



CHICKENPOX IN PREGNANCY

1. Purpose

Varicella, the primary infection with varicella zoster virus (VZV), in pregnancy may cause maternal mortality or serious morbidity. It may also cause fetal varicella syndrome (FVS) – previously known as congenital varicella syndrome – or varicella infection of the newborn. The aim of this guideline is to assess the evidence that these complications can be prevented or modified beneficially by the administration of varicella zoster immune globulin (VZIG) or by treatment of infected individuals with aciclovir. This information should guide the prudent use of VZIG, which is manufactured from the plasma of human blood donors and, hence, is a limited and expensive resource. The guideline will also address the role of varicella vaccination in susceptible women of reproductive age.

2. Identification and assessment of evidence

The Cochrane Database and Medline were searched using the terms: Chickenpox; Varicella Zoster; Pregnancy.

The definitions of the types of evidence used in this guideline originate from the US Agency for Health Care Policy and Research. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as ‘Good practice points’.

3. Background

VZV is a DNA virus of the herpes family that is highly contagious and transmitted by respiratory droplets and by direct personal contact with vesicle fluid or indirectly via fomites. The primary infection is characterised by fever, malaise and a pruritic rash that develops into crops of maculopapules, which become vesicular and crust over before healing. The incubation period is 10–21 days and *the disease is infectious 48 hours before the rash appears and continues to be infectious until the vesicles crust over.*

Chickenpox (or primary VZV infection) is a common childhood disease when it usually causes a mild infection, such that over 90% of the antenatal population are seropositive for VZV immunoglobulin G (IgG) antibody.¹ For this reason, although contact with chickenpox is common in pregnancy, especially in women with young children, primary VZV infection is uncommon, i.e. it is estimated to complicate three in every 1000 pregnancies.² Women from tropical and subtropical areas are more likely to be seronegative for VZV IgG and are therefore more susceptible to the development of chickenpox.³

Evidence
level III

Following the primary infection, the virus remains dormant in sensory nerve root ganglia but can be reactivated to cause a vesicular erythematous skin rash in a dermatomal distribution known as herpes zoster or simply zoster or shingles. Shingles in pregnancy does not appear to cause fetal sequelae.⁴

Evidence
level III

4. What are the maternal risks of varicella in pregnancy?

Although varicella infection is much less common in adults than in children, it is associated with greater morbidity, namely pneumonia, hepatitis and encephalitis. Most of the mortality associated with VZV occurs in those aged 15 years or older.⁵

Evidence
level IV

Pneumonia can occur in up to 10% of pregnant women with chickenpox⁶ and the severity of this complication seems increased in later gestation.⁷ Mortality rates reaching 25% were reported in the pre-antiviral era.⁸ However, between 1985 and 1996 there were only eight indirect maternal deaths and one late maternal death reported in the UK as complications of maternal varicella pneumonia,⁹⁻¹² suggesting a case fatality rate of less than 1%.

Evidence
level III

5. What are the fetal and neonatal risks of varicella infection in pregnancy?

5.1 Before 20 weeks of gestation

Spontaneous miscarriage does not appear to be increased if chickenpox occurs in the first trimester.¹³

Evidence
level IIb

FVS is characterised by one or more of the following:

- skin scarring in a dermatomal distribution
- eye defects (microphthalmia, chorioretinitis, cataracts)
- hypoplasia of the limbs;
- neurological abnormalities (microcephaly, cortical atrophy, mental retardation and dysfunction of bowel and bladder sphincters).

It does not occur at the time of initial fetal infection but results from a subsequent herpes zoster reactivation *in utero* and only occurs in a minority of infected fetuses. It is estimated to complicate 1–2% of maternal varicella infections that occur before 20 weeks of gestation^{4,13} and does not occur if the primary infection occurs later in gestation.

Evidence
level III

Prenatal diagnosis is possible using detailed ultrasound when findings such as limb deformity, microcephaly, hydrocephalus, soft tissue calcification and intrauterine growth restriction can be detected some weeks after the initial infection.¹⁴ VZV DNA can be detected by polymerase chain reaction (PCR) in amniotic fluid but its presence is not synonymous with the development of FVS. In one observational study nine (8.4%) out of 107 women who developed chickenpox before 24 weeks of gestation had VZV DNA detected in the amniotic fluid. Five of these nine women subsequently delivered normal infants. No case of FVS occurred when amniocentesis was negative for VZV DNA.¹⁵

5.2 After 20 weeks and before 36 weeks of gestation

Maternal infection after 20 weeks and up to 36 weeks does not appear to be associated with adverse fetal effect but may present as shingles in the first few years of infant life. This is thought to represent reactivation of the virus after a primary infection *in utero*.

5.3 After 36 weeks of gestation

Varicella infection of the newborn (previously called congenital varicella) refers to VZV infection in early neonatal life resulting from maternal infection near the time of delivery or immediately postpartum. If maternal infection occurs one to four weeks before delivery, up to 50% of babies are infected and approximately 23% of these develop clinical varicella despite high titres of passively acquired maternal antibody. Severe chickenpox is most likely to occur if the infant is born within seven days of onset of the mother's rash when cord blood VZV IgG is low.¹⁶

Evidence
level III

6. Can varicella be prevented?

6.1 In the non-immune adult who plans to become pregnant

A live attenuated varicella vaccine has been shown to be safe and effective in preventing chickenpox in adults.¹⁷ Some groups have argued for the immunisation of all susceptible women who are planning a pregnancy.¹⁸ Seronegative women undergoing infertility treatment or those presenting for preconceptual counselling may be offered vaccination in the USA and some European countries. The vaccine is not available in the UK for this indication at the present time. However, the importance of avoidance of contact with chickenpox should continue to be emphasised, particularly where the individual is non-immune or where the serologic status is uncertain.

6.2 In the pregnant woman at her initial antenatal visit

It would be beneficial to enquire about a previous history of chickenpox from women at their booking visit. If there is no such history, women must be advised to avoid contact with chickenpox during pregnancy and to immediately inform health care workers of a potential exposure. In cases of uncertainty, it is possible to check serum VZV IgG antibodies (80% of women will be seropositive).

6.3 In the pregnant woman who gives a history of contact with chickenpox

C When contact occurs with chickenpox, a careful history must be taken to confirm the significance of the contact and the susceptibility of the patient. If the pregnant woman is not immune to VZV and she has had a significant exposure, she should be given VZIG as soon as possible. VZIG is effective when given up to ten days after contact. Women who have had exposure to chickenpox (regardless of whether or not they have received VZIG) should be asked to notify their doctor or midwife early if a rash develops.^{19,20}

The history must be confirmed with particular respect to the certainty of the infection, the infectiousness (vesicular rash or development of rash within 48 hours of contact) and the degree of exposure (household, face-to-face for five minutes or indoors contact for more than 15 minutes).¹⁹ The UK Advisory Group on Chickenpox consider any close contact during the period of infectiousness to be significant.²⁰ The susceptibility of the woman should then be determined by eliciting a past history of chickenpox. If there is a definite past history of chickenpox, it is reasonable to assume that she is immune to varicella infection. If the woman's immunity to chickenpox is unknown and if there is any doubt about previous infection, or if there is no previous history of chickenpox, serum should be tested for VZV IgG. This can usually be performed within 24–48 hours and the virology laboratory may be able to use serum stored from booking antenatal bloods. At least 80–90% of women tested will have VZ IgG and can be reassured.²¹ Antibodies detected within ten days of contact must have been acquired before contact.

Evidence
level III

If the pregnant woman is not immune to VZV and she has had a significant exposure to chickenpox while the contact was infectious, she should be given VZIG as soon as

possible. The administration of VZIG can be delayed until serology results are available. VZIG may not prevent but may attenuate ten days after exposure.¹⁶ Women who have had contact with chickenpox (regardless of whether or not they have received VZIG) should be asked to notify their doctor or midwife early if a rash develops. Maternal death has been reported following the development of varicella pneumonia despite the administration of VZIG.⁷

Evidence
level III

7. How should we manage the pregnant woman who develops chickenpox?

7.1 Initial management

Pregnant women who develop the rash of chickenpox should immediately contact their GP. They should avoid contact with susceptible individuals, i.e. other pregnant women and neonates until at least five days after the onset of the rash or until the lesions have crusted over. Symptomatic treatment and hygiene is advised to prevent secondary bacterial infection of the lesions.

Oral aciclovir reduces the duration of fever and symptomatology of varicella infection in immunocompetent adults if commenced within 24 hours of developing the rash when compared to placebo.²² It is of no benefit if commenced after 24 hours. This RCT did not have sufficient power to comment on the impact of early oral aciclovir on the serious complications of chickenpox.

Evidence
level Ib

No adverse fetal or neonatal effects have been reported with the use of aciclovir in pregnancy and information accumulated by the aciclovir in pregnancy register has been reassuring thus far,²³ although the theoretical risk of teratogenesis persists in the first trimester.

Evidence
level IV

C The UK Advisory Group on Chickenpox recommends that oral aciclovir be prescribed for pregnant women with chickenpox if they present within 24 hours of the onset of the rash and if they are more than 20 weeks of gestation. Informed consent should be obtained from the patient when aciclovir is used in this context. VZIG has no therapeutic benefit once chickenpox has developed.²⁰

7.2 Criteria for referral to hospital

C Indications for referral to hospital include the development of chest symptoms, neurological symptoms, haemorrhagic rash or bleeding, a dense rash with or without mucosal lesions and significant immunosuppression. If the woman smokes cigarettes, has chronic lung disease, is taking steroids or is in the latter half of pregnancy, hospital assessment should be considered, even in the absence of complications. Appropriate treatment can be decided in consultation with the obstetrician, virologist and neonatologist.²⁰

The pregnant woman with chickenpox should be asked to immediately report respiratory or new symptoms to her doctor. Women at greater risk of pneumonitis are those who smoke cigarettes, have chronic obstructive lung disease, are immunosuppressed (including those who have taken systemic steroids in the preceding three months), have a more extensive or haemorrhagic rash or who are in the latter half of pregnancy.²⁰

Evidence
level III

Delivery during the viraemic period may be extremely hazardous. The maternal risks are bleeding, thrombocytopenia, disseminated intravascular coagulopathy and hepatitis. There is a high risk of varicella of the newborn with significant morbidity and mortality.^{16,24} Therefore, supportive treatment and intravenous aciclovir is recommended to facilitate resolution of the rash, immune recovery and transfer of protective antibodies from the mother to the fetus.

8. Can the fetal effects of chickenpox be prevented or ameliorated?

B If the pregnant woman develops varicella or shows serological conversion in the first 20 weeks of pregnancy, she has a 1–2% risk of fetal varicella syndrome and she will need to be informed of the implications.^{4,13}

There is no conclusive evidence that VZIG given within 24 hours of contact prevents intrauterine infection. In an observational study, there was no case of fetal varicella syndrome or shingles in infancy in 97 pregnancies where maternal varicella occurred despite VZIG administration to the mother post exposure before 36 weeks of gestation.⁴ However, there is a case reported of fetal varicella syndrome in a woman who received VZIG.¹³

Evidence
level III

Referral to a specialist centre for detailed ultrasound examination at 16–20 weeks or five weeks after infection should be considered. Neonatal ophthalmic examination should be organised after birth. Neonatal blood should be sent for VZV IgM antibody and later a follow-up sample after seven months of age should be tested for VZV IgG antibody.

9. Can the neonatal effects of varicella be prevented or ameliorated?

C If maternal infection occurs at term, there is a significant risk of varicella of the newborn. Thus, where relevant and practical, delivery should be delayed until five days after the onset of maternal illness to allow for passive transfer of antibodies. If delivery occurs within five days of maternal infection, or if the mother develops chickenpox within two days of giving birth, then the neonate should be given VZIG. The infant should be monitored for signs of infection for 14–16 days. If neonatal infection occurs, it should be treated with aciclovir. VZIG is of no benefit once neonatal chickenpox has developed.²⁰

The risk of varicella of the newborn is highest if maternal disease occurs up to seven days before or after delivery with the risk of severe neonatal infection being greatest when the onset of the rash is five days before and two days after delivery.^{16,24}

VZIG does not prevent neonatal infection when administered during this time period¹⁶ but mortality rates in these infants appear to be lower than the 30% previously reported without VZIG.²⁴ This difference in outcome may reflect developments in neonatal care over this time period and the efficacy of aciclovir.

Evidence
level III

Maternal shingles around the time of delivery is not a risk to the neonate because it is protected by transplacentally acquired maternal antibodies.

10. How can spread of the infection to further contacts be decreased?

10.1 What is the risk to the neonate if a sibling has chickenpox?

C If there is contact with chickenpox in the first seven days of life, no intervention is required if the mother is immune. However, the neonate should be given VZIG if the mother is not immune to varicella or if the neonate delivered prematurely.²⁵

On occasion, a sibling has varicella around the time that the mother and newborn are discharged from hospital. If the mother is immune to the VZV, the risk to the neonate is minimal because it is protected by passively acquired maternal antibodies. This may not apply to the baby who delivered before 28 weeks, weighing less than 1 kg who may lack maternal antibodies.²⁵

If the mother is susceptible and the newborn is up to seven days old, the newborn should be given VZIG. The mother does not fulfil the criteria for VZIG administration herself,

Evidence
level III

as she is no longer considered to be at high risk for the complications of chickenpox once she has delivered. Aciclovir prophylaxis may be considered for her as it appears to provide some protection from infection with an associated reduction in the chance of transmission to the newborn.^{26,27}

Evidence
level III

10.2 What precautions are advised for health care workers?

C Non-immune health care workers who are exposed to infection should be warned they may develop chickenpox and be re-allocated to minimise patient contact from day 8–21 post-contact.¹⁹

All reasonable steps should be taken to prevent contact between healthcare workers with chickenpox and pregnant women attending hospitals or GP surgeries. Staff who are thought (or known by previous testing) to be ‘non-immune’ should avoid contact with chickenpox. Non-immune healthcare workers who are exposed to infection should be warned they might develop chickenpox and be re-allocated to minimise patient contact from days 8–21 post contact. VZIG is not available for exposed non-immune healthcare workers unless they are considered at ‘high risk’ of the complications of infection. Currently, there are no UK recommendations for varicella vaccination of non-immune healthcare workers.

11. How do you manage the pregnant woman with shingles?

Shingles is usually mild in this age group and viraemia is uncommon unless the woman is immunocompromised. Ophthalmic shingles may require topical or oral aciclovir in consultation with an ophthalmologist. Maternal shingles does not pose a risk to the fetus or neonate as it is protected by passively acquired maternal antibody. The risk of acquiring chickenpox from an immunocompetent individual with non-exposed herpes zoster is remote. There is a risk of varicella infection if the contact has disseminated zoster or exposed lesions, e.g. ophthalmic zoster or is immunosuppressed.

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Clinical guidelines are: ‘systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions’. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in ‘Clinical Governance Advice No 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website: www.rcog.org.uk). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

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| Ia | Evidence obtained from meta-analysis of randomised controlled trials. |
| Ib | Evidence obtained from at least one randomised controlled trial. |
| IIa | Evidence obtained from at least one well-designed controlled study without randomisation. |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study. |
| III | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies. |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. |

Grades of recommendations

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| A | Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib) |
| B | Requires the availability of well-controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III) |
| C | Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV) |

Good practice point

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| <input checked="" type="checkbox"/> | Recommended best practice based on the clinical experience of the guideline development group. |
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