



MANAGEMENT OF GENITAL HERPES IN PREGNANCY

This is the second edition of this guideline, which was originally published in 2002 under the same title.

1. Purpose and scope

The severe consequences of neonatal herpes infection are well established and obstetricians and other health professionals caring for pregnant women need to be aware of interventions that may reduce the risk of perinatal transmission. The literature has been reviewed in order to update recommendations for the management of genital herpes in pregnancy made in the original RCOG Green-top Guideline No.30 published in March 2002.

2. Background

Neonatal herpes is a viral infection with a high morbidity and mortality which is most commonly acquired at or near the time of delivery.¹ It is classified into three subgroups: disease localised to skin, eye and/mouth, local central nervous system (CNS) disease (encephalitis alone) and disseminated infection with multiple organ involvement. Infants who present with skin, eye, and/mouth symptoms alone have the best prognosis: death is unusual and, with antiviral treatment, neurological and/or ocular morbidity is less than 2%. Disseminated disease and local CNS disease can present with or without skin, eye and/mouth infection. Disseminated disease carries the worst prognosis: with antiviral treatment, mortality is around 30% and 17% have long-term neurological sequelae. Infants with local CNS disease often present late (generally between 10 days and 4 weeks postnatally); with treatment, mortality is around 6% and neurological morbidity 70%. The poor outcomes of disseminated and local CNS disease have been attributed to delays between symptom onset and treatment.

Neonatal herpes is rare in the UK; active surveillance by the British Paediatric Surveillance Unit (BPSU) between 1986 and 1991 demonstrated an incidence of one in 60 000 live births annually (95% CI 1.3–2.0).² This is around 50% of that reported from other European countries and Japan. In the USA, the average reported incidence is one in 15 000 but there is considerable variation between populations; rates of up to one in 7500 have been reported in certain deprived inner city populations.^{3,4} A further surveillance programme by BPSU is due for completion in 2007 and will provide updated UK incidence data.

Neonatal herpes may be caused by herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2), as either viral type can cause genital herpes. Almost all cases of neonatal herpes occur as a result of direct contact with infected maternal secretions, although cases of postnatal transmission have been described.² Factors influencing transmission include the type of maternal infection (primary or recurrent), the presence of transplacental maternal neutralising antibodies, the duration of rupture of membranes before delivery, the use of fetal scalp electrodes and mode of delivery.^{1,3} The risks are greatest when a woman acquires a new

infection (primary genital herpes) in the third trimester, particularly within 6 weeks of delivery, as viral shedding may persist and the baby is likely to be born before the development of protective maternal antibodies.^{1,3} Very rarely, congenital herpes may occur as a result of transplacental intrauterine infection. Case reports suggest that the skin, eyes and central nervous system may be affected and there may be intrauterine growth restriction or fetal death.⁵⁻⁷ Disseminated herpes is more common in preterm infants and occurs almost exclusively as a result of primary infection in the mother. Although recurrent genital herpes is associated with a very low risk of neonatal herpes, recurrent herpes at the time of delivery which is commonly asymptomatic or unrecognised, may cause the localised forms of neonatal herpes, both local CNS disease and skin, eye and mouth infection. Transplacentally acquired HSV antibodies do not prevent neurogenic virus spreading to the brain of the neonate.⁸

Data from the USA suggest that around 2% of women acquire genital HSV infection in pregnancy.¹ Most of these maternal infections are asymptomatic or unrecognised.^{1,3} It may be difficult to distinguish clinically between recurrent and primary genital HSV infections, as many first episode HSV infections are not true primary infections.⁹

Disseminated herpes, which may present with encephalitis, hepatitis, disseminated skin lesions or a combination of these conditions, is rare in adults but has been more commonly reported in pregnancy, particularly in the immunocompromised. The maternal mortality associated with this condition is high.¹⁰ All immunocompromised women, such as those infected with the HIV virus, are at increased risk of more severe and frequent symptomatic recurrent episodes of genital herpes during pregnancy and of asymptomatic shedding of HSV at term.^{11,12} As coinfection with HSV and HIV results in an increased replication of both viruses,¹³ there are concerns that genital reactivation of HSV may increase the risk of perinatal transmission of both HIV and HSV.^{11,12}

Symptomatic genital herpes infections are confirmed by direct detection of HSV. Specimens from ulcerated lesions are sampled by swabbing the base of the ulcer and vesicular lesions are de-roofed and the fluid sampled. A swab for viral detection should be used. Subsequent analysis is by viral culture or polymerase chain reaction (PCR). Although type-specific HSV serological testing (immunoglobulin G antibodies to HSV-1 and HSV-2) is now widely available,¹⁴ its use for the management of herpes in pregnancy has not been fully evaluated.

3. Identification and assessment of evidence

A literature search was performed using Medline (1983–2005). The keywords used were ‘genital herpes’, ‘neonatal-herpes’, ‘herpes simplex virus’ and ‘pregnancy complications: infectious’. Reference lists of the articles identified were hand-searched for additional articles. 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’.

4. Primary episode of genital herpes

How should women be managed when presenting with a primary episode of genital herpes during pregnancy?

Women should be referred to a genitourinary physician and management of the woman should be in line with her clinical condition. Oral or intravenous aciclovir in standard doses should be offered. Type-specific HSV antibody testing, which can help to differentiate between primary and recurrent infections, should be undertaken if a woman presents with a first episode of genital herpes in the third trimester.



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

C

Aciclovir should be used with caution before 20 weeks of gestation.



Any woman with suspected first-episode genital herpes should be referred to a genitourinary physician, who will confirm the diagnosis by viral culture or PCR, advise on management and arrange a screen for other sexually transmitted infections. The use of aciclovir is associated with a reduction in the duration and severity of symptoms and a decrease in the duration of viral shedding. Aciclovir is well tolerated in pregnancy and dose adjustment is not necessary.^{15,16} Safety data from 1234 pregnancies reported to the aciclovir in the Pregnancy Registry have not shown evidence of teratogenicity.^{17,18} Although these data are reassuring, the number of pregnancies evaluated was insufficient to draw definite conclusions and aciclovir is not licensed for use in pregnancy. Treatment with oral aciclovir for 5 days at a dose of either 200 mg five times daily or 400 mg three times daily should be considered for women with severe symptoms. Disseminated HSV infection is an indication for intravenous aciclovir.

Evidence level IV

It may be difficult to distinguish clinically between recurrent and primary genital HSV infections, as many first-episode HSV infections are not true primary infections.⁹ For women presenting with first-episode genital herpes in the third trimester, particularly within 6 weeks of delivery, type-specific HSV antibody testing (immunoglobulin G antibodies to HSV-1 and HSV-2) is advisable. For these women, characterising the infection will influence the advice given regarding mode of delivery and risk of neonatal herpes. The presence of antibodies of the same type as the HSV isolated from genital swabs would confirm this episode to be a recurrence rather than a primary infection and elective caesarean section would not be indicated to prevent neonatal transmission.

5. Primary genital herpes at the time of delivery.

How should women be managed with a primary episode of genital herpes at the time of delivery?

Caesarean section should be recommended to all women presenting with primary episode genital herpes lesions at the time of delivery, or within 6 weeks of the expected date of delivery.

B

For women who develop primary genital herpes lesions within 6 weeks of delivery and who opt for a vaginal birth, rupture of membranes should be avoided and invasive procedures should not be used. Intravenous aciclovir given intrapartum to the mother and subsequently to the neonate may be considered. The neonatologist should be informed.

C

There is insufficient evidence to recommend use of daily suppressive aciclovir from 36 weeks of gestation to reduce the likelihood of HSV lesions at term for women who experience a primary episode of genital herpes earlier in the current pregnancy.

B

Where primary-episode genital herpes lesions are present at the time of delivery and the baby is delivered vaginally, the risk of neonatal herpes, calculated from five studies,^{1,19-21} was 19/46 or 41% (95% CI 26-56). The risk of perinatal transmission depends on the timing of maternal acquisition of HSV. In a large prospective study of 7046 women in Seattle, USA, the risk of neonatal herpes was highest in infants born to women who had not completed HSV seroconversion during pregnancy (most commonly in the third trimester, within 6 weeks of delivery). The rationale for elective caesarean section in the prevention of neonatal herpes is to reduce exposure of the fetus to HSV in genital secretions. A protective effect of elective caesarean section in the prevention of neonatal herpes was suggested by a large prospective study involving over 58 000 women in Washington, USA.³ In this study, 202 women had HSV isolated from genital secretions at term and of these 117 (58%) were delivered vaginally and 85 (42%) underwent caesarean section. Among the latter, lesions

Evidence level III

were the indication in 60 (71%) cases. After adjusting for the stage of infection (primary versus recurrent) and infection type (HSV-1 versus HSV-2), there was a trend towards a protective effect of elective caesarean delivery (OR 0.14; 95% CI, 0.02–1.26), although this did not reach statistical significance.³

Evidence level III

Intravenous aciclovir reduces maternal viraemia and genital viral shedding in women with primary genital herpes.²² It is used in labour for preventing neonatal herpes has not been assessed but it may be considered on the assumption that exposure of the fetus to HSV will be reduced. One poor-quality observational study found that caesarean section was not protective against neonatal herpes when the membranes had been ruptured for more than 4 hours.²³ The membranes should be left intact for as long as possible. Invasive procedures, such as fetal scalp electrode monitoring and fetal blood sampling, have also been associated with neonatal transmission.^{3,24} The paediatrician should conduct a clinical evaluation of the neonate and consider treatment with intravenous aciclovir.

Evidence level IV

In one double-blind randomised controlled trial, 46 women who presented with their first episode of genital herpes during their current pregnancy were randomised at 36 weeks of gestation to receive either daily suppressive aciclovir or placebo until delivery.²⁵ The protocol permitted vaginal delivery only if there were no HSV lesions at the time of delivery. No infants in either group developed neonatal herpes. None of the 21 women treated with aciclovir and nine of the 25 women (36%) treated with placebo who had clinical evidence of recurrent genital herpes at delivery had caesarean section delivery ($P = 0.002$).

6 Recurrent episodes of genital herpes

6.1 How should we manage the pregnant woman with recurrent episodes of genital herpes?

Antiviral treatment is rarely indicated for treatment of recurrent episodes of genital herpes during pregnancy.



Cultures during late gestation to predict viral shedding at term are not indicated.



A recurrent episode of genital herpes occurring during the antenatal period is not an indication for delivery by caesarean section.



For women with a history of recurrent genital herpes, who would opt for caesarean delivery if HSV lesions were detected at the onset of labour, daily suppressive aciclovir given from 36 weeks of gestation until delivery may be given to reduce the likelihood of HSV lesions at term.



The majority of recurrent episodes of genital herpes are short lasting and resolve within 7–10 days without antiviral treatment. Supportive treatment measures using saline bathing and analgesia alone will suffice.

Guidelines from the USA in the 1980s recommended that all women with a history of genital herpes should have weekly viral cultures taken during the last 6 weeks of pregnancy, with the aim of detecting recurrent herpes episodes, both symptomatic and asymptomatic. Positive cultures near term were an indication for delivery by caesarean section.²⁶ However, this practice is no longer recommended following a study by Arvin *et al.*,²⁰ which demonstrated that antenatal swabbing did not predict the shedding of virus at the onset of labour.

Evidence level III

The efficacy of aciclovir in preventing recurrent HSV episodes at term was evaluated in several small studies, of which four were randomised controlled trials.^{27–30} In these trials, the presence of recurrent HSV lesions at the onset of labour was an indication for caesarean section. A meta-analysis

Evidence level IV

of these studies, involving 799 women, found that acyclovir suppression reduced the risk of clinical HSV recurrence (OR 0.25; 95% CI 0.15–0.4), asymptomatic HSV shedding (OR 0.09; 95% CI 0.02–0.31) and delivery by caesarean section (OR 0.3; 95% CI 0.13–0.67).³¹ Aciclovir did not prevent HSV shedding in all women.

Evidence level IV

For HIV positive women with recurrent genital herpes occurring before or during pregnancy, careful consideration should be given regarding management, particularly the use of daily suppressive aciclovir to prevent HSV lesions at term and the role of caesarean section if recurrent lesions are present at term. Early liaison with the genitourinary medicine physicians and paediatricians is vital and detailed recommendations are beyond the scope of this guideline. These women are at increased risk of more severe and frequent symptomatic recurrent episodes of genital herpes during pregnancy and of asymptomatic shedding of HSV at term.^{11,12} As coinfection with HSV and HIV results in an increased replication of both viruses,¹³ there are concerns that genital reactivation of HSV may increase the risk of perinatal transmission of both HIV and HSV.^{11,12}

6.1 *How should we manage the pregnant woman with recurrent episodes of genital herpes at the onset of labour?*

Women presenting with recurrent genital herpes lesions at the onset of labour should be advised that the risk to the baby of neonatal herpes is very small.

B

Caesarean section is not routinely recommended for women with recurrent genital herpes lesions at the onset of labour. The mode of delivery should be discussed with the woman and individualised according to the clinical circumstances and the woman's preferences.

B

Women with recurrent genital herpes lesions and confirmed rupture of membranes at term should be advised to have delivery expedited by the appropriate means.

C

Invasive procedures in labour should be avoided for women with recurrent genital herpes lesions.

✓

The neonatologist should be informed of babies born to mothers with recurrent genital herpes lesions at the time of labour.

✓

Recurrent genital herpes infection is associated with a much smaller risk of neonatal herpes. Where vaginal delivery is associated with recurrent genital HSV lesions, the risk calculated from several studies is 1–3%.^{21,32} This risk must be balanced against the risks to the mother of caesarean section. A cost–benefit analysis derived from American data has suggested that, if all women with an episode of recurrent genital herpes at the onset of labour were to undergo caesarean section, 1583 (range 632–6340) caesarean sections would be performed to prevent one case of herpes-related mortality or morbidity, at a cost of US\$2.5 million/case averted.³³

Evidence level III

For women with recurrent genital HSV lesions who deliver vaginally, prolonged rupture of membranes should be avoided and invasive procedures (fetal scalp electrodes, fetal blood sampling) should not be used.

Where recurrent genital herpes complicates preterm prelabour rupture of membranes, the risk of neonatal transmission is very small and is likely to be outweighed by the morbidity and mortality associated with premature delivery. One prospective study of 29 women with ruptured membranes up to 31 weeks of gestation with active recurrent genital herpes lesions found no cases of neonatal herpes developed in the delivered newborn infants and all neonatal cultures were negative for HSV (0 of 29 cases; 95% CI 0.0–10.4%).³⁴

Evidence level III

7 How can acquisition of genital herpes infection during pregnancy be prevented?

Women may volunteer at their first antenatal visit a history that they or their partner have had genital herpes. Women without a history of genital herpes who have partners with genital herpes should be advised about reducing their risk of acquiring this infection.

C

Identifying women susceptible to acquiring genital herpes in pregnancy by means of type-specific screening for HSV antibodies in pregnancy is not currently indicated.

C

Women who report a history of genital herpes can be reassured that, in the event of an HSV recurrence during pregnancy, the risk of transmission to the neonate is very small, even if genital lesions are present at delivery.^{20,26} Women with no history of genital herpes may reduce their risk of acquiring herpes during pregnancy and of subsequent transmission to the neonate by using condoms or abstaining from sexual intercourse during the third trimester.³⁵ It should also be explained that women can acquire genital herpes through receptive orogenital contact if their partners have orolabial herpes (cold sores).

Asking a pregnant woman at her screening visit whether she or her partner has ever had genital herpes is not an accurate way of determining her risk of acquiring primary HSV infection in pregnancy, because of the prevalence of asymptomatic or unrecognised HSV infection. Sensitive, type-specific serological tests are now commercially available and can accurately determine a woman's susceptibility to HSV infection in pregnancy. It has been proposed that serological testing be undertaken either in early pregnancy³⁶ or in the third trimester.^{1,37} An HSV-seropositive woman can be reassured that her risk of transmission to the neonate is extremely low. An HSV-seronegative woman is susceptible to genital HSV infection. If her partner has a history of genital herpes or is tested and found to be HSV seropositive, the couple can be advised on measures to reduce the woman's risk of acquiring genital herpes (see above). A UK study evaluating the knowledge and attitudes of women to antenatal serum screening for genital herpes found that the population surveyed had a good knowledge about genital herpes and would accept antenatal testing.³⁸

One study has evaluated the use of serum screening for HSV for a hypothetical cohort of women in early pregnancy with no clinical history of HSV infection, using a decision analysis model.³⁹ The study compared universal serum screening and targeted screening (for women estimated to be at high risk of infection) with current care (no screening). Although both screening strategies reduced cases of neonatal transmission and caesarean section deliveries for recurrent herpes, there were very high medical resource costs. As the most recent UK surveillance data (1986-1991) demonstrated a very low incidence of neonatal herpes, it seems unlikely that such a screening programme would be cost-effective at the present time.

Evidence level IV

8. How can postnatal HSV transmission to the neonate be prevented?

Healthcare workers and family members with active HSV infection, such as orolabial herpes or herpetic whitlow, should take measures to avoid transmission of the virus to the neonate.

C

Neonatal herpes may occur as a result of nosocomial or community-acquired infection.^{40,41} Mothers, family members and healthcare workers should be aware of the risk of neonatal transmission from active HSV lesions, including orolabial herpes and herpetic whitlows. Breastfeeding is only contraindicated in the event of a herpetic lesion on the breast.

Evidence level IV

9. Website addresses

British Paediatric Surveillance Unit: <http://bpsu.inopsu.com>
International Herpes management Forum: www.ihmf.org

10. Auditable Standards

1. Appropriate referral and management of women with primary genital herpes.
2. Documentation of delivery decisions for women with recurrent genital herpes.
3. Appropriate management of labour in women with recurrent genital herpes lesions.
4. Notification to neonatologists of neonates exposed or potentially exposed to genital herpes.

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This guideline was produced on behalf of the Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists by:

Dr NM Low-Beer MRCOG, London, and Professor GR Kinghorn, Department of Genitourinary Medicine, Royal Hallamshire Hospital, Sheffield

and peer reviewed by:

British Association of Perinatal Medicine; British Association for Sexual Health and HIV; British Maternal and Fetal Medicine Society; Professor P Brocklehurst FRCOG, Oxford; Mr David Fraser, Norfolk and Northwick University Hospital; Health Protection Agency; Royal College of General Practitioners; Royal College of Midwives; RCOG Consumers' Forum; Dr SB Welch, Consultant Paediatrician, Heartlands Hospital, Birmingham.

The Guidelines and Audit Committee lead reviewers were: Dr TA Mahmood FRCOG, Kirkcaldy, Scotland, and Dr RG Hughes FRCOG, Edinburgh, Scotland.

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

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	Grades of recommendations
Ia Evidence obtained from meta-analysis of randomised controlled trials.	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)
Ib Evidence obtained from at least one randomised controlled trial.	B Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
IIa Evidence obtained from at least one well-designed controlled study without randomisation.	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)
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.	Good practice point
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.	

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.