GENITAL HERPES IN PREGNANCY

KEY POINTS

- The risk of maternal-fetal transmission (MFT) is high in primary genital herpes infection if acquired at the time of labour (about 50%) or within 6 weeks prior to delivery. Delivery by 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. Maternal antibodies are protective.
- Recurrent lesions at term are a relative (not absolute) indication for caesarean section. The risk of MFT is low from recurrent lesions during labour (1–3%), although may be greater with HSV-1 than HSV-2 based on a cohort study of viral shedding at delivery. Management of this scenario should be discussed with the woman antenatally.
- There is an increased incidence of viraemia in primary herpes infection in pregnancy. Herpes simplex infection should be considered in the differential diagnosis in the management of the acutely unwell pregnant woman.
- Antiviral medications, particularly aciclovir, have been widely used in pregnancy without apparent adverse sequelae. In general, pregnant women (any trimester) should be offered treatment as for non-pregnant women following a discussion regarding the relative benefits versus possible disadvantages.
- Suppressive antivirals from 36 weeks gestation may reduce the chance of a recurrence at term and hence the need for caesarean section. An increased frequency of administration is recommended because of the increased plasma volume in pregnancy.
- 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.
- The use of antiviral medications and delivery by caesarean section may not be completely protective. Women should be given the same advice on postnatal surveillance of their babies regardless of use of antiviral treatment or mode of delivery.
- Specialist obstetric and paediatric advice on management should be sought for a woman with active recurrent lesions at the time of delivery and especially in the high risk situation of a first episode within 6 weeks of delivery (see **Neonatal HSV Infection**, page 25).

Maternal Fetal Transmission

Primary infection

Neonatal herpes is a rare but potentially serious infection, which may be associated with significant morbidity and mortality. Infection may be acquired antenatally, at the time of delivery or post-partum:

- About 85–90% 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).
- In 5–10% of cases the infection is acquired post partum.[35]

Primary maternal infection in early pregnancy may be associated with miscarriage,[36] 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.[37] 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.[38]

Recurrent infection

Antenatal recurrent disease, where HSV is not shed at delivery, is rarely associated with adverse neonatal outcomes. The risk of intrauterine fetal infection from recurrent maternal HSV infection is extremely low:[39]

- 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.[40]
- One cohort found that untreated recurrent genital herpes infection may predispose to preterm delivery which may be prevented by the use of suppressive antiviral treatment. Further studies are required to confirm this finding.[41]

Comparison between primary and recurrent infection at delivery

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.[42,43] **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 50%.

Although reactivation of HSV-1 is less common than that of HSV-2, there is evidence that reactivated HSV-1 may be more readily transmitted to the neonate. The same strategies are required for prevention of both HSV-1 and HSV-2.[44]

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.[42,45] Maternal antibodies cross the placenta and are protective. If lesions are present at delivery, there is a small risk of transmission of 0.25–3%.[43] Specifically, the risk for transmission of reactivated HSV-2 infection appears to be less than 1%.[46]

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.[47]

Of infants with proven HSV infection, 80% have no documented history of herpes infection in either the mother or her partner. The decreasing prevalence of HSV-1 in childhood increases the susceptibility of young adults to genital HSV-1 including women of reproductive age and hence increases the risk of neonatal HSV.[48]

Use of Antivirals in Pregnancy and Breastfeeding

Aciclovir has been used widely in pregnancy. There is less experience with valaciclovir but it is expected that valaciclovir as a prodrug of aciclovir should be safe. In the majority of situations, the benefits of antiviral therapy outweigh possible risks.

Antiviral therapy is indicated for treatment of primary and recurrent episodes as in non-pregnant women and for prophylaxis to reduce the risk of recurrence at the time of delivery. An increased frequency of dose is indicated in late pregnancy because of an increased plasma volume.

The following is a summary of the available evidence on the use of antivirals in pregnancy:

- Data collected via the Aciclovir Pregnancy Register (1984-99) on 1,234 infants exposed to aciclovir in pregnancy and in 1,804 infants exposed to aciclovir, valaciclovir or famciclovir in first trimester in a large Danish cohort demonstrated that there was not an observed increase in birth defects compared to the general population. This data is reassuring although the numbers are insufficient to assess individual defects.
- 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.[49-52] 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.[53,54] Grade B
- Aciclovir has been categorised as B3 in the Australian TGA Prescribing Medicines in Pregnancy database on the basis of fetal animal effects of unknown relevance to humans.
- A possible association between antiherpetic medications and gastroschisis has been reported from a case control study but numbers of affected infants were small and the association was unproven.
- There are theoretical concerns that maternal antiviral therapy may suppress rather than treat newborn infections, thus leading to a delay in presentation of neonatal disease.
- 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.[55] Grade B

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

First episode

Valaciclovir 1g bd for 7/7

- Alternative: Aciclovir

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

- Valaciclovir 500 mg **bd**
- Aciclovir 400mg orally 3 times daily (more frequent dosing indicated because of increased clearance in pregnancy)

Mode of Delivery

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

Primary infection

Caesarean section has been demonstrated to significantly reduce vertical transmission in women with primary infection in late pregnancy or at the time of delivery.

Recurrent infection

Because the risk of vertical transmission in recurrent disease is low there has been debate about the benefit of delivery by caesarean section in women who have recurrent episodes at the time of labour. In the US delivery by caesarean section in this situation is recommended but in the Netherlands there has been a policy of offering vaginal delivery for recurrent genital herpes at the time of delivery since 1987 without an apparent increase in neonatal herpes infection.

It has been shown that the presence of symptoms at delivery correlates relatively poorly with the detection of HSV from genital sites or lesions by HSV PCR. Assessment of viral shedding is based on clinical assessment.[56]

Efficacy of caesarean section in reducing maternal fetal transmission

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.[57]

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, there is no evidence that there is a duration of premature rupture of membranes beyond which the fetus does not benefit from caesarean delivery.[58]

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.[59]

Observational study data

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%).[43] 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
  - Of 26 first episode cases, transmission occurred in 8.
- HSV-1 vs HSV-2 isolation at the time of labour
  - None of the 140 women with viral shedding due to HSV-2 reactivation infected their babies.
  - HSV-1 reactivation in 2/11 women resulted in neonatal infection.
- The use of invasive monitoring.
- Premature delivery.
- Young maternal age.

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.[60]

Audit data

In the Netherlands 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.

- There were 26 cases of neonatal herpes 1981–1986 before the change in policy compared to 19 cases 1987–1991.[48]
- A follow-up audit 1999–2005 concluded that there was again a low rate of neonatal infection in the Netherlands despite a low caesarean section.[61]
- A higher rate of neonatal infection 2006–2011 was attributed to failure of adherence to the guideline recommending caesarean section for primary infection in late pregnancy. The recommendation for vaginal delivery for recurrent episodes remain unaltered.[62]

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]

In summary, there is a lack of robust evidence to guide management in the case of recurrent lesions at the onset of labour. Traditionally delivery by cesarean section has been offered and ideally discussion about the relative risks should occur antenatally in the event of this scenario. Because the risk of transmission is low (1–3%) some women may opt for a vaginal delivery. Factors such as prematurity, HSV-1 rather than HSV-2 and an expected long labour which may all predispose to maternal fetal transmission should be considered.

Special Situations in Pregnancy

Disseminated infection

Disseminated infection 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.[63,64]

Hospital admission and the use of intravenous aciclovir are required for severe disease in pregnancy. The diagnosis of disseminated disease should be considered in any woman presenting with systemic disease in pregnancy.

Premature prelabour rupture of membranes in primary infection

Little data is available on the management of preterm prelabour rupture of membranes in association with primary herpes simplex infection. Multidisciplinary discussion is required taking into consideration the gestation reached. Treatment with aciclovir 5mg/kg 8 hourly should be administered pending delivery. Caesarean section is considered to be beneficial despite prolonged rupture of membranes. Corticosteroids are not contraindicated.[58]

Premature prelabour rupture of membranes in recurrent infection

One study has shown that 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.[65] 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.

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.[56] 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

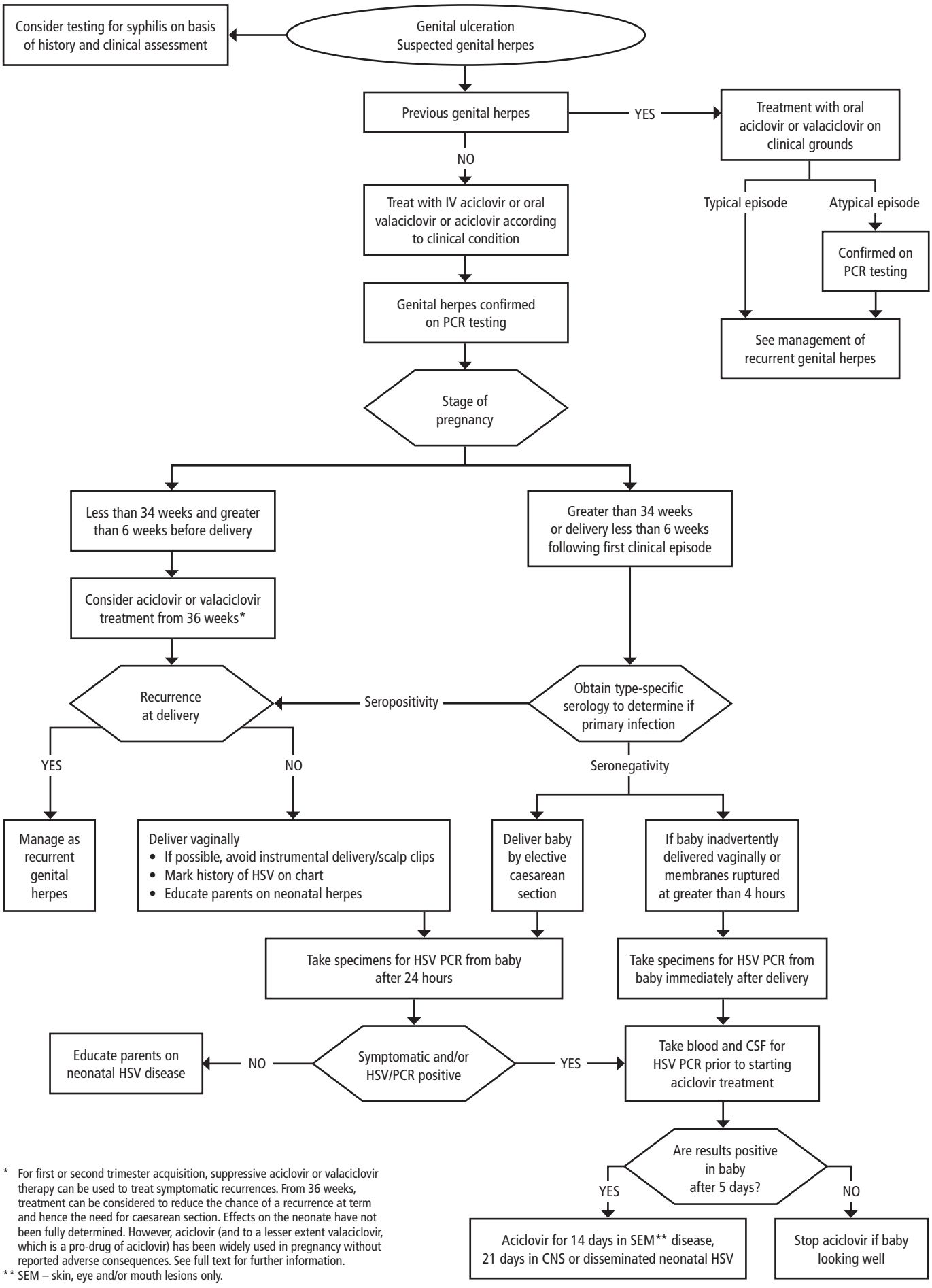
- Female partners of men with genital herpes should avoid sex when lesions are present.
- Asymptomatic female partners of men with genital herpes should have serology to check their HSV status.
- Consistent use of condoms throughout pregnancy may prevent acquisition.
- Suppressive therapy should be considered 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. If partner has oral herpes and HSV status unknown, avoid oral sex.
- 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.[66]

Summary of Clinical Management of First Episode Genital Herpes in Pregnancy

Note: All women with a history of genital herpes infection should be given information on postnatal neonatal surveillance. No interventions are completely protective against maternal fetal transmission.

Management of Women with Suspected Genital Herpes in Pregnancy
(in consultation with a specialist)



* For first or second trimester acquisition, suppressive aciclovir or valaciclovir therapy can be used to treat symptomatic recurrences. From 36 weeks, treatment can be considered to reduce the chance of a recurrence at term and hence the need for caesarean section. Effects on the neonate have not been fully determined. However, aciclovir (and to a lesser extent valaciclovir, which is a pro-drug of aciclovir) has been widely used in pregnancy without reported adverse consequences. See full text for further information.

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

First Episode Genital Herpes: First and Second Trimester Acquisition

- Management of the woman should be in keeping with her clinical condition, using antivirals in standard doses as indicated (see **page 19**) for primary and recurrent episodes. GRADE C
- Provided delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated.
- Continuous antivirals in the last 4 weeks of pregnancy reduce 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 23.

First Episode Genital Herpes: 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 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.*

- Offer treatment with aciclovir or valaciclovir according to clinical condition as per non-pregnant individuals (see **page 19**).
- Offer suppressive valaciclovir 500mg bd or aciclovir 400mg tds to reduce viral shedding and risk of recurrences.
- 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 intravenous aciclovir treatment of the mother and request an urgent referral to a paediatrician experienced in HSV infection (see **Neonatal HSV Infection**, page 25). GRADE C

Management of Pregnant Women with Recurrent Genital Herpes

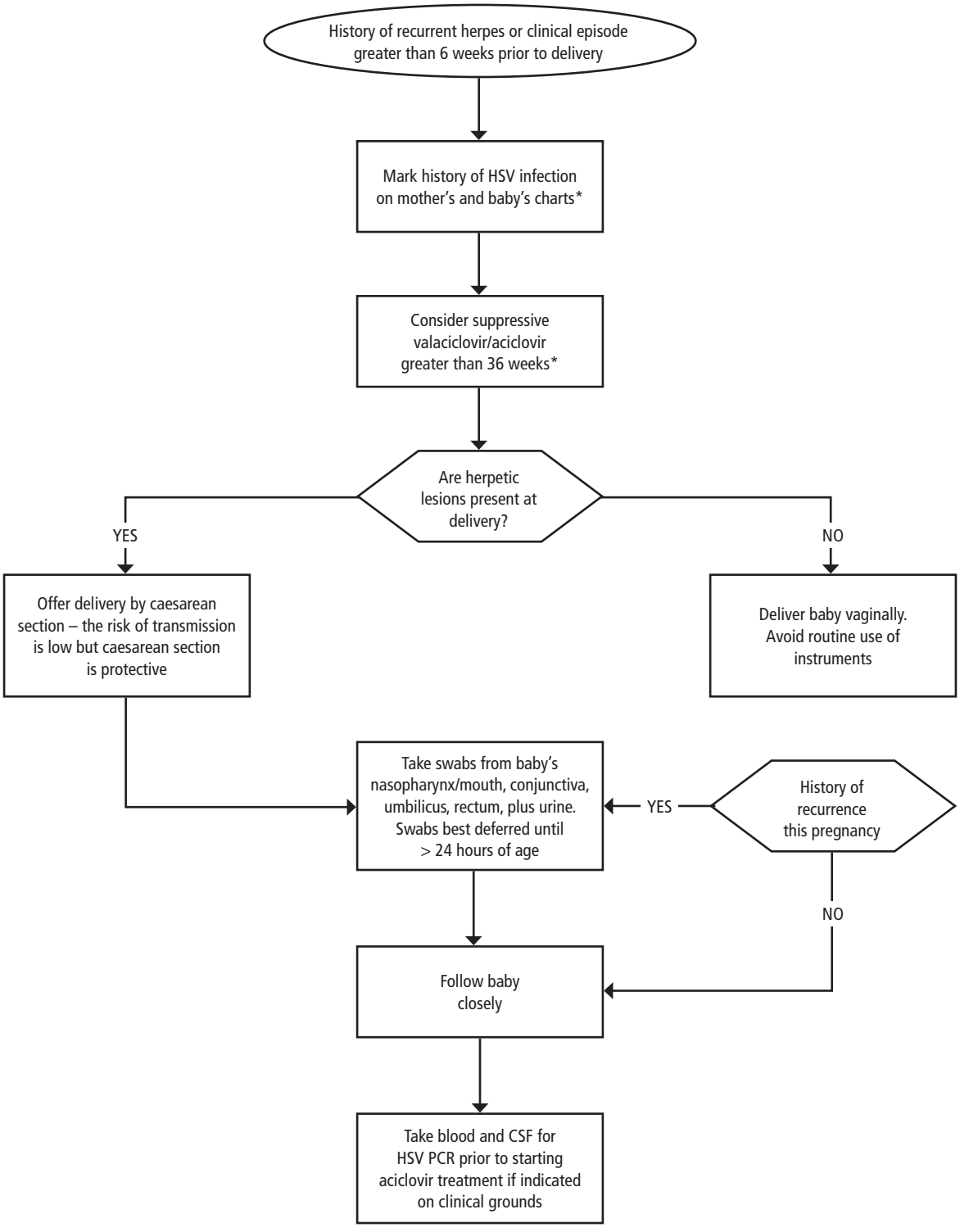
- Document the history in both mother's and infant's notes.
- Symptomatic recurrences during pregnancy are usually brief but can be treated with oral antivirals if troublesome, using the standard non-pregnancy regimens in 1st and 2nd trimesters.
- Prophylactic use of aciclovir 400mg tds or valaciclovir 500mg bd from 36 weeks decreases the number of clinical recurrences and reduces the need for caesarean section GRADE B
- Vaginal delivery is appropriate if no lesions are present at delivery.[38]
- Sequential testing in the third trimester to predict viral shedding at delivery is not indicated.[67]
- Caesarean section should not be performed in women who do not have lesions at delivery.[38] 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.[38] GRADE C
  - Ideally, this scenario should be discussed with the woman early in pregnancy by the primary caregiver in conjunction with specialist advice.
  - The risk of maternal fetal transmission is higher with shedding of HSV-1 than with HSV-2.
- 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 IV aciclovir may be considered based on anecdotal evidence, although there have been no trials to assess the value of such therapy.
- In a woman who presents with a recurrent episode in late pregnancy antiviral treatment will 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 antivirals.[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 27.

Management of Women with History of Genital Gerpes Prior to Pregnancy and Women with First Clinical Episode Greater than 6 Weeks Prior to Delivery (in consultation with a specialist)



* For women with recurrences during pregnancy, suppressive aciclovir or valaciclovir therapy can be used to treat symptomatic recurrences. From 36 weeks treatment can be considered to reduce the chance of a recurrence at term and hence the need for caesarean section. Effects on the neonate have not been fully determined. However, aciclovir (and to a lesser extent valaciclovir, which is a pro-drug of aciclovir) has been widely used in pregnancy without reported adverse consequences. See full text for further information.