Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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CHICKENPOX IN PREGNANCY

This is the third edition of the guideline originally published in 1997 and reviewed in 2001 under the same title.

1. Purpose and scope

Varicella, the primary infection with herpes 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 and varicella infection of the newborn, which includes syndromes previously known as congenital varicella and neonatal varicella. The aim of this guideline is to assess the evidence regarding the maternal and fetal risks of VZV infection in pregnancy and to assess whether or not 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 healthcare workers and in susceptible women of reproductive age.

2. Identification and assessment of evidence

The Cochrane Library and Cochrane Register of Controlled Trials were searched for relevant randomised controlled trials, systematic reviews and meta-analysis. A search of Medline and PubMed electronic database from 1966 to 2006 was also carried out. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search 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 1–3 weeks and **the disease is infectious 48 hours before the rash appears and continues to be infectious until the vesicles crust over**. The vesicles will usually have crusted over within 5 days.

Evidence level III

Chickenpox (or primary VZV infection) is a common childhood disease that usually causes a mild infection, such that over 90% of the antenatal population in the UK and Ireland are seropositive for VZV immunoglobulin (IgG) antibody.[1,2] For this reason, although contact with chickenpox is common in pregnancy, especially in women with young children, primary VZV infection is uncommon; it is estimated to complicate three in every 1000 pregnancies.[3] 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.[4]

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 (HZ), or simply zoster or shingles. The risk of acquiring infection from an immunocompetent individual with herpes zoster in non-exposed sites (for example, thoracolumbar) is remote. However, disseminated zoster or exposed zoster (such as ophthalmic) in any individual or localised zoster in an immunosuppressed patient should be considered to be infectious.[5]

4. Varicella prevention

Can varicella be prevented?

4.1 In the non-immune woman preconceptually

Varicella vaccination prepregnancy or postpartum is an option that should be considered for women who are found to be seronegative for VZV IgG before pregnancy or in the postpartum period. ✓

Varicella vaccine contains live attenuated virus derived from the Oka strain of VZV and has been licensed for use in the USA since March 1995. Following its introduction, the incidence of primary infection (chickenpox) has fallen by 90% and the mortality related to the condition has decreased by two-thirds.[6] Immunity from the vaccine may persist for up to 20 years.[7,8] Two varicella vaccines are licensed for use in the UK, Varivax® (Oka/Merck) and Varilrix® (Oka–RIT).

The varicella immune status of women planning a pregnancy or receiving treatment for infertility can be determined by obtaining a past history of chickenpox and by checking the serum for varicella antibodies in those who have no history or uncertain history of previous infection; however, this is not a national screening recommendation in the UK.

If a woman of reproductive age is vaccinated, she should be advised to avoid pregnancy for 3 months and to avoid contact with other susceptible pregnant women should a post-vaccination rash occur.[5] Transmission of vaccine virus in the absence of a rash is rare despite it being a live attenuated virus. Inadvertent exposures to the vaccine in pregnancy have been reported to a register. There have been no cases of FVS and an increase in the baseline risk of fetal abnormality has not been detected.[9]

4.2 In the pregnant woman at her initial antenatal visit

Women who are seronegative for VZV IgG must be advised to avoid contact with chickenpox and shingles during pregnancy and to immediately inform healthcare workers of a potential exposure. ✓

A previous history of chickenpox infection is 97–99% predictive of the presence of serum varicella antibodies.[10] Therefore, a reasonable policy is to ask about previous chickenpox/shingles and restrict advice to women who have no history or an uncertain history of previous infection. A history of chickenpox can be a less reliable predictor of immunity in individuals born and raised overseas and it may be appropriate to undertake serum testing routinely in this group of women.[11]

Although a recent study has demonstrated that antenatal varicella screening by history and serological testing for VZIG antibody in those with a negative history followed by postpartum vaccination was cost effective,[12] this is not currently part of a UK screening programme.

4.3 In the pregnant woman who gives a history of contact with chickenpox or shingles

When contact occurs with chickenpox or shingles, a careful history must be taken to confirm the significance of the contact and the susceptibility of the patient. C

Women should have a blood test for confirmation of VZV immunity. ✓

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 10 days after contact. C

If VZIG is given, the pregnant woman should be managed as potentially infectious from 8–28 days after VZIG (8–21 days if no VZIG given). C

Women who have had exposure to chickenpox or shingles (regardless of whether or not they have received VZIG) should be asked to notify their doctor or midwife early if a rash develops.[5,13] C

A second dose of VZIG may be required if a further exposure is reported and 3 weeks have elapsed since the last dose. ✓

The history must be confirmed with particular respect to:

- the type of VZV infection
- the timing of the exposure
- the closeness and duration of contact.

The risk of infection following contact with herpes zoster (shingles) that is not exposed (for example, in the thoracolumbar region) is remote. If shingles is disseminated or exposed (such as ophthalmic) or occurs in an immunocompromised individual where viral shedding may be greater, there is a risk of infection when the lesions are active and until they have crusted over. Chickenpox is not only infectious during this period but also for the 2 days before the onset of the rash. Significant contact is defined as contact in the same room for 15 minutes or more, face-to-face contact and contact in the setting of a large open ward.[5] The UK Advisory Group on Chickenpox considers any close contact during the period of infectiousness to be significant.[13] The susceptibility of the woman should then be determined by eliciting a past history of chickenpox or shingles. 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 or shingles, 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.[14]

Evidence level III

If the pregnant woman is not immune to VZV and she has had a significant exposure to chickenpox or shingles, she should be given VZIG as soon as possible. If the immune status of the woman is unknown, the administration of VZIG can be delayed until serology results are available (if the laboratory turnaround time is 24–48 hours). The evidence that VZIG prevents or attenuates the disease in pregnancy comes from 212 seronegative women who received an appropriate dose of VZIG either intramuscularly or intravenously within 10 days of significant exposure to chickenpox. Fifty percent of the women developed either modified or normal chickenpox and a further 5% had subclinical infection.[15] VZIG is a human immunoglobulin product manufactured from the plasma of

non-UK donors with high VZV antibody titres. When supplies are limited, issues to pregnant women may be restricted and clinicians are advised to check the availability of VZIG before offering it to pregnant women.[5] Rare anaphylactoid reactions have occurred in individuals with hypogammaglobulinaemia who have IgA antibodies or in those that have atypical reactions to blood transfusion. No case of blood borne infection has been reported with its use.[5]

Evidence level III

Susceptible women who have had contact with chickenpox or shingles (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.[16]

5. The pregnant woman who develops chickenpox

5.1 What are the maternal risks of varicella in pregnancy?

Clinicians need to be aware of the excess morbidity associated with varicella infection in adults, including pneumonia, hepatitis and encepahalitis and, occasionally, mortality. ✓

Although varicella infection is much less common in adults than in children, it is associated with greater morbidity, namely pneumonia, hepatitis and encephalitis. Chickenpox results in the death of 25 people/year in England and Wales and 75% of these deaths occur in adults.[17]

Pneumonia can occur in up to 10% of pregnant women with chickenpox[18] and the severity of this complication seems increased in later gestation.[19] Mortality rates between 20% and 45% were reported in the pre-antiviral era[20–22] but have fallen to 3–14% with antiviral therapy and improved intensive care.[18,20,23] However, between 1985 and 2002 there were nine indirect maternal deaths and one late maternal death reported in the UK as complications of maternal varicella pneumonia,[24–26] suggesting a case fatality rate of less than 1% but a rate five times higher in pregnancy than in the nonpregnant adult.

Evidence level III

5.2 How should the pregnant woman who develops chickenpox be managed?

Pregnant women who develop the rash of chickenpox should immediately contact their GP. ✓

Women should avoid contact with susceptible individuals; that is, other pregnant women and neonates, until the lesions have crusted over. This is usually about 5 days after the onset of the rash. ✓

Symptomatic treatment and hygiene is advised to prevent secondary bacterial infection of the lesions. ✓

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 gestation. C

Aciclovir should be used cautiously before 20 weeks of gestation. ✓

Women should be informed of the potential risk and benefits of treatment with aciclovir. C

VZIG has no therapeutic benefit once chickenpox has developed.[13] C

Oral aciclovir (800 mg five times a day for 7 days) reduces the duration of fever and symptomatology of varicella infection in immunocompetent adults if commenced within 24 hours of

Evidence level Ib

developing the rash when compared with placebo.[27] This randomised controlled trial did not have sufficient power to comment on the impact of early oral aciclovir on the serious complications of chickenpox.

Evidence level Ib

Data suggest that there is no increase in the risk of fetal malformation with aciclovir in pregnancy, although the theoretical risk of teratogenesis persists in the first trimester.[28,29]

Evidence level IV

5.3 Should women be referred to hospital?

Women who develop any of the following symptoms should be referred immediately to a hospital: chest symptoms, neurological symptoms, haemorrhagic rash or bleeding, a dense rash with or without mucosal lesions; women with significant immunosuppression should also be referred.

C

If the woman smokes cigarettes, has chronic lung disease, is taking corticosteroids or is in the latter half of pregnancy, a hospital assessment should be considered, even in the absence of complications. Appropriate treatment should be decided in consultation with a multidisciplinary team: obstetrician or fetal medicine specialist, virologist and neonatologist.

C

Women hospitalised with varicella should be nursed in isolation from babies or potentially susceptible pregnant women or non-immune staff.

✓

The pregnant woman with chickenpox should be asked to report immediately respiratory or other 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 corticosteroids in the preceding 3 months), have a more extensive or haemorrhagic rash or who are in the latter half of pregnancy.[13]

Depending on the severity of the maternal condition, a respiratory physician and intensive care specialist may also be involved. Timing and mode of delivery must be individualised. 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 infection of the newborn with significant morbidity and mortality.[30,31] Supportive treatment and intravenous aciclovir is therefore desirable, allowing resolution of the rash, immune recovery and transfer of protective antibodies from the mother to the fetus. However, delivery may be required in women to facilitate assisted ventilation in cases where varicella pneumonia is complicated by respiratory failure.

Evidence level III

There is no evidence available to us to inform decisions about the optimum method of anaesthesia for women requiring delivery by caesarean section. General anaesthesia may exacerbate varicella pneumonia. There is theoretical risk of transmitting the varicella virus from skins lesions to the central nervous system via spinal anaesthesia. This results in advice that epidural anaesthesia may be safer than spinal anaesthesia, because the dura is not penetrated. A site free of cutaneous lesions should be chosen for needle placement.[32]

6. Risks during pregnancy

6.1 What are the fetal risks of varicella infection in pregnancy and can they be prevented or ameliorated?

Women should be advised that the risk of spontaneous miscarriage does not appear to be increased if chickenpox occurs in the first trimester.

B

If the pregnant woman develops varicella or shows serological conversion in the first 28 weeks of pregnancy, she has a small risk of fetal varicella syndrome and she will need to be informed of the implications. B

Spontaneous miscarriage does not appear to be increased if chickenpox occurs in the first trimester.[33] 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; and neurological abnormalities (microcephaly, cortical atrophy, mental restriction 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.

FVS has been reported to complicate maternal chickenpox that occurs as early as 3 weeks and up to 28 weeks of gestation. Pooled data from nine cohort studies detected 13 cases of FVS following 1423 cases of maternal chickenpox occurring before 20 weeks of gestation: an incidence of 0.91%. The risk appears to be lower in the first trimester (0.55%).[19] Cases of fetal varicella syndrome have been reported following maternal infection between 20 and 28 weeks.[19,34,35] This is thought to be extremely rare, based on the fact that only one case has been reported in all the cohort studies of varicella in pregnancy. No case of FVS has been reported when maternal infection has occurred after 28 weeks.[19] Evidence level III

6.2 Can varicella infection of the fetus be diagnosed prenatally?

Referral to a fetal medicine specialist should be considered at 16–20 weeks or 5 weeks after infection for discussion and detailed ultrasound examination. ✓

Amniocentesis is not routinely advised because the risk of FVS is so low, even when amniotic fluid is positive for VZV DNA. The risks versus benefits of the procedure should be discussed with the woman in conjunction with the findings on ultrasound examination. ✓

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. A time lag of at least 5 weeks after the primary infection is advised because ultrasound performed at 4 weeks has failed to detect the deformities.[36] Fetal magnetic resonance imaging can be useful to look for morphological abnormalities.[37] VZV DNA can be detected by polymerase chain reaction (PCR) in amniotic fluid. VZV DNA has a high sensitivity but a low specificity for the development of FVS. In one observational study nine (8.4%) 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. Ultrasound detected abnormalities in two of these cases. One had features of FVS that were confirmed histologically after termination of pregnancy. The other had microcalcifications of the lungs, liver and spleen and was healthy following delivery. One baby with a positive PCR had a normal ultrasound but was born with bilateral microphthalmia. No case of FVS occurred when amniocentesis was negative for VZV DNA.[38] Evidence level III

If amniotic fluid is PCR positive for VZV and the ultrasound is normal at 17–21 weeks, the risk of FVS is low. If repeat ultrasound is normal at 23–24 weeks the risk of FVS is remote. The risk of FVS is very high if the ultrasound shows features compatible with FVS and the amniotic fluid is positive (there were two cases, however, that were exceptions to these guidelines in the study mentioned above).[38] A negative result in amniotic fluid and a normal ultrasound from 23 weeks onwards, suggest a low risk of intrauterine infection.[15]

It is not known whether VZIG reduces the risk of FVS. A prospective study was carried out of 108 women who developed chickenpox despite VZIG prophylaxis. Eighty percent of these women received VZIG in the first and second trimester and there were no cases of FVS or infants with IgM antibodies at birth.[15] However, no conclusion can be drawn from this, given the rarity of FVS. One case of FVS has been reported in a woman who developed chickenpox following VZIG administration.[33]

Evidence level III

6.3 What are the neonatal risks of varicella infection in pregnancy and can they be prevented or ameliorated?

If maternal infection occurs at term, there is a significant risk of varicella of the newborn. Elective delivery should normally be avoided until 5–7 days after the onset of maternal rash to allow for the passive transfer of antibodies from mother to child.

C

Neonatal ophthalmic examination should be organised after birth. Neonatal blood should be sent for VZV IgM antibody and later a follow-up sample after 7 months of age should be tested for VZV IgG antibody.

✓

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 or from contact with a person other than the mother with chickenpox or shingles during this time. The route of infection could be transplacental, ascending vaginal or result from direct contact with lesions during or after delivery. If maternal infection occurs 1–4 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 7 days of onset of the mother's rash or if the mother develops the rash up to 7 days after delivery when cord blood VZV IgG is low.[30]

Evidence level III

Maternal infection during pregnancy may have no fetal or neonatal effect other then the development of shingles in the first few years of infant life. This is thought to represent reactivation of the virus after a primary infection *in utero*.

6.4 What treatment is advised following onset of maternal rash at term?

If birth occurs within the 7-day period following the onset of the maternal rash, or if the mother develops the chickenpox rash within the 7-day period after birth, the neonate should be given VZIG. The infant should be monitored for signs of infection until 28 days after the onset of maternal infection. VZIG is also recommended for non-immune neonates that are exposed to chickenpox or shingles (other than maternal) in the first 7 days of life.[5]

C

Neonatal infection should be treated with aciclovir following discussion with a neonatologist and virologist.

C

VZIG is of no benefit once neonatal chickenpox has developed.[13]

C

The risk of varicella of the newborn is highest if maternal disease occurs up to 7 days before or after delivery with the risk of severe neonatal infection being greatest when the onset of the rash is 5 days before and up to 2 days after delivery.[30,31] Approximately 50% of the neonates exposed to maternal varicella will develop chickenpox despite the administration of VZIG[30] but mortality rates in these infants appear to be lower than the 30% previously reported without this treatment.[31] This difference in outcome may reflect developments in neonatal care over this time period and the efficacy of aciclovir. VZIG may prolong the incubation period of the virus for up to 28 days and

Evidence level III

therefore exposed neonates that are given VZIG should be monitored for signs of infection for this time period.

Maternal shingles around the time of delivery is not a risk to the neonate because it is protected by transplacentally acquired maternal antibodies. This may not apply to the baby who delivers before 28 weeks or weighs less than 1 kg who may lack maternal antibodies.[5]

Evidence level III

7. Spread of the infection to further contacts

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

If there is contact with chickenpox in the first 7 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.[39] C

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 delivers before 28 weeks or weighs less than 1 kg who may lack maternal antibodies.[5]

If the mother is susceptible and the newborn is up to 7 days old, the baby should be given VZIG. The mother does not fulfil the criteria for VZIG administration herself, 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.[40,41]

Evidence level III

7.2 Precautions for healthcare workers

What precautions are advised for healthcare workers?

The immune status of healthcare workers in maternity and neonatal units should be determined by history of past infection and by serological testing if the history is negative or equivocal. C

Non-immune healthcare workers should be offered varicella vaccination. C

If non-immune healthcare workers have significant exposure to infection they should either be warned they may develop chickenpox and should be reallocated to minimise patient contact from 8–21 days post-contact or advised to report to their occupational health department before patient contact if they are feeling unwell or develop a fever or rash.[5] C

Non-immune healthcare workers should be immunised. All reasonable steps should be taken to prevent contact between healthcare workers with chickenpox and pregnant women attending hospitals or general practitioner surgeries. Non-immune healthcare workers who are exposed to infection should be warned that they might develop chickenpox and should be reallocated to minimise patient contact from 8–21 day post-contact or they are advised to report to their occupational health department if they are feeling unwell or develop a fever or rash before they make further patient contact.[5] There is some evidence that administration of the varicella vaccine within 3 days of exposure may prevent chickenpox.[5] VZIG is not available for exposed non-immune healthcare workers unless they are considered at 'high risk' for the complications of infection.

8. Auditable standards

1. Documentation of appropriate advice and investigations for chickenpox-exposed non-immune women.
2. Appropriate use of VZIG.
3. Rates of vaccination of vulnerable women.
4. Rates of vaccination of vulnerable healthcare workers.
5. Neonatal follow-up of babies at risk of varicella infection of the newborn.

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APPENDIX

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 at **www.rcog.org.uk/clingov1**). 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

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

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

✓	Recommended best practice based on the clinical experience of the guideline development group.

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

The guideline review process will commence in September 2010
unless otherwise indicated