

Review

Varicella and the pregnant woman: Prevention and management

Andrew J. DALEY,^{1,2,3} Susan THORPE¹ and Suzanne M. GARLAND^{2,4}

¹Infection Control Department and ²Department of Microbiology and Infectious Diseases, The Royal Women's Hospital and The Royal Children's Hospital, Melbourne, ³Departments of Pathology and ⁴Obstetrics and Gynaecology, University of Melbourne, Melbourne, Victoria, Australia

Infection with varicella zoster virus (VZV) is often considered a childhood 'right of passage'; however, primary infection occurring in women of child-bearing age can have significant adverse consequences both for the mother and for her fetus. During the first trimester, primary VZV infection may result in stillbirth or a baby born with the stigmata of the congenital varicella syndrome, while infection in the peripartum period can result in neonatal varicella, which carries a significant mortality rate despite appropriate antiviral therapy. Varicella in pregnant women can progress to pneumonitis and other severe sequelae that may also compromise the viability of the fetus. Exposure to VZV most commonly occurs in the community or from children in the household, but occasionally, exposure may occur in the hospital environment. Determining a woman's serostatus prior to pregnancy is advised, as effective vaccines are now available and should be administered to non-pregnant seronegative women of child-bearing age. Clinical practice guidelines for management of a pregnant woman exposed to VZV are presented.

Key words: congenital varicella syndrome, neonatal infection, pregnancy, varicella.

Introduction

Varicella is one of several infections that has significant consequences for the pregnant woman and her developing fetus. Varicella zoster virus (VZV) is a highly infectious agent spread by respiratory droplets as well as direct contact with fluid in vesicles, which are the hallmark of infection. Exposure of non-immune individuals to VZV in neonatal and maternity settings can cause serious illness in these relatively compromised high-risk patients. Other non-immune subjects, including health-care workers (HCW), may become a source of infection for others. Despite the recent introduction of varicella vaccine and the recommendation that non-immune HCW be vaccinated, particularly those having contact with children and pregnant women,

reducing the risk of exposure to VZV in the maternity setting remains a challenge.

The disease and transmission

VZV is a herpes virus that causes the primary infection varicella (chickenpox) and the secondary or clinical manifestation of latent infection, varicella zoster (shingles). While generally mild and of short duration in healthy children, varicella can be associated with significant morbidity and mortality in pregnant women, neonates and those with underlying conditions that may compromise their immune function.

VZV is transmitted primarily from person-to-person by airborne respiratory secretions and by direct inoculation onto mucous membranes or the conjunctiva. The incubation period is classically 14 days (range ten to 21 days) with the initial presentation being fever with mild respiratory symptoms, followed within one to two days by a pruritic vesicular rash that exists in different stages of development and, in uncomplicated cases, lasts for five to seven days. Varicella occurs most commonly in late winter and spring.

Correspondence: Dr Andrew Daley, Department of Microbiology, The Royal Children's Hospital, Flemington Road, Parkville, Vic. 3052, Australia.
Email: andrew.daley@rch.org.au

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Patients are contagious for a variable period ranging up to 72 h before the onset of rash. For practical purposes, particularly for exposure management, the pre-rash infectious period is taken as a maximum of 48 h. This period of infectivity is challenging because a large number of individuals, including patients, staff and visitors in a health-care setting, may be exposed before diagnosis occurs, thus perpetuating the outbreak. Moreover, patients remain contagious until the vesicles have crusted over, usually taking a further five days after rash onset. The incubation period may be prolonged to 28 days if varicella zoster immunoglobulin (ZIG) has been administered. This poses important strategic problems in relation to patient placement in wards, as well as staff deployment issues.

Transplacental transmission from mother to fetus occurs during maternal viraemia and the incubation period for neonatal infection is 11 days (range 9–15 days) from the onset of maternal disease. Attack rates among susceptible contacts range from 60 to 90%; therefore efficient outbreak or exposure management is required, particularly in the hospital setting.

Incidence

In Australia, there are 124 000 cases, 1500 hospitalisations and seven deaths each year from varicella; the overall case fatality rate being in the order of three per 100 000 cases.^{1,2} In adults, including pregnant women, clinical illness can be more severe, complications more frequent and case-fatality rates 20-fold greater than in childhood infection.³

Varicella in pregnancy

Varicella during pregnancy can lead to maternal infection, intrauterine infection (which can result in fetal loss or an infant born with a constellation of physical abnormalities known as the 'congenital varicella syndrome' (CVS)⁴) or perinatal infection when primary disease occurs in the mother around the time of delivery.⁵

In North America, an estimated 0.5% of varicella cases occur during childbearing age⁶ and in the UK this rate is 0.3%;⁷ no such data are available from Australia. Some evidence suggests that pregnant women are at greater risk of developing severe complications, such as pneumonitis, from varicella as compared to their non-pregnant counterparts.^{8,9} Many of the reports are anecdotal, however, and it is difficult to determine the actual morbidity and mortality associated with varicella in pregnancy.⁹ The

morbidity is highest if infection occurs in the third trimester. Several risk factors for pneumonitis have been postulated including the presence of pharyngeal lesions and the number of skin lesions. In a multicentre case-control study, 100 or more papulovesicular lesions at the peak of the rash were significantly associated with VZV pneumonitis (odds ratio (OR) 15.9; 95% confidence interval (CI) 1.9–130.2). Smoking was also an independent variable associated with a poor outcome for VZV pneumonitis in this study (OR 5.1; 95% CI 1.6–16.7).¹⁰

Respiratory symptoms develop when skin lesions have been present for two to five days. The first sign may be a non-productive cough, but clinicians should beware that this can rapidly progress to respiratory failure over 36–48 h, with an increasing productive cough (which may be blood stained or progress to frank haemoptysis), tachypnoea, dyspnoea, cyanosis and chest pain. Chest X-ray may demonstrate a widespread interstitial and nodular infiltrate and early in the course of the illness the X-ray findings may be more severe than the clinical appearance. Multiorgan involvement including hepatitis, myocarditis and pericarditis, encephalitis and pancreatitis is associated with a high mortality. Fetal loss may result from maternal sepsis, fever and hypoxia.

Infection early in the gestation, as the fetal organs are developing, can cause more severe damage or stillbirth. The incidence of CVS has been previously reported to be as high as 2% when maternal infection occurs between 13 and 20 weeks gestation.^{11,12} A more recent pooled estimate from cohort studies suggests a rate of 1.4% in the second trimester (12–28 weeks) and 0.55% in the first trimester (two to 12 weeks). Virtually all cases occur in the first 20 weeks of gestation, with the overall rate in this period being 0.91%. The latest gestation associated with CVS has been reported as 28 weeks.¹³ This syndrome is manifest by dermatomal scarring (70%), limb hypoplasia (68%), ocular abnormalities (cataracts, chorioretinitis, microphthalmos, Horner syndrome, nystagmus; 66%), low birthweight (50%), cortical atrophy and mental retardation (46%) and early death (28%).¹⁴ Survivors may have long-term learning defects and other developmental problems, although case-control studies do not suggest significant long-term neurodevelopmental disorders in asymptomatic children.¹⁵ Maternal infection following the critical first trimester of organogenesis may be associated with reactivation zoster *in utero*, with a characteristic pattern of cicatricial skin scarring associated with the distribution of dermatomes.¹⁶ Asymptomatic infants

born to women who are infected with VZV between 25 and 36 weeks gestation, also have an increased incidence (0.8–1.7%) of zoster in the first years of life; indeed this may be the only evidence of exposure.⁴ Subclinical maternal infection has occasionally been reported as causing seizures and abnormalities in muscular tone during the neonatal period.¹⁷ Herpes zoster in an otherwise healthy pregnancy is not associated with intrauterine infection, even when the dermatomes innervating the uterus (T10-L1) are involved.¹¹

Maternal varicella in late pregnancy may result in neonatal infection.¹⁸ The severity in the neonate depends to some extent on the timing of the maternal illness. When maternal clinical infection occurs less than five days prior to delivery to two to five days postdelivery, severe neonatal disease is common. If maternal rash develops outside of these times then the clinical illness is less severe, probably due to the transplacental passage of protective antibody and the lower viral load to which the baby is exposed.⁸ Neonatal varicella occurs in 17–30% of newborn infants exposed to VZV in the peripartum period. Prior to the availability of ZIG, the case fatality rate was 30%.¹³

Management

Maternal varicella can result in fetal, neonatal and maternal morbidity and susceptible pregnant women with a significant exposure (see definition in algorithm 2, ‘*significant exposure’) should be offered passive immunoglobulin (ZIG) to prevent or attenuate maternal disease.¹⁹ Ideally, varicella IgG levels should be determined prior to administering ZIG as 70–80% of adults who do not recall having varicella are actually immune. The administration of ZIG should not, however, be delayed by this testing. ZIG will reduce the incidence of symptomatic disease in the pregnant women, but does not clearly influence the risk of CVS occurring. Although controlled clinical trials examining the efficacy of ZIG in neonates, infants and healthy adults have not been performed, studies in immunocompromised patients demonstrate that clinical disease and complications are reduced by 75%²⁰ and the benefits of ZIG in these groups is likely to be great.²¹ The timing of ZIG is controversial. Optimum protection is obtained when the dose is administered within 96 h of exposure, although some guidelines suggest that ZIG may be administered with benefit up to 10 days after exposure.²² This may be important in seronegative contacts who have risk factors for more

severe disease, such as smoking, underlying pulmonary disease or immunosuppression.

If ZIG is not administered at the optimum time after exposure, oral acyclovir may be considered as postexposure prophylaxis. Although this approach has not been evaluated in a controlled fashion in pregnant women, it may provide some additional protection, particularly in women with additional risk factors. Although acyclovir is not licensed for use in pregnancy, data from the pregnancy registry suggest that it is safe.²³ If varicella subsequently develops, the woman should be immediately evaluated clinically and treated appropriately with acyclovir. Oral acyclovir is not available under the Australian Pharmaceutical Benefits Scheme (PBS) for this indication.

Valaciclovir and famciclovir are prodrugs of acyclovir and penciclovir, respectively, with higher oral bioavailability than the parent drugs. There are little data on their use in treating primary varicella infection, but they are likely to be effective. Animal studies and limited human data suggest that valaciclovir is safe in pregnancy. Very little data are available for famciclovir. Given that more safety data and experience are available with acyclovir, this is currently the drug of choice for prophylaxis and treatment of varicella during pregnancy. Postnatal varicella exposure of a neonate in the first month of life (or up to 44 weeks gestational age in a premature infant) whose mother is seronegative for VZV can also result in significant disease and ZIG is usually recommended in this setting. Postexposure prophylaxis with varicella vaccine should not be used in non-immune pregnant women, as it is a live attenuated vaccine.

Costs of outbreak management

Varicella and varicella exposure increase the cost of hospital care because of prolonged length of stay, increased laboratory testing, use of ZIG, varicella vaccines and antiviral agents. Infection can also cause anxiety for the pregnant or postnatal woman and her family. Exposure of non-immune HCW also necessitates staff redeployment to non-patient areas. Smith *et al.*²⁴ evaluated the economic and clinical outcomes of a program of routine antenatal varicella screening and post-partum vaccination of sero-negative women. They found that a selective serotesting strategy could prevent nearly half of the varicella cases in their cohort. Faoagali and Darcy estimated a cost of \$A18 000 for monitoring and control of an outbreak, which occurred in a large urban adult hospital in Brisbane.²⁵

Varicella screening

Ideally, varicella screening should be performed with preconception counselling and include discussion of the risks of varicella infection, especially for those working in high-risk areas such as day care and primary teaching as well as those in institutional settings.⁴ Another important group that should be protected are those undergoing expensive and invasive assisted fertility procedures such as *in vitro* fertilisation.

We recommend that all pregnant women presenting to antenatal booking clinics have their varicella status documented. The position statement on antenatal screening from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommends that varicella serology be considered when there is no history or uncertain history of varicella.²⁶ This is an ideal opportunity to screen those women who may rarely have contact with the health-care system. It is simple and quick to ask a woman if she has a past history of chickenpox. If the answer is yes, no further follow up is required, but clear documentation in the patient history is essential. If she is unsure, serological testing should be undertaken with varicella immunisation being offered postnatally for the non-immune patient, as for rubella.

The need to screen pregnant women who have been previously vaccinated is less clear. Vaccine-induced immunity does not appear to be as durable as that induced by natural infection. Routinely available enzyme immunoassays for the detection of varicella IgG are not sensitive enough to reliably detect vaccine-induced antibody levels, so screening will not be useful. The majority of women of child-bearing age will be protected from severe disease following routine vaccination and screening is not required.

In a seroprevalence survey of antenatal patients in a large Melbourne obstetric population for the period 1998–1999, 94% were positive for VZV antibodies. Of the 66% who reported a past history of chickenpox, 95% had serological evidence of past infection; 86% of those with no history and 96% of those who were unsure of their varicella history were also seropositive.²⁷ The 5% of women who gave a history of varicella but lacked detectable antibodies may have waning antibody levels due to natural fluctuation over time.²⁸ In the event of a significant exposure they may have an anamnestic response and still be protected from significant clinical disease. The pragmatic approach, however, is still to screen only those with no history or uncertain history of prior infection. The community needs to be aware of the

consequences of this preventable disease and the importance of immunisation, not only for babies and children, but also for non-immune adults particularly in child-bearing years.

Vaccine

A varicella vaccine based on a live attenuated Oka strain has been available in Australia since 2000. The National Health and Medical Research Council recommend that non-immune parents of young children be immunised against varicella, although the live attenuated vaccine is contraindicated in pregnancy. Adults require two 0.5-mL doses administered at least one to two months apart and pregnancy should be avoided for one month postimmunisation.²⁹ A cohort of women inadvertently vaccinated during pregnancy have been actively followed and there have been no cases of CVS or increase in other abnormalities detected.³⁰ The vaccine should not be administered for at least three months to those who have received intramuscular immunoglobulin or for nine months to those who have received intravenous immunoglobulin. Immunoglobulin should not be given for at least three weeks after vaccination.²⁹ Seroconversion occurs in 90–100% of those vaccinated and 99% of adults will have humoral and cell-mediated immunity after two doses. Approximately 70% of the recently vaccinated are protected following a household exposure. During outbreaks, the VZV vaccine is protective for varicella in 85–90% of exposed children, and 100% effective for prevention of moderate or severe disease.

The duration of immunity is unknown, but is likely to be long lived. As wild-type VZV reduces, natural boosting from exposure may become less and booster doses may be required. Vaccine-associated virus transmission has been rarely documented, and only when a rash develops on the vaccinee. This should not, however, deter the vaccination of young children in a family where contact with a pregnant woman may occur. In fact, vaccination of household contacts of immunosuppressed persons is strongly recommended.²⁹ Vaccine virus does not appear to be excreted in breast milk, and post-partum vaccination should not be delayed in the seronegative nursing mother.³¹

Postexposure prophylaxis and outbreak control

Strategies for the management of patients with or who are exposed to varicella in the hospital setting to minimise risk to patients, visitors and staff are

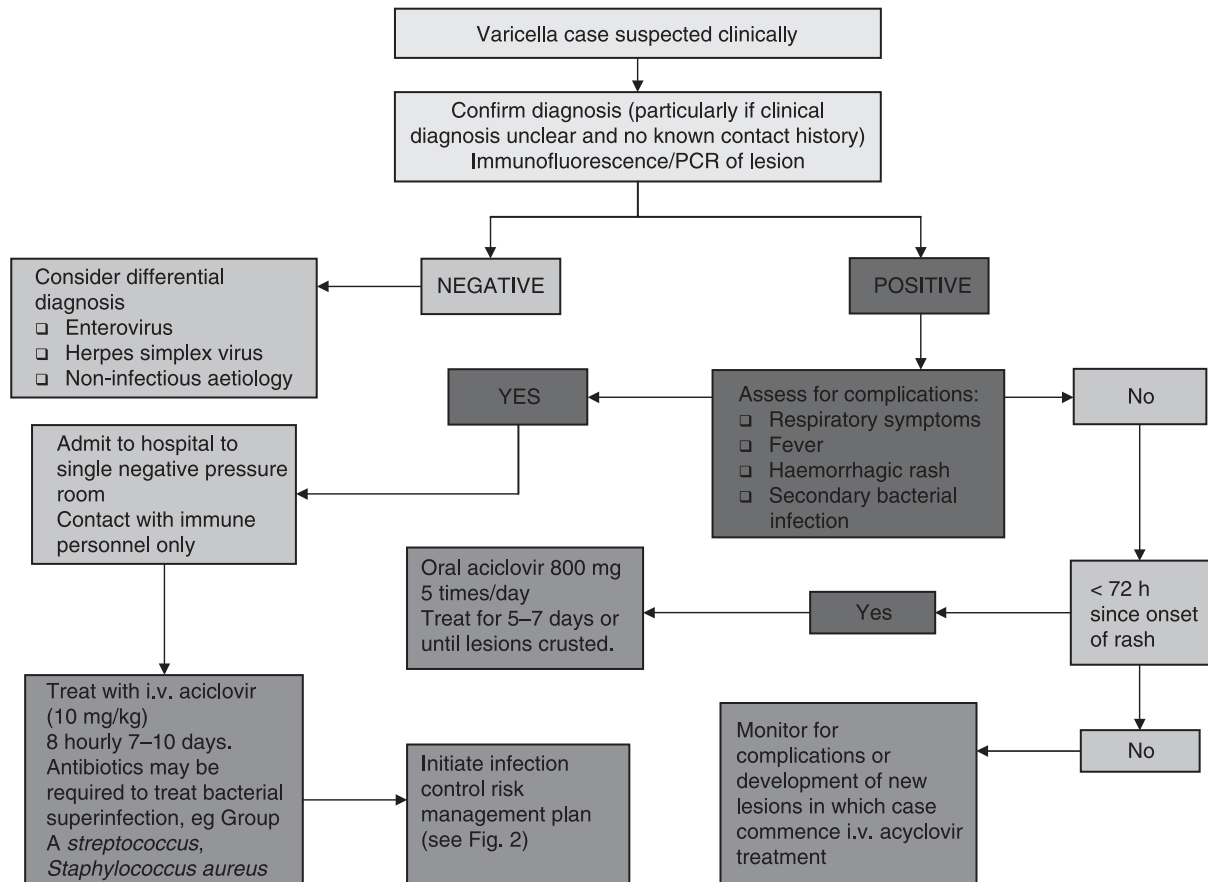


Figure 1 Management of suspected varicella.

summarised in Figures 1 and 2, respectively. These algorithms are based on the principles of effective risk management.

VZV vaccine has been shown to be effective in preventing infection following exposure and is most successful when given within three days of exposure (although it may have some benefit when given up to seven days after the exposure).^{32,33} Postexposure prophylaxis also effectively protects against moderate to severe disease; however, some breakthrough mild disease may occur.

Non-immune HCW should be vaccinated. The need for vaccination should preferably be determined in a pre-employment environment. Because a small number of HCW will be seronegative despite giving a history varicella, the most rigorous approach is to serologically confirm immunity in all HCW.⁸ This may be particularly important for HCW who have contact with high-risk patients such as pregnant women and neonates. At the very least, HCW with negative or uncertain history should be sero-tested.

A mild rash may occur in < 5% of vaccinated adults in the six weeks following vaccination. Staff with a generalised rash should be excluded from care of high-risk patients for the duration of the rash. More commonly, a localised minor rash should pose little risk of transmission, particularly if it can be covered. Discussion with an infectious diseases physician or infection control department, with consideration of the type of patient contact the HCW would have will help guide the decision to redeploy. The vaccine strain is not transmitted via the respiratory route.

Conclusions

Varicella is a common viral illness in the community, with a significant impact on non-immune pregnant women and their babies. Nosocomial transmission is a potentially controllable occurrence and staff should be aware of their immune status. Women of child-bearing age should also be aware of their serostatus and be offered the varicella vaccine when appropriate.

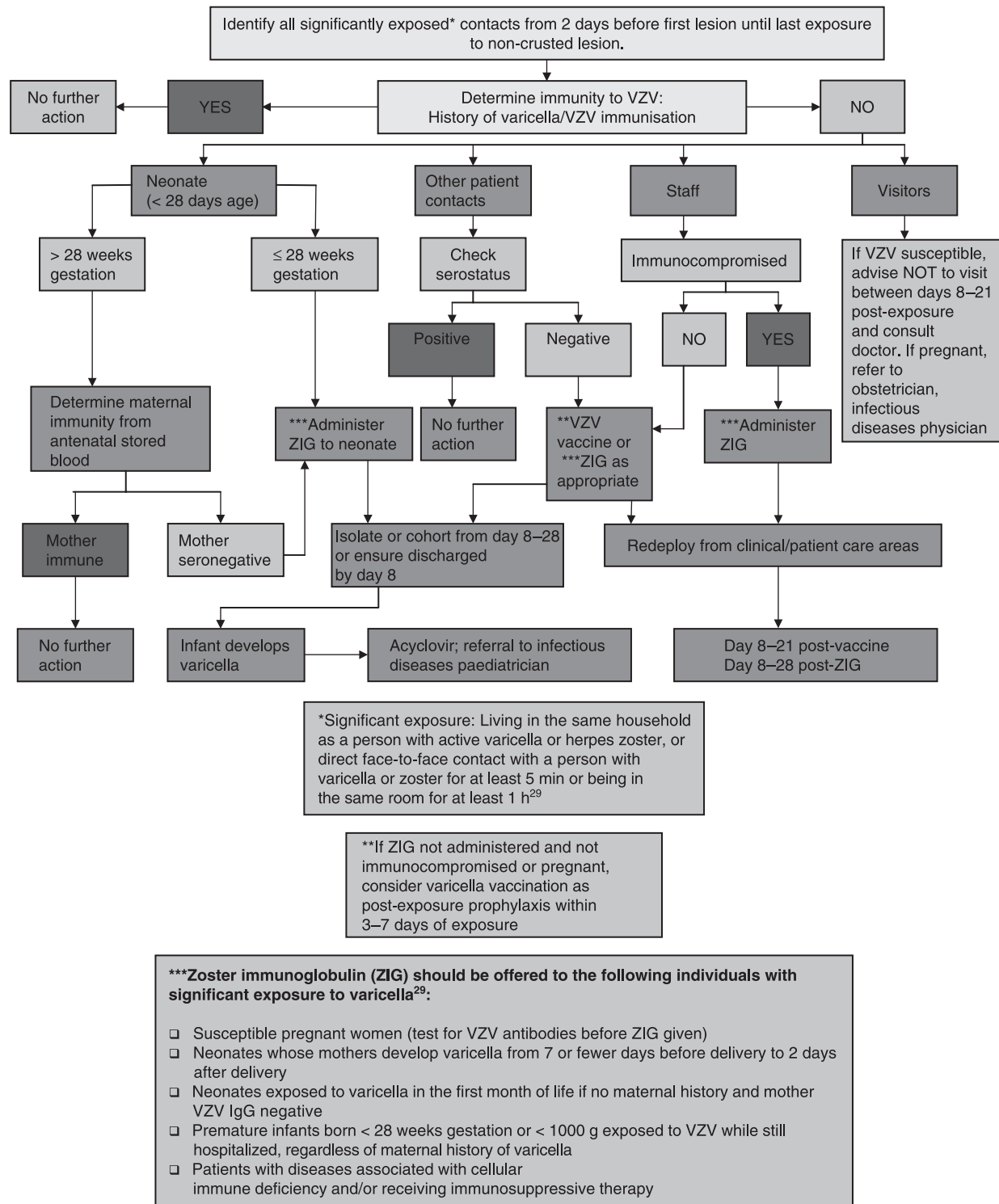


Figure 2 Management of varicella contact. VZV, varicella zoster virus; ZIG, zoster immunoglobulin.

Case scenario

Busy antenatal clinics and general practice waiting rooms are high-risk areas for transmission of infections. Recently, an antenatal patient in the early stages of varicella sat in a waiting area with antenatal and oncology patients for one hour. Follow up of 105 patient contacts was required, with 26 needing serological testing because of uncertain varicella history. Four patients (three pregnant and one postnatal) required ZIG as they were not immune.

This incident caused unnecessary anxiety for many patients, especially those pregnant or visiting babies in the neonatal unit and those with neoplasias. Significant staff time was also required from infection control, infectious diseases, laboratory services, outpatient department ward clerks and interpreter services. This situation was avoidable as a patient with a rash should have been triaged to a separate room, rather than be allowed to sit in a busy waiting area with other patients.

It is important that reception and triage staff are aware of the risk and impact that varicella can have. The presentation of any patient or visitor to the hospital or clinic with a rash should trigger immediate clinical assessment and appropriate isolation if required.

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