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Varicella Zoster Virus (Chickenpox) Infection in Pregnancy

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Abstract

Congenital varicella syndrome, maternal varicella zoster virus pneumonia and neonatal varicella infection are associated with serious fetomaternal morbidity and not infrequently with mortality. Vaccination against Varicella zoster virus can prevent the disease and outbreak control limits the exposure of pregnant women to the infectious agent. Maternal varicella zoster immune globulin (VZIG) administration before rash development, with or without antiviral medications can modify progression of the disease.

Keywords

Varicella; Zoster; Virus; Chickenpox; Infection; Pregnancy

INTRODUCTION

Varicella Zoster virus (VZV) is a highly contagious infectious agent and chickenpox is a common childhood illness. Accordingly, contact between a pregnant woman and a contagious individual is not uncommon. In temperate climates, 90% of women of child bearing age will be immune to the disease but this is not the case among migrant women from tropical climates. While the complications of chickenpox are rare, the potential for significant fetomaternal morbidity and even mortality cannot be ignored. This being the case, obstetricians should be aware of the potential for serious adverse sequelae, the steps needed to implement a program for management of exposure incidents, and the proper use of vaccination prophylaxis and intervention with Varicella Zoster Immune Globulin (VZIG) and/or antiviral therapy.

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EPIDEMIOLOGY

The incidence of chickenpox varies between temperate and tropical climates. In temperate climates, the disease occurs most commonly in late winter and early spring. Prior to the introduction of childhood vaccination, by the age of 15, 90% of individuals in temperate climates would have had a primary infection,^{1,2} and hence seropositive compared to only 25–80% tropical countries.^{3,4} The incidence of chickenpox is not precisely known since it is not a reportable disease. Best estimates suggest an incidence of 2–3/1000 in the UK⁵ and between 1.6 and 4.6/1000 in the USA among 15–44 year old individuals during the 1990s.⁶ In both of these countries, the incidence appears to be increasing^{7–9} which may be due to increasing immigration^{8,10} of susceptible individuals. If this is the case, the rate is expected to decrease due to uptake of vaccination programmes.¹¹

PATHOPHYSIOLOGY

VZV is a DNA virus of the herpes family and is highly contagious. The human is the only source and the virus enters the host through the conjunctivae and mucus membranes of the nasopharynx.¹² At the end of the second viremic phase, non-specific prodromal symptoms such as headache, fever and malaise occur. This is followed by pruritis and a maculopapular rash which becomes vesicular before crusting occurs usually about five days later. The sufferer is contagious from two days prior to the development of rash until crusting of the vesicles occurs. Primary infection generally provides lifelong immunity but symptomatic re-infections have been reported and 13.3% of individuals with varicella reported a previous episode of chickenpox^{13,14} and subclinical re-infections have been detected serologically.¹⁵ The reason for re-infection may be due to failure to develop, maintain or reactivate immune memory cells at the time of infection or due to a high inoculum from close contacts which overwhelm the immune system.¹⁶

Chickenpox in pregnancy

First trimester spontaneous abortion is not associated with chickenpox.^{17–20} Before 24 weeks gestation, vertical transmission to the fetus has been detected clinically/serologically and by PCR in approximately 24% and 8% of cases of virologically confirmed maternal chickenpox respectively. Intrauterine growth restriction (IUGR) occurs in approximately 23% of cases²¹ and low birth weight is virtually universal.²² In a case-controlled study, non-exposed controls had a spontaneous preterm birth rate of 5.6% compared with 14.3% for cases of chickenpox in pregnancy ($P=0.05$).¹⁸ The highest rate of mortality and morbidity associated with chickenpox in pregnancy occurs in the presence of Congenital Varicella Syndrome (CVS), Maternal Varicella Pneumonia, and Neonatal Varicella.

CONGENITAL VARICELLA SYNDROME

The CVS was first described in 1947 from which time to the present, at least 130 cases have been reported in the literature,²⁰ most of which have been reported in the last 15 years. CVS is associated with a mortality rate of 30% in the first few months of life and a 15% risk of developing HZ between the 2nd and 41st month of life. However, in spite of a poor initial prognosis, a good long-term outcome for the survivors can occur.²³

Incidence of CVS According to Gestational Age of Acquiring Chickenpox

Primary VZV infection in the first two trimesters of pregnancy results in intrauterine infection in up to 25% of cases,²⁰ and congenital anomalies described in the CVS can be expected in approximately 12% of infected fetuses.²⁴ Maternal chickenpox in the first 20 weeks of pregnancy was associated with an incidence of CVS of 0.91% (13 cases of CVS in 1423 live births).²⁵ While cohort studies and case reports, have recorded CVS following

maternal chickenpox between 20 and 28 weeks gestation, no cases of CVS have been reported following maternal chickenpox after 28 weeks gestation.²⁵ It has been calculated that the annual number of cases of CVS in the USA, UK, Germany and Canada would be forty-one, seven, seven and four respectively.⁶

Clinical features of Congenital Varicella Infection

The clinical features of CVS are multi-system but some tissues and organs are selectively damaged.²² Skin lesions occur in approximately 70% of cases and limb hypoplasia in 46–72%.^{6,21} Neurological abnormalities such as microcephaly, cortical atrophy, hydrocephaly and mental retardation occur in 48–62% of cases. Eye disorders such as microphthalmia, chorioretinitis, and cataracts occur in 44–52% of cases.^{26–28} Muscle hypoplasia, developmental delay and abnormalities of the gastrointestinal and genitourinary tracts and the cardiovascular system occur in 7–24% of cases.^{6,13,18} Survivors may have long term learning difficulties and developmental problems yet case controlled studies do not suggest long term neurodevelopmental disorders in asymptomatic children.²⁹

Mechanism of CVS

The mechanism of CVS is thought to be due to the reactivation of the VZV in utero³⁰ akin to the mechanism of HZ development rather than being due to the primary infection. The short period of latency between primary infection and reactivation may be due to immature fetal cell-mediated immunity.³¹ The evidence for reactivation stems from the dermatomal pattern of skin lesions, similar to HZ,²² the segmental maldevelopment of the musculoskeletal system and the segmental dysfunction of the somatic and autonomic nervous systems.³⁰

Diagnosis of CVS

The diagnosis of CVS can be confirmed by a record of maternal chickenpox in pregnancy together with congenital skin lesions in a dermatomal distribution with or without the presence of neurological signs, eye defects, limb deformities and neonatal seizures.³² Retrospective evidence of maternal VZV IgG seroconversion during pregnancy is also helpful. Proof of intrauterine infections irrespective of whether or not CVS develops can be deduced from detection of VZV DNA in the fetus or neonate, the presence of specific IgM in fetal or cord blood, the persistence of specific IgG beyond seven months of age, and the development of HZ during infancy.^{30,33} Nearly 20% of infants with intrauterine acquisition of VZV infection develop neonatal or infantile HZ which is usually uncomplicated.²¹ While fetal serological detection of specific IgM is useful in confirming evidence of intrauterine infection, in general, serology has a low sensitivity and is therefore unreliable and not recommended for the diagnosis of CVS caused by maternal chickenpox.³⁴ Similarly, viral isolation is often unsuccessful and VZV DNA detection by PCR is much more reliable for demonstrating fetal infection.³⁵ Since VZV and Herpes Simplex Virus (HSV) share common surface antigens, there is serological cross-reactivity¹³ albeit that no cross-protection has been demonstrated. Accordingly any rise in heterologous antibody titres may be due to cross-reactivity, but may also signify simultaneous infection. Coxsackie B and HSV-2 can cause similar congenital lesions,^{36–38} and one case has been reported in which there was cutaneous scarring and limb hypoplasia, but serology and PCR revealed HSV-2 infection rather than VZV.³⁶ Cases which present with rare abnormalities and subclinical maternal infection may need confirmation with molecular virological methods to establish a causal relationship between maternal infection and congenital abnormalities.³⁹

Prenatal Diagnosis of CVS

PCR of AF for VZV DNA is now the method of choice for determining whether or not the fetus has been infected. Prenatal diagnosis relies on the identification of a combination of signs on a detailed ultrasound examination, such as limb deformities, microcephaly, hydrocephaly, polyhydramnios, soft tissue calcification and IUGR.^{6;40–42} Since the clinical features are due to reactivation of the VZV, time will be needed for this damage to manifest itself. Accordingly, no less than five weeks from the time of maternal rash should be permitted before the first detailed scan is performed, since scans at four weeks have resulted in missed diagnoses.⁴³

Can Maternal HZ cause CVS?

Since VZV remains latent in the sensory root ganglia, and the enervation for the uterus arises from T10 to L4, theoretically, intrauterine shedding of virus from HZ is a possibility. However, in 301 cases of HZ in first and second trimesters, no cases of CVS were reported,^{6;15;18;34;44} although there has been one case report of a child born with typical findings of CVS from a mother who had disseminated HZ at 12 weeks gestation.³⁰ There have been no reports of clinical or serological evidence of VZV in infants whose mothers developed perinatal HZ⁴⁵ and so varicella zoster immunoglobulin (VZIG) is not indicated.

Maternal Varicella Pneumonia

The average incidence of chickenpox in pregnancy has been calculated to be 0.7–3/1,000 pregnancies.^{46;47} Maternal pneumonia complicates about 10–20% of cases of chickenpox in pregnancy resulting in a higher mortality/morbidity than in non-pregnant adults.^{48–50} Pregnant women with VZV pneumonia should be hospitalized for monitoring and to initiate antiviral therapy because up to 40% of women may need mechanical ventilation.⁵¹ Mortality in severe cases (those who require mechanical ventilation) in the pre-antiviral era was 20–45%.^{52–54} and is currently estimated to be 3–14%.^{54–57} Between 1985 and 2002, in the confidential enquiries into maternal deaths in the UK, there were nine indirect and one late maternal death associated with maternal VZV pneumonia.⁵⁸

The risk for pneumonia also increases with increasing gestational age. While this has been associated with relative maternal immunosuppression,⁵⁷ it still remains unproven and may be purely mechanical with increasing splinting of the diaphragm as the gravid uterus occupies more space.⁵⁹

Neonatal Varicella

In the era before neonatal intensive care, VZIG and antivirals, the mortality rate for neonatal chickenpox was 31%^{51;54;60–62} and is still 7% in the modern era.⁴⁵ Maternal chickenpox in late pregnancy may result in neonatal chickenpox before passive immunity from mother to baby can be conferred⁵⁴ and the cell-mediated immune response of the neonate is unlikely to be sufficient to prevent hematogenous spread of VZV.⁶³ Neonatal chickenpox may occur by transplacental transmission, ascending infection or via the neonatal respiratory tract. The incubation period of intrauterine transmitted VZV from the beginning of maternal rash to the outset of neonatal rash varies. Accordingly, neonatal chickenpox in the first 10–12 days of life is caused by intrauterine transmission, whereas after this time it is by post-natal infection. When maternal chickenpox occurs 1–4 weeks before delivery, up to 50% of neonates will be infected⁴⁵ and 23% of these will develop clinical chickenpox despite high titres of passively acquired antibodies. The mortality of neonatal chickenpox is low.⁶⁴ The exception is babies born <28 weeks gestation or <1000g who are at increased risk of severe chickenpox,⁶⁵ because they have less protection from maternally transmitted antibodies.^{66;67}

Passively acquired antibodies can be detected in all babies whose mothers developed the VZV rash more than seven days before delivery.

PREVENTION OF CHICKENPOX IN PREGNANCY

Vaccination

In women who reach childbearing age without natural immunity or vaccination as part of a childhood immunization programme, chickenpox in pregnancy can be avoided by vaccination. Although two vaccines are licensed for use in the UK,⁵⁸ they are not included in the standard childhood immunization programmes nor routinely recommended for non-immune adult women apart from health care workers. VZV vaccine has been shown to be effective in preventing infection following exposure and is most effective when given within three days of exposure.^{68;69} The Varivax vaccine is a live attenuated vaccine therefore some advise avoidance of pregnancy for one month,⁷⁰⁻⁷² or three months⁵⁸ post-vaccination though no birth defects related to inadvertent vaccine exposure have been reported.^{49;73} There is one case report of a VZV susceptible pregnant woman, who following vaccination of her one year old child, developed chickenpox. Transmission was confirmed using PCR. A therapeutic termination of pregnancy was performed but no virus was isolated from fetal tissue.⁷⁴ Vaccinees who develop chickenpox <42 days after vaccination are likely to represent wild virus infection⁷⁵ but the disease is mild, infectivity is low, and there is little or no risk of complications.⁷⁶ Breast feeding is safe following postnatal vaccination and post VZV vaccination breast milk samples have failed to detect any VZV DNA.^{77;78}

Management of Exposure Incidents

An essential part of the prevention strategy to avoid or reduce the incidence of chickenpox in pregnancy and the cost of managing an outbreak requires an organized approach to management of exposure incidents. Screening should be carried out pre-pregnancy if there is an opportunity to do so (eg family planning/infertility clinics).³⁰ Screening should also be carried out in early pregnancy so that those who are uncertain⁷⁹ can be tested, and those who are susceptible can be counseled about the risks, instructed on procedure should contact occur, and co-opted into a protocol for management of exposure incidents. All healthcare workers who deal with pregnant women should be screened and vaccinated or identified as susceptible, to permit redeployment to non-patient areas.⁸⁰ An evaluation of the economic and clinical outcomes of a programme of routine antenatal screening and post-partum vaccination of seronegative women found that a selective serotesting strategy prevented nearly half of the VZV cases in their cohort. This will be particularly true in those areas with high immigrant populations from tropical climates where immunity is much less likely and immune status is much less likely to be known.¹⁰ However, this evaluation was based upon an analytical cost-effectiveness model following a hypothetical cohort of over 4 million women over a 20 year period.

MANAGEMENT OF CHICKENPOX IN PREGNANCY

Antivirals for use in VZV infections

Acyclovir is a synthetic nucleoside analogue of guanine which is highly specific for cells infected by VZV or HSV. When phosphorylated by viral thymidine kinase in the cells infected with VZV, there is inhibition of viral DNA polymerase which stops replication of human herpes viruses. Oral acyclovir has low bioavailability and must be given in frequent doses to achieve therapeutic levels.⁴⁹ Further bioavailability data suggests that the physiological changes of pregnancy do not alter maternal pharmacokinetics from non-pregnant women.^{81;82} Valacyclovir and famciclovir are pro-drugs of acyclovir and penciclovir respectively. As pro-drugs they have a longer half-life and better oral absorption

and bioavailability, so due to less frequency of administration are a better choice of oral therapy with improved compliance.^{82;83}

Antiviral therapy either alone or in combination with VZIG has been recommended in the management of chickenpox in pregnancy.^{84;85} Antiviral prophylaxis is best given on the 7th day post exposure.⁸⁶ All pregnant women with established chickenpox should receive oral acyclovir 800mg five times daily for seven days or valacyclovir 1g three times daily.⁴⁹ Compared with placebo, this reduces the duration of fever and symptoms of chickenpox in immunocompetent adults if commenced within 24 hours of rash development.⁸⁷ If given within 24 hours and up to 72 hours of the development of rash, acyclovir is effective in reducing the fetomaternal mortality and morbidity associated with VZV infection,⁷⁰ particularly if used IV.^{59;88;89} Intravenous acyclovir in severe pregnancy complications such as pneumonia is preferred to oral treatment because of bioavailability, especially in the second half of pregnancy. The dose is usually 10–15mg/kg of body weight IV every 8-hours for 5–10 days for VZV pneumonia and should be started within 24–72 hours of rash. There is no evidence of fetal benefits with respect to CVS or chickenpox but acyclovir crosses the placenta and can be found in AF, umbilical cord blood and other fetal tissues,²² though it does not appear to accumulate in the fetus.⁸¹ Acyclovir may inhibit viral replication during maternal viremia which may inhibit transplacental transmission of VZV.^{90;91}

Neonates showing signs of chickenpox or those with chickenpox showing evidence of neurological or ophthalmic complications have been reported to benefit from the use of acyclovir intravenously.^{92–94}

Registries of neonates exposed to acyclovir *in utero* have found no significant risk of teratogenesis from the use of acyclovir in pregnancy but theoretical risks exist with use in the first trimester.^{58;95;96} Though there is a potential for complications of *in utero* exposure,⁹⁷ small studies of valacyclovir use in late pregnancy have found no clinical or laboratory evidence of toxicity in infants followed up to one month⁹⁸ or six months of age.⁹⁹

Varicella Zoster Immune Globulin

Susceptible pregnant women with significant VZV exposure should be offered VZIG, to prevent or attenuate maternal disease.^{100;101} Significant VZV exposure is defined differently in different guidelines but reflects the proximity and duration of contact and the potential for droplet and vesicular fluid contact with the conjunctivae and nasopharyngeal mucous membranes.^{49;58} A history of chickenpox negates the need for serological testing. With no history of chickenpox, serology should be checked if time permits, otherwise VZIG should be given.⁵⁸ The main indication for VZIG is to modify disease and prevent maternal morbidity.^{91;102}

VZIG should be given to susceptible women within 72 hours but can be given up to 96 hours after exposure to the virus.^{58;91} Beyond 96 hours VZIG has not been evaluated,⁷⁰ but some recommend VZIG for up to 10 days after exposure.^{58;103;104} This may be because a more concentrated immunoglobulin formation is available in some countries.¹⁰⁵ VZIG is ineffective and should not be given once clinical illness has developed.^{59;106}

It is not known whether VZIG prevents viremia or CVS but this is unlikely to be tested bearing in mind the numbers required to test the hypothesis and the ethics of randomization of care. The Royal College of Obstetricians and Gynecologists' guidelines⁵⁸ point out that VZIG is derived from non-UK donors with high VZV antibody titers but that no cases of blood borne infections have been reported. Since VZIG is in scarce supply and is expensive, treatment should be optimized rather than liberal, and availability should be checked before a patient is offered the choice.

The optimal dose of VZIG is unclear and calculation of unit dosage differs internationally, but in the USA, VZIG is recommended in a dose of 125 U/10kg to a maximum of 625U⁷⁰ (equivalent to a 50kg woman receiving 125U/10kg). Alternatively, 1mg/kg body weight can be administered intravenously (IV).¹⁰⁷ Whether 625U is sufficient for women weighing >50kg is not clear.¹⁰³ VZIG may also prolong incubation and this should be considered when arranging surveillance, monitoring, isolation and follow up, where many suggest adding a week to standard operating procedure compared to those who do not receive VZIG. Intravenous administration appears to demonstrate benefit over IM administration with more rapid achievement of optimal serum levels.¹⁰⁸ The duration of action of VZIG is unknown but is likely to be at least one half-life of the IgG (three weeks). Accordingly, subsequent exposure within three weeks after a dose of VZIG may require additional doses.⁷⁰

MANAGEMENT OF PERINATAL INFECTIONS

Primary maternal infection with VZV around the time of delivery poses important problems.¹⁰⁹ Following maternal chickenpox around term, elective delivery may be delayed by 5–7 days to facilitate passive immunity of the neonate but experience with this practice is limited.^{110;111} Theoretically, epidural rather than spinal anaesthesia may be safer because the dura mater is not penetrated and a site which is free of cutaneous lesions should be chosen for needle placement.¹¹² A neonatal ophthalmic examination should be performed together with serological testing of the neonate for IgM at birth and IgG at seven months of age.

VZIG is recommended for neonates whose mothers develop VZV rash from five days before delivery up to two days after delivery.⁹² Neonates born before or after this time probably do not need passive immunization because they are not at risk of severe neonatal chickenpox.^{24;113} While VZIG may not prevent infection, it may reduce the severity of neonatal infection,⁴⁵ but is of no benefit once signs of chickenpox become evident.^{114;115} Monitoring of the neonate should be prolonged to 28 days because VZIG may prolong the incubation period. VZIG is also recommended for the non-immune neonate who is exposed to VZV or HZ from an index subject other than the mother in the first seven days of life.

If signs of neonatal infection develop despite VZIG, the neonate should be treated with acyclovir, and there are anecdotal reports of benefit of a combination of VZIG and acyclovir in maternal VZV exposure near term or in exposed neonates to prevent neonatal varicella.^{84;85} Maternal HZ peripartum does not require any action because the neonate will have passive immunity. This does not apply to babies born before 28 weeks or those less than 1000g birth weight because they may not have developed passive immunity.¹¹⁶

CONCLUSIONS

Chickenpox is a common childhood illness but if this develops in pregnancy it is associated with serious adverse sequelae such as congenital varicella syndrome, maternal VZV pneumonia and neonatal varicella infection which may lead to foeto-maternal morbidity and mortality. Vaccination against VZV is available but is not currently included in the standard childhood immunization programmes nor routinely recommended for non-immune adult women in the UK. Prevention strategies should also include plans for the management of exposure incidents. When chickenpox occurs in pregnancy, antiviral therapy either alone or in combination with VZIG has been recommended for management. The use of antivirals decreases the risk of mortality and morbidity from chickenpox but this will still occur. VZIG reduces the incidence and severity of chickenpox but does not eliminate them completely, and is of no benefit once signs of chickenpox become evident. The scenario of a pregnant woman with a history of contact with an index subject with chickenpox, either arriving at a hospital public area, or telephoning for advice, merits each obstetric unit having a written

protocol to reduce unnecessary costs, at the same time offering the best available protection for those most susceptible to adverse sequelae.

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