Chickenpox in Pregnancy

Prof. Terence T LAO  
MD, FRCOG  
Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong, Prince of Wales Hospital

Dr. Tak Yeung LEUNG  
MD, FRCOG  
Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong, Prince of Wales Hospital

Background

Chickenpox is due to infection with the varicella zoster virus (VZV), a human alphaherpesvirus found worldwide. It causes varicella (chickenpox) as the primary infection. Afterwards, it establishes latency in the cells of the sensory nerve ganglia and manifests as varicella zoster when it is reactivated. Classically, the clinical disease is a febrile illness with a pruritic vesicular rash. Although many adults are immune, there may be susceptible individuals in the childbearing age. The virus is highly contagious and enters the host through the conjunctivae and mucous membranes of the nasopharynx. Maternal manifestations occur in the second viraemic phase with headache, fever, malaise, followed by pruritus and a maculopapular rash, which turns to vesicular before crusting about 5 days later. The disease is contagious from 2 days before the rash until crusting, and subclinical infections occur. Infection in pregnancy may be associated with significant foetal, perinatal, and maternal morbidity and mortality\(^1^,\(^3^,\(^5^,\(^14^)\).

In Hong Kong, chickenpox is a reportable disease. In 2009 and 2010 there were 6777 and 11617 cases respectively notified, with the median age of infection being 6 years and 81% being children aged below 13, with the majority of cases being in the form of institutional outbreaks\(^2\). Thus chickenpox is still a highly prevalent disease with an increased incidence observed in the past year with most of the infections occurring in children and adolescents, and susceptible women with exposure to children and adolescents are prone to become infected.

In this review, the foetal and neonatal effects, maternal effects, management in pregnancy, and prevention will be discussed.

A. Foetal and Neonatal Effects of Intrauterine Varicella Infection

In most cases of primary VZV in pregnancy, the timing of intrauterine infection is the major determinant of foetal outcome. In the majority of cases, the foetus is either not infected, or that the foetal infection is controlled without consequences, so that the newborn infant is normal. Even where foetal infection has occurred, the commonest feature is the persistence of IgG at one to two years of age. For most parents and clinicians, the greatest concern is congenital varicella syndrome (CVS) which was first described in 1947, but there are only about 130 cases of CVS reported since\(^1^,\(^3^,\(^5^,\(^14^)\). The relationship between gestation at maternal infection and foetal/neonatal outcome is summarised in Table 1.

### Table 1. Gestation at maternal infection and risk on the fetus / infant

<table>
<thead>
<tr>
<th>Gestation / trimester</th>
<th>Outcome</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st – 2nd trimester</td>
<td>Intrauterine infection and Congenital varicella syndrome</td>
<td>25% of primary infection</td>
</tr>
<tr>
<td>2nd trimester to peripartum period</td>
<td>Vertical transmission</td>
<td>8% by PCR</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Intrauterine growth restriction</td>
<td>23%</td>
</tr>
<tr>
<td>Neonatal chickenpox</td>
<td>Up to 23% of infected neonates</td>
<td></td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>Up to 7%, higher in preterm (&lt;28 weeks) or &lt;1000g neonates</td>
<td></td>
</tr>
</tbody>
</table>

1. Congenital Varicella Syndrome (CVS)

This arises from infection in the first and second trimesters (up to 28 weeks), but no cases were reported from infection after 28 weeks. However, most of the cases were due to infection before 20 weeks, which could also result in spontaneous abortion, and the overall risk of infection was only 0.91%\(^1\). In a prospective cohort study, out of 252 women with maternal infection before 20 weeks of pregnancy and completed follow-up, only 2 (0.8%) had confirmed foetal infection, while 1 (0.39%) had confirmed CVS\(^14\). Of the two foetuses with confirmed intrauterine infection, one was totally asymptomatic and normal up to the age of five years, while the other with CVS had lower limb deformities.

The mortality for affected infants in the first few months of life was 30% and there is a 15% risk of herpes zoster (HZ) between the second and 41st month of life. The mechanism of CVS is thought to be reactivation of VZV in-utero, similar to that of HZ, and the short latency between primary infection and reactivation is thought to be related to the immature foetal cell-mediated immunity. Involvement of CVS is multisystem but there tend to be selective damage on the central nervous system, the eye, the skin, and musculoskeletal systems, which follow the dermatome pattern with segmental involvement of the musculoskeletal and neurological systems, and intrauterine growth restriction (IUGR) is common (Table 2). While the survivors may have long term learning disabilities and developmental problems, neurological development in the asymptomatic children is unaffected.

2. Neonatal Varicella Syndrome

This results from peripartum infection, and may lead to
significant morbidity. The mortality rate could be as high as 31% before the era of VZIG and antiviral treatment, while it could still be as high as 7% now. Neonatal chickenpox in the first 10-12 days of life is caused by intrauterine infection. If maternal infection occurs 1-4 weeks before delivery, up to 50% of the infants will be infected, and 23% of these infants will develop clinical chickenpox and manifest with only skin lesions despite maternal transfer of antibodies.

2. Herpes Zoster (HZ)

As the enervation of the uterus is from T10 to L4, there is a theoretical risk of intrauterine infection, but no cases of CVS have occurred in women with HZ in the first and second trimesters, or in the perinatal period, probably because the neonates have passive immunity. This however does not apply to neonates born before 28 weeks or less than 1000g.

C. Management in Pregnancy

Diagnosis by the various available tests like foetal serum tests (IgM, virology culture, haematological and biochemical tests), ultrasound findings, and amniotic fluid VZV particles by PCR technique have been evaluated and is shown in Table 3.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>False positive rate</th>
<th>Positive predictive value</th>
</tr>
</thead>
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<tr>
<td>Fetal serum biochemistry</td>
<td>50.0</td>
<td>25.1</td>
<td>14.3</td>
</tr>
<tr>
<td>Ultrasound findings</td>
<td>66.6</td>
<td>16.1</td>
<td>40.1</td>
</tr>
<tr>
<td>Fetal serum IgM</td>
<td>95.5</td>
<td>0.95</td>
<td>75.5</td>
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<tr>
<td>AF viral particles by PCR</td>
<td>99.5</td>
<td>0.03</td>
<td>95.5</td>
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After Sanchez et al. Results in %

1. Diagnosis of CVS

(a) After birth, the diagnosis can be made clinically from the combination of maternal history / serology together with the characteristic pattern of lesions in the offspring, while the proof of foetal infection is obtained from the detection of VZV DNA by PCR in the foetus or neonate, specific IgM in cord blood, the persistence of IgG beyond 7 months of life, and the development of HZ during infancy.

(b) Before birth, the condition may be suspected from detailed ultrasound examination with the finding of features including limb deformities, microcephaly, hydrocephaly, polyhydramnios, soft tissue calcification, and IUGR.

2. Treatment

(a) Acyclovir, a synthetic nucleoside analogue of guanine, stops replication of human herpes viruses, and is the standard antiviral treatment in this situation. In severe maternal complications and the second half of pregnancy, treatment should be given intravenously at the dose of 10-15 mg/kg body weight every 8 hours for 5-10 days and started within 24-72 hours of rash development. As it crosses the placenta, there is the benefit of inhibiting transplacental transmission. Oral acyclovir has low bioavailability so that it has to be given as 800mg five times daily for 7 days to achieve therapeutic levels, which reduces the duration of symptoms if commenced within 24 hours of rash development. Given within 24-72 hours, it can reduce the

### Table 3. Diagnostic tests for foetal varicella zoster virus infection

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foetal toxicity or teratogenic effect has been reported with these medications.

(b) Varicella-zoster immunoglobulin (VZIG) can be given after significant exposure to prevent or attenuate the maternal disease, and can be given in combination with acyclovir. It should be given within 72 hours of exposure, the intravenous route being preferable as optimal serum level is achieved more rapidly, but its effectiveness of treatment commencing beyond 96 hours has not been evaluated, and it should be given for up to 10 days. It is ineffective and should not be given once clinical illness has developed. The optimal dose is unclear, but the usual recommendation is 125 units / 10kg up to a maximum of 625 units, or 1 mg/kg body weight. The duration of VZIG is unknown, but should be at least equal to one half-life of IgG which is 3 weeks, so that subsequent exposure within 3 weeks of a dose may call for additional doses. As it can prolong the incubation period, one more week should be added to the period of surveillance, monitoring and isolation relative to those who have not received VZIG.

(c) Timing of delivery is dependent on the timing of exposure / manifestation of maternal illness and foetal involvement. Around term, delivery should best be carried out 5-7 days after maternal chickenpox to enable passive transfer of immunity to the foetus. Analgesia for labour or anaesthesia for caesarean delivery is preferably provided by epidural anaesthesia, using a site free of cutaneous lesions for needle insertion, as the dura mater is not penetrated.

D. Prevention of Chickenpox in Women of Reproductive Age

To prevent chickenpox infection, a live attenuated varicella vaccine is available, which has been shown to be safe and effective in preventing chickenpox in adults. As a live attenuated vaccine, pregnancy should be avoided for 3 months after vaccination. Where possible, screening should be performed before pregnancy and susceptible individuals should be vaccinated. However, in Hong Kong, there is neither a policy of routine vaccination of all children or susceptible women in the reproductive age, nor routine antenatal screening. Therefore when pregnant women with suspected chickenpox contact are encountered, all would have to be checked for immunity, monitored for clinical manifestation, and urgent treatment may have to be given until maternal immune status is ascertained. In the UK, the current policy is to check immune status post-VZV exposure with VZIG administration where necessary, and which was estimated to be similar in cost to antenatal screening and postpartum vaccination of non-immune mothers, and it was suggested that varicella immunity testing should be included in the antenatal routine screening, either as part of the

universal vaccination programme or solely as an antenatal programme. In some countries, such as the USA, universal varicella vaccination for children was implemented since 1995. According to the Varicella Active Surveillance Project from the Centers for Disease Control and Prevention (CDC), there has been a decline in the number of cases, deaths and hospitalisations after introduction of the vaccination over the years, which reflected the benefits of herd immunity with decreasing number of cases of varicella infection in all age groups and decreased social costs. Therefore, this is evidence in support of the merits of universal vaccination. As well, epidemiology may change with time, and population shift and increasing immigration could lead to an age-shift in varicella outbreaks in the future.

In Hong Kong, a study conducted in 2010 on 500 women studied in the first trimester, 56.0%, 14.8% and 29.2% respectively reported a positive history, a negative history, and were uncertain, of previous chickenpox, yet immunity was found in 95.4% overall, which was among the highest figures reported in the literature, with 96.4%, 90.5% and 95.9% respectively of these three groups being tested to be seropositive. Among the 280 women with a history of infection, 91.4% recalled the infection occurring before 13 years of age, with 38.1% before 6 years of age. Of note, while 79.8% were aware of the vaccine, 69.2% of them thought that the vaccine was provided by the government. While 64.2% of the entire cohort understood that the live-attenuated vaccine should not be given during pregnancy, 31.4% were unsure of vaccine safety in pregnancy, and 4.4% thought that the vaccine is safe during pregnancy, and the suboptimal knowledge on the vaccine was probably related to the fact that it is not included in the universal vaccination programme. Therefore clinicians should recommend vaccination in individuals found to be non-immune to varicella.

Conclusion

While the incidence of CVS is low and seroprevalence among the obstetric population appears high in Hong Kong, the problem should not be taken lightly in view of the recent trend of increasing prevalence. Further work should be conducted to evaluate the need for routine vaccination and antenatal screening of women of different age groups and residency status in the obstetric population in order to prevent avoidable cases of CVS and maternal and perinatal mortality that would be encountered in due course, given the unpredictable and uncontrollable flux of pregnant women into Hong Kong for their deliveries.

References

4. Centre of Health protection, Department of Health, Hong Kong SAR. www.chp.gov.hk/


