



NEW ZEALAND HERPES FOUNDATION

Guidelines for the Management of Genital Herpes in New Zealand

10th Edition - 2012

Produced by the Professional Advisory Board (PAB) of the
Sexually Transmitted Infection Education Foundation

Sexually Transmitted Infection Education Foundation resources

Helpline

HERPES

Tollfree 0508 11 12 13

HPV

Tollfree 0508 11 12 13

Website

www.herpes.org.nz

www.hpv.org.nz

Resources

Patient information pamphlets

1. The Facts: A guide for people with Herpes Simplex

Includes -
Genital Herpes - The Facts
Herpes and Relationships
Herpes and Pregnancy
Facial Herpes

2. Herpes: Myth vs Fact

Patient information pamphlets

1. Some Questions and Answers about HPV and Genital Warts

2. A Patient Guide: HPV (wart virus) in perspective

3. Cervical Smears and Human Papilloma Virus Infection (HPV)

4. What everyone should know about Genital HPV (Human Papilloma Virus) Infection and the Cervical Cancer Vaccines

These resources are available through the
Sexually Transmitted Infection Education Foundation

Phone: 09 433 6526

Fax: 09 360 2835

Email: info@herpes.org.nz

or: info@hpv.org.nz

For international resources please see inside back cover.

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The Objectives of the NZHF are:

*To provide support, current educational material and management options
in a caring, friendly, confidential environment for people with genital herpes.*

*To liaise with health professionals, providing a support network to assist in
the responsible management of genital herpes.*

*Ultimately, to improve the social context in which people with genital herpes
live their lives.*

Table of contents

IFC	Sexually Transmitted Infection Education Foundation resources
3	About this document
3	What's new – Changes at a glance
4	Genital herpes – Common misconceptions
5	Genital herpes – Key Points
6	EPIDEMIOLOGY AND TRANSMISSION
3	Epidemiology
7	Transmission
8	Reducing risk of transmission
9	Diagnostic tests
11	Key information to discuss with a patient who asks for a blood test
12	MANAGEMENT OF CLINICAL EPISODES OF GENITAL HERPES
12	Management of first clinical episode
14	Treatment of first episode genital herpes
17	Treatment algorithm – Management of first episode of genital herpes
18	Management of recurrent episodes of genital herpes
20	Treatment of recurrent genital herpes
22	Genital herpes in immunocompromised individuals
23	Treatment algorithm – Management of recurrent episodes of genital herpes
24	GENITAL HERPES IN PREGNANCY
26	Management of pregnant women with first episode genital herpes
27	Treatment algorithm – Management of first episode genital herpes in pregnancy
28	Treatment algorithm – Management of recurrent genital herpes in pregnancy
29	Management of pregnant women with recurrent genital herpes
29	Treatment of genital herpes in pregnancy
30	Use of acyclovir in pregnancy and breastfeeding
30	Prematurity
30	Prevention of HSV in the neonate
31	NEONATAL HSV INFECTION
31	Transmission to the fetus and newborn
32	Disease classification
34	Management of neonatal HSV infection
36	Guidelines for talking to parents of a baby diagnosed with neonatal herpes
37	GENITAL HSV INFECTION IN CHILDHOOD
40	ISSUES IN COUNSELLING
42	Key information for health professionals to give patients in counselling
44	References
47	Members of the Professional Advisory Board
IBC	International resources

About this document

These guidelines have been produced by considering available literature and by basing the recommendations on the available evidence, both local and international. The three levels of evidence used are:

GRADE A: Very strong evidence

Based on well-designed prospective randomised controlled clinical trials.

GRADE B: Fairly strong evidence

Based on evidence from case-control or cohort studies, or clinical trials lacking one or more of the above features.

GRADE C: Weak evidence or firmly held opinion

Based on published case reports, well-written reviews or consensus.

What's new... since the 2009 Guidelines for the Management of Genital Herpes in New Zealand (9th edition)

CHANGES AT A GLANCE

Treatment of first episode genital herpes

- Oral aciclovir 400mg 3 times daily (8 hourly) for 7 days.

Treatment of recurrent genital herpes

Episodic treatment

- Oral aciclovir 800mg (2 x 400mg) 3 times daily for 2 days.
Prescribe 56 x 400mg tablets for patients to be able to self-initiate treatment at onset of symptoms.

Note: Famciclovir is not subsidised or marketed in New Zealand.

Suppressive therapy

- Oral aciclovir 400mg twice daily
- Valaciclovir (Valtrex™) 500mg daily is listed for suppressive treatment of recurrent genital herpes, subject to a Special Authority restriction, in the pharmaceutical schedule
 - **Initial application:** From any practitioner. Approvals valid for 12 months where the patient has genital herpes with two or more breakthrough episodes in any 6 month period while treated with aciclovir 400mg twice daily.
 - **Renewal:** From any practitioner. Approvals valid for 12 months where the treatment remains appropriate and the patient is benefiting from treatment.

GENITAL HERPES – COMMON MISCONCEPTIONS

Patient feedback suggests some health providers still believe that:

-
- ***Most, if not all, genital herpes infections are due to HSV-2.***

FACT: Genital herpes is caused by both HSV 1 and HSV2 although HSV 1 is less likely to cause recurrent symptoms.

- ***Visible genital herpes infection is very typical and does not require diagnostic testing.***

FACT: Herpetic lesions are often atypical and other conditions may cause genital ulceration; genital lesions should be swabbed and tested for HSV.

- ***Herpes simplex virus subtype determination is unnecessary.***

FACT: As HSV 1 and 2 have different natural histories, it is important to ask for specific typing (so patients can be better informed).

- ***Serological testing can be used to diagnose genital herpes in the setting of an active genital ulcer.***

FACT: Serological testing is not recommended as a routine diagnostic or screening tool. It is recommended only in specific clinical scenarios (see page 10).

- ***Herpes simplex virus infection can be ruled out with negative serologic testing.***

FACT: HSV antibodies take several weeks and even months to develop after infection; false negatives and false positives are common.

- ***The 72 hour zoster treatment rule applies to herpes simplex.***

FACT: All first episodes of genital herpes should be treated regardless of timing of onset of symptoms (see page 12).

The purpose of this guideline is to dispel common misconceptions and hopefully improve current management of those with herpes infection.

GENITAL HERPES – KEY POINTS

- Genital herpes is a common infection caused by Herpes Simplex Virus Type One (HSV-1) and Herpes Simplex Virus Type Two (HSV-2) and as many as one in five adults in New Zealand have genital herpes due to HSV-2. Up to 50% of first episode genital herpes is due to HSV-1.
- Genital herpes is under-recognised and under-treated. Minor lesions are common; any recurring localised genital symptoms or lesions should be investigated as possible genital herpes.
- Laboratory confirmation of the diagnosis and typing is important, but should not delay treatment.
- Oral antiviral treatment is safe, effective and generic brands are very cheap.
- Oral antiviral treatment of the first clinical episode should always be offered regardless of the time of symptom onset.
- **The '72 hour' herpes zoster rule does NOT apply to first episode genital herpes infection.**
- Antiviral therapy of recurrent genital herpes may be suppressive or episodic. Many patients prefer suppressive antiviral therapy. It is particularly recommended for those with frequent and/or severe recurrences or associated psychosocial morbidity. For those choosing episodic antiviral therapy, it is more effective when patients start therapy themselves at the first signs of a recurrence; this requires anticipatory prescribing.
- Neonatal HSV infection is a rare but potentially fatal disease of babies, occurring within the first 4-6 weeks of life. Symptoms are non-specific and a high index of suspicion is required. Most neonatal HSV infections are acquired at birth, generally from mothers with an unrecognised first genital herpes infection acquired during pregnancy.
- Specialist advice on management should be sought for a woman with a history of genital herpes and active lesions at term and especially in the high risk situation of a first episode up to 6 weeks prior to delivery.

A diagnosis of genital herpes can have a profound effect. Patients tell us they want –

- To be given accurate up-to-date information.
- To be provided with the best treatment available.
- To be involved in decisions about treatment and management.
- To be referred for specialist care or advice when appropriate.

The NZHF has a range of resources to assist patients and clinicians.

Phone: Herpes Helpline toll free **0508 11 12 13**

Website: www.herples.org.nz

GENITAL HERPES IN PREGNANCY

KEY POINTS

- Neonatal HSV infection is a rare, but potentially fatal, disease of babies occurring within the first 4-6 weeks of life.
- Most neonatal HSV infections are acquired at birth, generally from mothers with an unrecognised genital herpes infection acquired during pregnancy.
- All women should be asked by their primary caregiver at their first antenatal visit if they or their partner have ever had genital herpes and given information on the potential risks of transmission in pregnancy; this includes the risk of genital HSV-1 from oral-genital contact.
- Women with genital herpes lesions during their pregnancy should be referred to a specialist obstetrician and/or a sexual health physician.

Concerns around herpes infection during pregnancy tend to relate to the risk of neonatal infection. Disseminated maternal herpes in pregnancy (from genital or oro-labial infection) is rare, but may be life-threatening; viraemia in the mother during primary infection may result in neonatal multi-organ involvement with significant mortality. The diagnosis may be delayed if vesicular skin lesions are absent or sparse.^{39,40}

Neonatal herpes is a rare but potentially serious infection, which may be associated with significant morbidity and mortality. About 90% of neonatal herpes infections are acquired during labour through direct contact with infected genital secretions. In 5% of cases the infection is acquired in utero (either via ascending infection or transplacentally secondary to maternal viraemia) and in 5% of cases the infection is acquired post partum.⁴¹

Primary maternal infection before the 20th week of pregnancy may be associated with miscarriage,⁴² and in the second and third trimesters may be associated with preterm delivery. Rarely, primary maternal infection may result in disseminated infection of the fetus with skin lesions, chorioretinitis or microcephaly or hydrocephalus at birth.⁴³ The long-term outlook for these infants is very poor. A minority with late intrauterine HSV infection will present at delivery with skin or eye lesions. The prognosis for successful anti-viral therapy in these infants is far better than that for newborns with more long-standing intrauterine infection.⁴⁴ Antenatal recurrent disease, where HSV is not shed at delivery, does not have an adverse affect on neonatal outcome and the risk of intrauterine fetal infection from recurrent maternal HSV infection appears to be very low. A nested case-control serology study assessing HSV-2 antibodies in stored serum samples from 283 women with a fetal loss after 20 weeks compared to 970 randomly selected women from a large source population found no association between herpes simplex infection and fetal loss.⁴⁵

Several factors influence the risk of a newborn acquiring HSV infection at the time of delivery, the most important of which is whether the mother has newly acquired vs recurrent genital disease.^{46,47} **The greatest risk of perinatal transmission is when a previously seronegative woman has a primary first episode of genital herpes near or at the time of delivery.** Under such circumstances the risk of neonatal HSV infection is 57%, while vertical transmission rates of 25% are found in those with a non-primary first episode (infection with one virus type in the presence of antibodies to the other virus type) near or at the time of delivery.

Although reactivation of HSV-1 is less than common than that of HSV-2, there is evidence that the reactivated HSV-1 may be more readily transmitted to the neonate. Although developmental abnormalities are less common in neonatal survivors of HSV-1 infection compared to HSV-2, the mortality of disseminated infection is similar and the same strategies are required for prevention of both HSV-1 and HSV-2.⁴⁸

Transmission rates are lowest for women who acquire herpes before pregnancy, with the risk being about 0.05% for such women who have no signs or symptoms of an outbreak at delivery.^{46,49} If lesions are present at delivery, there is a small but still reasonable risk of transmission of 0.25-3% because of protection from maternal antibodies passing across the placenta⁴⁷ Specifically, the risk for transmission of reactivated HSV-2 infection appears to be less than 1%.⁵⁰

Women with HIV and HSV-2 co-infection have a greater risk of transmitting HSV-2, as HSV-2 shedding is increased in HIV co-infected women.⁵¹

Of infants with proven HSV infection, 80% have no documented history of herpes infection in either the mother or her partner.

Mode of delivery

There are no randomised controlled trials to guide optimal delivery management for pregnant women with genital herpes.

In a large prospective cohort study of women who had herpes cultures taken in labour, HSV was isolated in 202 women and, overall, neonatal transmission occurred in 10 (5%).⁴⁷ Caesarean delivery significantly reduced the HSV transmission rate in women from whom HSV was isolated (1 of 85 [1.2%] caesarean vs 9 of 117 [7.7%] vaginal). Risk factors for neonatal HSV infection included first-episode infection, HSV-1 vs HSV-2 isolation at the time of labour, the use of invasive monitoring, premature delivery and young maternal age. None of the 140 women with viral shedding due to HSV-2 reactivation infected their babies, compared to 2/11 women with HSV-1 reactivation. Of 26 first episode cases, transmission occurred in 8. There was a high caesarean section rate in those noted to have genital lesions in labour. The data from this study was pooled with two other cohorts (from the USA and Sweden) and provided further evidence that during reactivation HSV-1 may be more readily transmissible to the neonate than HSV-2. This pooled cohort study also showed that maternal HSV-1 antibody does not offer significant protection against HSV-2.⁵²

However caesarean section is not completely protective, as transmission of infection has occurred occasionally in the presence of intact membranes. Prolonged contact with infected secretions may further reduce the benefits of abdominal delivery.⁴³

No definitive studies have been carried out on the relationship between the duration of rupture of membranes in the presence of clinical lesions and the transmission of HSV to the fetus. Previously, 4 hours has been suggested as a cut-off time beyond which caesarean section may be no longer beneficial. However, the ACOG guideline states that there is no evidence that there is a duration of premature rupture of membranes beyond which the fetus does not benefit from caesarean delivery.⁵³

Because the risk of maternal-fetal transmission is high when primary infection is acquired within 6 weeks of delivery, maternal and neonatal aciclovir therapy should be considered if there has been membrane rupture for more than 4 hours or where a vaginal delivery is unavoidable.⁵⁴

In the case of recurrent genital herpes, maternal antibodies are protective and it has been argued that the benefits of caesarean section are low in this group of women, even if lesions are present at the time of delivery. Policy in the USA has been to offer delivery by caesarean section if the woman has signs or symptoms of a recurrence at the onset of labour and there is data to support this approach, as discussed above.⁴⁷ In the Netherlands, however, since 1987 it has been the policy not to offer women caesarean section in the presence of a recurrence at term and there has not been a resultant increase in the incidence of neonatal herpes (26 cases of neonatal herpes 1981-1986 compared to 19 cases 1987-1991).⁵⁵ A follow-up audit 1999–2005 concluded that a low rate of neonatal infection in the Netherlands continues despite a low caesarean section rate to prevent neonatal infection and there was therefore not a need to revise the current guidelines in that country.⁵⁶ In other countries, guidelines recommend that women who have signs or symptoms of a recurrent infection in labour should be offered caesarean section, but as a relative, rather than absolute, indication for abdominal delivery.⁵⁷⁻⁵⁹ It has also been shown that the presence of symptoms at delivery correlates relatively poorly with the detection of HSV from genital sites or lesions by culture or PCR.⁶⁰ The development of rapid PCR testing for detection at the time of labour is currently being investigated.⁴⁸

Use of prophylactic aciclovir

Small studies have shown that prophylactic use of aciclovir from 36 weeks decreases the number of clinical recurrences and reduces the need for caesarean section, but treatment does not eliminate viral shedding completely.^{55,61-63} Two meta-analyses have confirmed that there is a reduction in clinical recurrences at delivery, a reduction in caesarean section for active herpes, and a reduction in viral shedding.^{64,65} **GRADE B**

However, there are theoretical concerns that maternal aciclovir therapy may suppress the production of neutralising antibodies to the immunogen, glycoprotein D, thus having an effect on passive immunity to the fetus, and may suppress rather than treat newborn infections, thus leading to a delay in presentation of neonatal disease. In the absence of definitive data, it is recommended that prophylactic aciclovir from 36 weeks should be used selectively, rather than routinely offered, for women with a history of recurrent genital herpes, e.g. to those women who have had an episode in the current pregnancy, and that women should be given the same advice on postnatal surveillance of their babies as those who have not had suppressive therapy. This may be updated when more information on the effects of aciclovir on the neonate is available.

More frequent dosing may be required during pregnancy because of increased drug clearance. A small study of plasma levels of aciclovir at delivery in women on suppressive acyclovir at a dosage of 400mg tds from 36 weeks showed that levels were often suboptimal despite good adherence. Time since the last dose was correlated with levels rather than duration of labour. Suboptimal aciclovir levels at the time of delivery could lead to viral shedding although none of the women in the study had clinical recurrences.⁶⁶

Management of pregnant women with first episode genital herpes

First and second trimester acquisition

Management of the woman should be in keeping with her clinical condition, using aciclovir in standard doses as indicated (see page 30). **GRADE C**

Provided delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated. Continuous aciclovir in the last 4 weeks of pregnancy reduces the risk of both a clinical recurrence at term and delivery by caesarean section. However, the effects on the neonate have not been fully evaluated.

For further management advice, see **Management of Pregnant Women with Recurrent Genital Herpes**, page 29.

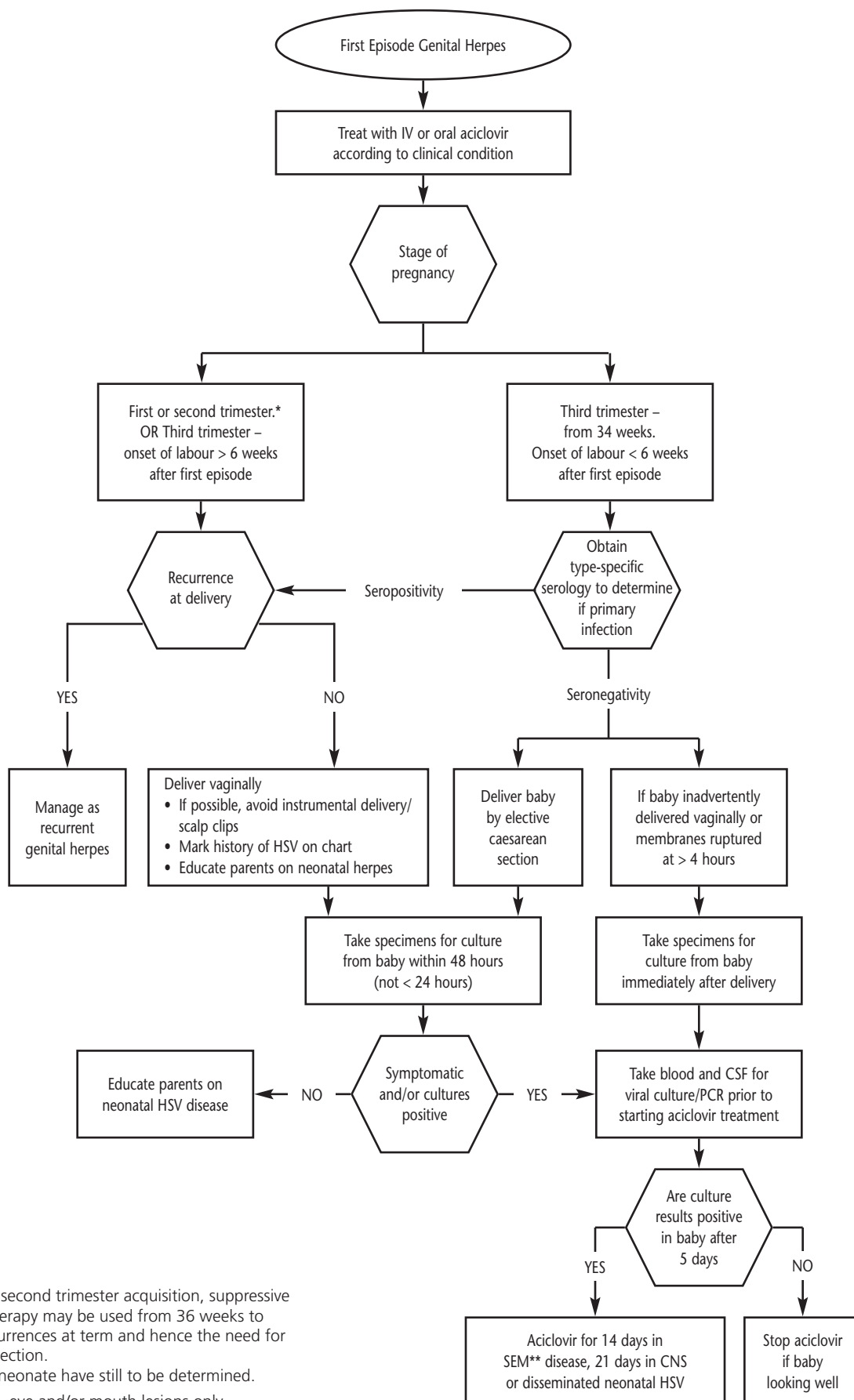
Third trimester acquisition

Note: The first clinical episode may not be due to a primary infection, as previous infection may not have been recognised. Type specific culture or PCR and serological testing in conjunction with clinical evaluation will help identify primary HSV in pregnancy. All results should be discussed with an expert knowledgeable in interpreting these results and who is aware of the sensitivity and specificity of available testing methods. Consider treatment with aciclovir (see page 30).

Delivery should be by caesarean section, particularly in those women infected within 6 weeks of delivery because of high rates of asymptomatic shedding of HSV and insufficient time for a complete antibody response between infection and delivery. **GRADE B**

If vaginal delivery is unavoidable, consider treatment of mother with aciclovir and request an urgent referral to a paediatrician experienced in HSV infection (see **Neonatal HSV Infection**, page 31). **GRADE C**

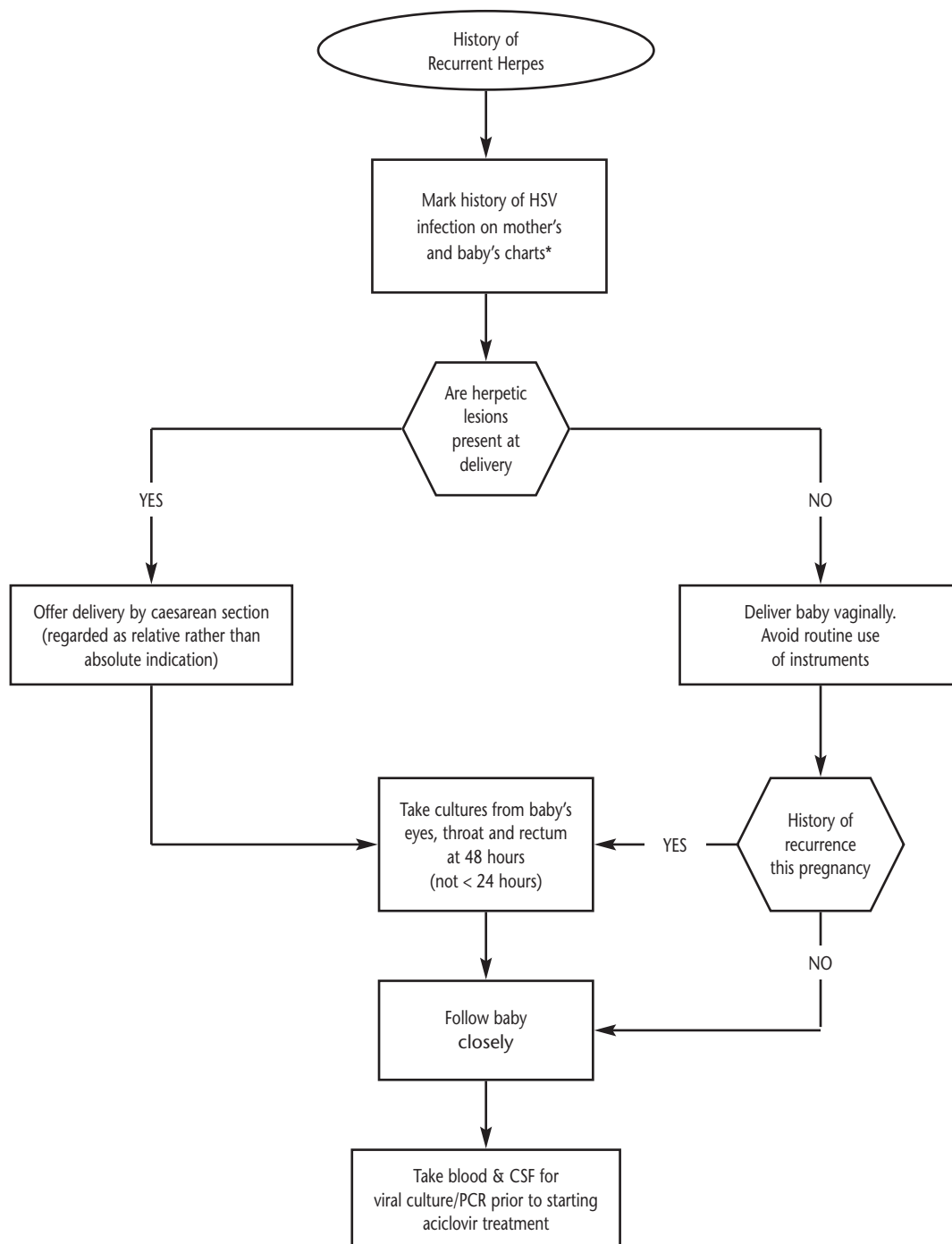
Management of first episode genital herpes in pregnancy (in consultation with a specialist)



* For first or second trimester acquisition, suppressive aciclovir therapy may be used from 36 weeks to reduce recurrences at term and hence the need for caesarian section. Effects on neonate have still to be determined.

** SEM – skin, eye and/or mouth lesions only.

Management of recurrent genital herpes in pregnancy (in consultation with a specialist)



* For women with recurrences during pregnancy, suppressive aciclovir therapy can be considered to reduce recurrence at term and hence the need for caesarean section. Effects on the neonate have still to be determined.

Management of pregnant women with recurrent genital herpes

Document the history in both mother's and infant's notes. Symptomatic recurrences during third trimester are usually brief and vaginal delivery is appropriate if no lesions are present at delivery.⁴⁴ Prophylactic use of aciclovir from 36 weeks decreases the number of clinical recurrences and reduces the need for caesarean section, but treatment does not eliminate viral shedding completely (see above) and should be used selectively rather than routinely. **GRADE B**

Sequential cultures in the third trimester to predict viral shedding at delivery are not indicated.⁶⁷ Caesarean section should not be performed in women who do not have lesions at delivery.⁴⁴ **GRADE B**

In women who have recurrent genital lesions at onset of labour:

- It is common practice to deliver by caesarean section because of the small risk of infection in the neonate.
- However, because the fetal risk is low, this must be set against the risks to the mother of caesarean section and this is therefore regarded as a relative rather than absolute indication for caesarean section.⁴⁴ **GRADE C**
- Ideally, this scenario should be discussed with the woman early in pregnancy by the primary caregiver.
- Caesarean section does not itself provide total protection.⁶⁸
- If vaginal delivery occurs, scalp electrodes and instruments should not be used unless there is a clear obstetrical indication as skin trauma may increase the risk of transmission of HSV.
- Intrapartum aciclovir may be considered based on anecdotal evidence, although there have been no trials to assess the value of such therapy.
- In women who have recurrences in late pregnancy, starting aciclovir 400mg tds should reduce the duration of symptoms and viral shedding. There are no studies documenting the duration of viral shedding in this situation, but it has been stated that vaginal delivery is safe if labour commences after 48 hours of treatment with aciclovir.⁶⁹ This recommendation is consistent with the principles of episodic treatment.

Other issues in perinatal care

Investigation and surveillance in the neonate

See **Management of Neonatal HSV Infection**, page 34.

Treatment of genital herpes in pregnancy

KEY POINTS

- The risk of maternal-fetal transmission (MFT) is highest with primary genital herpes infection during labour or within 6 weeks of delivery. Caesarean section is indicated.
- Women with a past history of genital herpes and no recurrences in pregnancy can be reassured that the risk of MFT is extremely low.
- Recurrent lesions at term are a relative (not absolute) indication for caesarean section. The risk of MFT is low from recurrent lesions during labour, although may be greater with HSV-1 than HSV-2.
- Suppressive aciclovir from 36 weeks gestation may reduce the chance of a recurrence at term and hence the need for caesarean section. This should be used selectively rather than routinely, for example for women who have had an episode during pregnancy.
- Specialist obstetric and paediatric advice on management and anticipatory guidance should be sought for a woman with a history of genital herpes and active lesions at term and especially in the high risk situation of a first episode within 6 weeks of delivery (see **Neonatal HSV Infection**, page 31).

Use of aciclovir in pregnancy and breastfeeding

Data collected via the Aciclovir Pregnancy Register (1984-99) found the observed rates and types of birth defects for 1234 pregnancies exposed to aciclovir did not differ significantly from those in the general population.⁷⁰ Some studies on the use of valaciclovir (an aciclovir prodrug) from 36 weeks gestation have addressed toxicity issues and identified no safety concerns in mothers, fetuses or neonates.^{54,71} Monitoring in the neonates included assessment of white cell counts, renal and hepatic function. The studies were underpowered to confirm safety with certainty, but the results, in conjunction with the lack of reported adverse events from other trials of prophylactic aciclovir and valaciclovir in late pregnancy, are reassuring.

While aciclovir is not licensed for use in pregnancy, there is substantial clinical evidence supporting its safety. Women who are inadvertently exposed to aciclovir in early pregnancy can be informed that the available information is reassuring and the use of aciclovir can be recommended where clinically indicated.⁷²

There are no established protocols for the use of aciclovir in pregnancy, but the following regimens are frequently used:

First episode:

- Aciclovir 400mg orally 3 times daily for 7 days.

First episode (severe disease) or in immunosuppressed:

- Aciclovir 5mg/kg IV (over 60 minutes) 8-hourly until able to switch to oral therapy, based on symptoms.

Recurrent disease suppressive therapy:

- Aciclovir 400mg orally 3 times daily (in consultation with a specialist; more frequent dosing indicated because of increased clearance in pregnancy).

The American Academy of Pediatrics has approved use of aciclovir for treating first episode or recurrent genital herpes in breastfeeding mothers. Although concentrations are high in breast milk and the baby, toxicity is low.⁷³ **GRADE B**

Prematurity

One study has shown expectant management of 29 women with preterm premature rupture of membranes at <31 weeks gestation, complicated by active recurrent genital herpes, was not associated with neonatal transmission. It was concluded that the risks of prematurity outweighed the risks of transmission of infection in the presence of a recurrent episode.⁷⁴ The mean duration of membrane rupture was 13.2 days (range 1-35 days), 45% were delivered by caesarean section and 8% received antiviral therapy for control of symptoms. Little data is available on the management of preterm premature rupture of membranes in association with primary herpes simplex infection.

Prevention of HSV in the neonate

All women should be asked at the first antenatal visit if they or their partner have had genital herpes. A study of 3192 pregnant women and their partners identified that 22% of women were at risk of HSV-1 or HSV-2. ⁷⁵ Of 582 women susceptible to HSV-1, 14 women or 2.5% (3.5% adjusted for length of gestation) acquired HSV-1; the only independent risk factor was a history of a partner with oral herpes. Of 125 women susceptible to HSV-2 infection, 17 or 14% (20% adjusted for length of gestation) acquired HSV-2 infection. Also, the risk of becoming infected was eight times greater in relationships of a year or less, than for those in longer duration relationships. Most newly acquired infections were subclinical.

Although there is no clear evidence to support guidelines in the situation of the partner with a history of previous herpes infection, the following are recommended on theoretical grounds: **GRADE C**

- Female partners of men with genital herpes should avoid sex when lesions are present.
- Consistent use of condoms throughout pregnancy may prevent acquisition.
- Suppressive therapy should be considered in the male partner if the couple is discordant for antibodies to HSV-2.
- Pregnant women should be advised of the risk of acquisition of HSV-1 from oral-genital contact.
- Parents, staff and relatives/friends with active oral lesions should be advised about the risk of post-natal transmission.

Although routine serological screening in pregnancy has been recommended by some authors, universal screening is not likely to be cost effective because of the high number needed to treat to prevent a single case of neonatal herpes.