivity[468-470].

Microarray and electrospray ionisation mass spectrometry techniques have also been developed for the detection of amplification products[471,472].

The materials that can be used include skin swabs, cerebrospinal fluid (CSF), broncho-alveolar lavage (BAL) fluid, nasopharyngeal secretions, urine, saliva, blood, intraocular fluid, amniotic fluid, follicular fluid, corneal tissue and other body fluids. BAL is important[159] as pneumonia is found in 5%-20% of pregnant women with varicella[54,121,158,163], although it can also be caused by bacterial superinfection. Saliva can be useful for diagnosing neurological diseases without rash[473], and CSF for diagnosing encephalitis[429]. The materials of choice in the case of varicella are the vesicles and scabs[23,449,450,474-476] and so, once the lesions have resolved, the probability of finding viral DNA by means of PCR is virtually zero[30]. Leung *et al*[474] (simultaneously considered the use of skin lesions (vesicles, macular and/or papular lesions, and scabs), buccal and throat swabs, oral fluid, urine and blood in patients at the time of the beginning of the rash and two weeks later, and found that all of the material taken from skin lesions at the time of the (and not just vesicles and scabs) are suitable for search purposes, even the macules and papules that have always been regarded critically[30,408], This is important because some atypical symptoms occur only with macules/papules, as in the case of BV[222,477]. Sensitivity therefore does not vary depending on the type of lesion and, during the rash, any skin lesion may be suitable. Of the other tested materials, only the oral samples were sufficiently sensitive to be used at the beginning of symptoms.

Serology: Serology has been used to diagnose varicella, but it has many limitations because it can be negative in immunosuppressed subjects, falsely positive in transfused subjects, or cross-reactive with HSV[364,478-480]. IgM and IgA antibodies have been used as indicators of recent or current infection, but they may also be present during re-infections and reactivations[30,64,153,410]. In general, neither direct or capture IgM tests are as sensitive as molecular biology tests[5,30,410,443,446], and they may also be non-specific in the presence of high IgG titres[5,30,348]. It is probable that the time of sampling may be important because Leung *et al*[474] found that only 25% of their PCR-positive patients with varicella showed IgM in samples taken 0-3 d after the onset of the rash, whereas other authors found that the percentage rose to 48% after four days[85] or 77% after 1-7 d[410]. Samples may therefore be IgM negative if they are taken too soon.

IgG positivity in the absence of IgM usually indicates past infection, and a search has limited usefulness in the acute phase of the disease. However, it may be of help when assessing seroconversion or a 4-fold increase in titre between acute and convalescent serum samples taken 7-10 d apart, although the need for two samples postpones the diagnosis[74,408,410]. Furthermore, people with a history of varicella or vaccination may have higher levels of basic IgG, and a 4-fold increase may therefore not be noticeable in the case of re-infection or BV[30], especially in the elderly[30,474], and IgG may sometimes no longer be present after two weeks of rash, thus lengthening seroconversion times[481]. It has also been found that differences in titres during the acute phase may be found in only 33% of PCR-positive cases[474]. However, a search for IgG in CSF may be useful to evaluate intrathecal synthesis in cases of VZV-induced encephalitis[482,483].

IgG avidity: The determination of IgG avidity may be useful, and is usually done by separating low and high antibody avidity using denaturing agents in an EIA, IFA or CLIA test[58]. Avidity is generally expressed as a percentage of antibody titre by comparing the results with and without the denaturing agent[484-486], which can be helpful in differentiating primary infection (low avidity) and past infection, reactivations or re-infections (high avidity), and then discriminating varicella and herpes zoster[287,393,454,484,487].

It has also been used to differentiate patients with past infection and naïve patients after vaccination[393], although a number of points need to be borne in mind. IgG maturation times are approximately 40-80 d depending on the test used[393,484,486,487], and this needs to be taken into account. Antibodies against some

nuclear proteins (p32 and p36) mature differently from those against surface glycoproteins (they are more likely to have low avidity)[484], and establishing a cut-off value can sometimes be arbitrary[30]. The results are different in immunocompromised and immunocompetent subjects[488,489], and age may also be a factor[490,491]: Low avidity may be found during re-infections in the elderly and in some cases of recurrent infections in children[485,492]. Other things to consider are the time since vaccination (first or second dose), and the time since exposure or the onset of rash: Individual situations (low responders to vaccination can maintain lower antibody titres and low avidity over time)[393]; and the type of infection (*e.g.*, it is not useful in cases of BV because it is likely that vaccinated subjects already have high avidity in response to the vaccination itself)[30].

Prenatal infection and the diagnosis of CVS

CVS is diagnosed using ultrasonography, computed axial tomography (CAT) or magnetic resonance imaging (MRI) and a search for VZV DNA in amniotic fluid[164], placental villi[348], and/or fetal blood[164,493,494].

Ultrasonography is particularly useful for detecting fetal malformations (limb deformity, microcephaly, hydrocephalus, polydramnios, soft tissue calcification, and intra-uterine growth restriction)[90,180,495,496], and is recommended after 16-22 wk of gestation or five weeks after infection[16,187,493,497]. It is not sensitive enough to detect congenital defects before the fourth week[16,493,497]. The limitation of ultrasonography is that it is not very much sensitive or specific[169], and so cannot detect all abnormalities[498]; however, its predictive value is better if there is a diagnosis of fetal infection with positive VZV DNA[499].

Fetal MRI and cranial CAT may sometimes be useful for further investigating the morphological abnormalities detected by ultrasonography[180,181,497].

VZV DNA can be sought in amniotic fluid, which is considered the material of choice, but this should not be done less than a month after maternal infection in order to avoid false negative results[53,164,187]. VZV DNA can persist for weeks in the peripheral blood of infected pregnant mothers and, as a false positive result in amniotic fluid due to maternal contamination has been reported, it has been suggested that aminiocentesis should performed after maternal viremia has become negative[498]. The main limitation of searching for VZV DNA in amniotic fluid is that the presence of viremia does not automatically mean the presence of fetal damage[164,500]. Only a small percentage of VZV DNA-positive fetuses present CVS at birth[164], and so amniocentesis has a good negative predictive value but poor positive predictive value[16].

Given the limitations of ultrasonography and a search for VZV DNA in amniotic fluid, Enders *et al*[90] studied the risk of CVS by combining both methods during pregnancy (Table 3). In literature, their use over time was evaluated separating, which can be approached in two ways[169]. It may be better to perform an amniocentesis first (but in any case not until the mother's skin lesions have disappeared) because, if it is negative, the mother can be reassured she is carrying healthy fetus in 90% of cases, although there is still the small risk of miscarriage associated with amniocentesis[16,501]. If the amniocentesis is positive, ultrasonography can be used for confirmation, although it is possible that a mother knowing the amniocentesis findings would prefer to undergo an immediate abortion[169]. The alternative is to use amniocentesis to confirm ultrasonographic findings of anomalies, although it must be remembered that ultrasonography is not very sensitive or specific, and so it does not detect all malformations[169,498]. Some authors recommend following-up mothers who have contracted varicella during pregnancy by means of ultrasonography, and then searching for viral DNA in the case of malformations[19,159], insisting on always searching for VZV DNA because other micro-organisms such as Coxsackie B and HSV can cause congenital lesions similar to those of CVS[502-504]. There is a report of a case of fetal malformations due to HSV2 and not VZV in a mother who contracted varicella during pregnancy[502], and conditions such as microphthalmia dermal aplasia scleroderma (MIDAS) or microphthalmia with linear skin defects (MLS) may also lead to malformations, with maternal varicella being just a coincidence[505,506].

There are few and unconvincing data concerning chorionic villi as the PCR-detected presence of viral DNA is not necessarily associated with an infected fetus, but may due to false positivity caused by maternal contamination or a placental infection not transmitted to the fetus[169,506,507].

In relation to other tests used in the past, viral cultures in amniotic fluid and a search for IgM in fetal blood are less sensitive[164,500]. The detection of IgM (which was used before the advent of PCR)[508,509] was positive in only 25% of the cases in a post-natal study[145]. Furthermore, it can only be detected in fetal blood after 24 wk of gestation and so, if the infection occurs earlier, the fetus may not show an immune response[164,348]. Finally, sampling is more invasive and less safe than amniocentesis.

Diagnosis in newborns

In most cases, a baby born after maternal infection is healthy and there are no long-term consequences in terms of intellectual performance and neurodevelopment[152,169]. Previous infection may possibly be demonstrated by the presence of IgM at birth, but as the search is positive in only 25% of cases, it more likely to be negative[53,145,169]. As the IgG antibodies passively passed from mother to child have a limited half-life, their detection more than seven months after birth may be the only indication of intrauterine infection[131,192]. However, it is important to monitor the child in order to identify the occurrence of herpes zoster in the first 1-2 years of life[510].

The morbidity neonatal varicella is generally low in the children of immune mothers because of the presence of maternal antibodies[193] but in their absence, the children

Table 3 Prenatal congenital varicella syndrome diagnosis combining ultrasoonography and a search for varicella-zoster virus DNA in amniotic fluid[90]

Weeks of pregnancy	VZV DNA in amniocentesis	Ultrasound	Risk of CVS
Initial			
17-21	Positive	Normal	Uncertain
Follow-up			
23-24	Positive	Normal	Unlikely
	Positive	Abnormal	High
15-22/> 23	Negative	Normal	Low

VZV: Varicella-zoster virus; CVS: Congenital varicella syndrome.

are at risk of contracting primary infection during the first months of life from their mothers or other people[16]. Premature infants born after 28 wk of gestation are at risk in the first six weeks of life because the reduced gestational period means that they do not have maternal antibodies[5,88], and a diagnosis of varicella in the newborn should therefore be related to maternal varicella in the last month of pregnancy. Neonatal varicella is more severe if varicella appears in the mother between seven days before and seven days after delivery, especially between five days before and two days after delivery when the neonatal mortality rate can be as high as 30%[153,169,196]. A diagnosis of neonatal varicella is typically clinical but the contribution of a microbiology laboratory may be important using molecular biological tests (PCR) on vesicles or other biological liquids such as CSF in cases of encephalitis[429]. Also it is crucial in the differential diagnoses with similar clinical manifestations, such as those caused by HSV or enterovirus, syphilis or incontinentia pigmenti[87,147,165,511].

In the absence of a prenatal diagnosis (*e.g.*, in the case of sub-clinical maternal infection), and an infant born with typical malformations of CVS the relationship between these malformations and maternal infection should be confirmed[283,512]. A search for VZV DNA using molecular biology techniques on neonatal tissues (*e.g.*, skin lesions, CSF) can provide evidence of intrauterine infection[182,494,512]. Viral cultures are not recommended because they are insensitive[26,147,159,165,169], as is the presence of IgM in blood (only 25% positive)[145,147]. Molecular biology tests are also indicated in the case of rare or uncharacteristic malformations, or when the relationship between maternal infection and congenital malformations is doubtful[513]. Consideration should be given to differential diagnoses of congenital varicella with rubella, cytomegalovirus, HSV, Coxsackie virus, *Toxoplasma gondii*, and MIDAS or MLS[165,502-504,514].

CONCLUSION

Although varicella during pregnancy is fortunately infrequent and CVS is even rarer, every available means should be used to prevent and diagnose them. Microbiology laboratories can be crucial in both situations because the development of increasingly sensitive and specific tests for the detection of antibodies makes it possible to evaluate a mother's immune status more precisely. Quantitative ELISAs and CLIAs can help to determine whether the detected antibody level is protective or not on the basis of proposed cut-off values because, although further studies are needed to assess whether these can be extended universally to all pregnant women regardless of age, geographical origin or race, they are certainly valuable in case assessment. However, it is important to stress the need for a widespread information campaign to ensure that pregnant women are aware of the risks of exposure, and promptly consult a doctor quickly because, for example, specific immunoglobulins need to be administered to susceptible women as soon as possible after exposure.

The tests for the diagnosis of varicella have also become increasingly sensitive and specific. The introduction of molecular biology tests has opened up new scenerios in all fields of microbiological diagnostics, and the availability of simple and rapid multiplex tests capable of simultaneously detecting multiple microorganisms simultaneously can allow a rapid diagnosis when a clinical manifestation may be due to different viruses, as in the case of the skin lesions caused by HSV and VZV.

Finally, close collaboration between molecular biology investigators (VZV DNA) and specialists in imaging diagnostics (ultrasonography) is important in the follow-up of pregnant woman with varicella because this makes it possible to make a prenatal diagnosis of CVS.

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