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 placenta[47] 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 aciclovir 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.

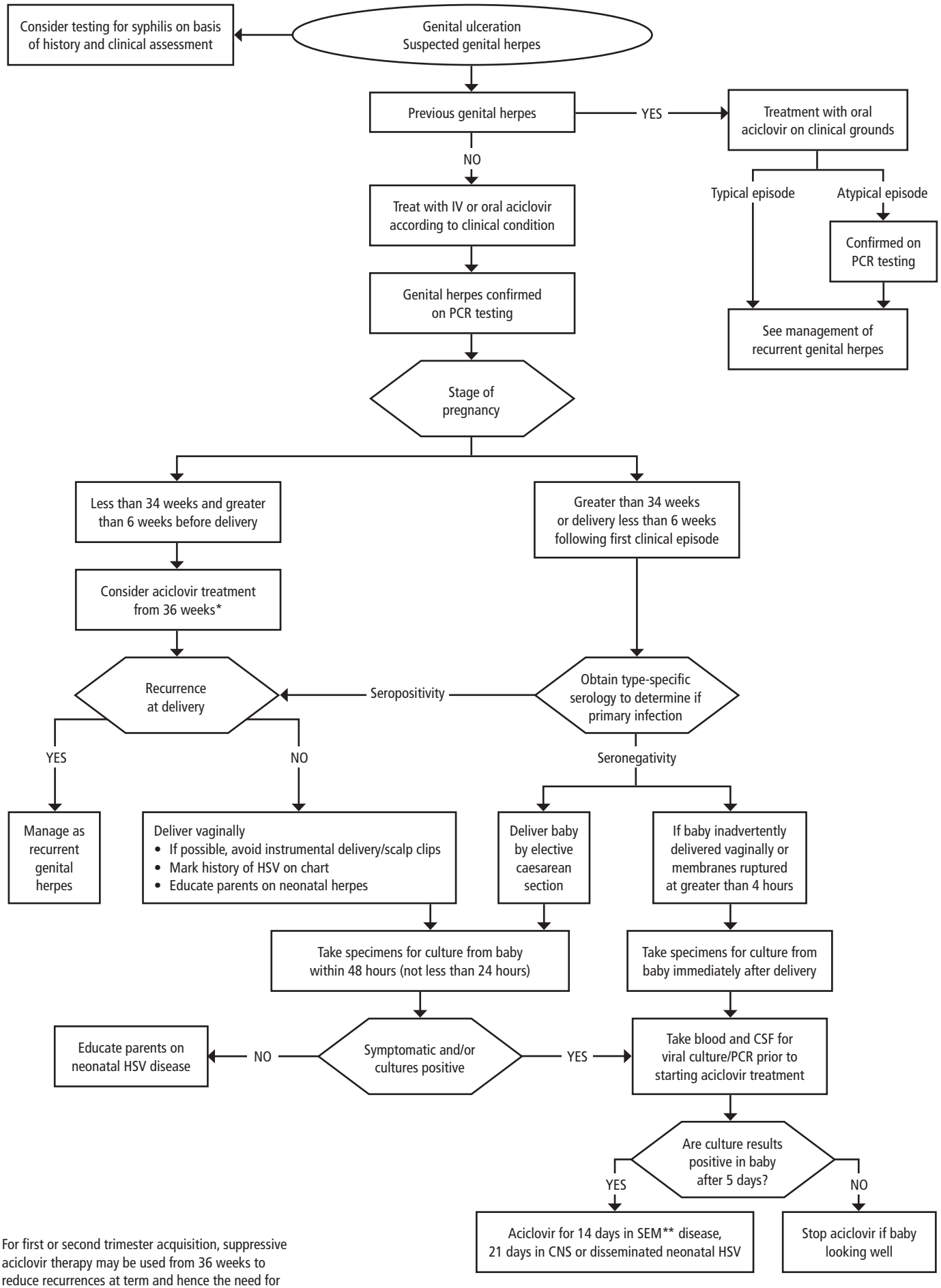
Third trimester acquisition

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 valaciclovir/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 valaciclovir/aciclovir and request an urgent referral to a paediatrician experienced in HSV infection (see **Neonatal HSV Infection**, page 31). GRADE C

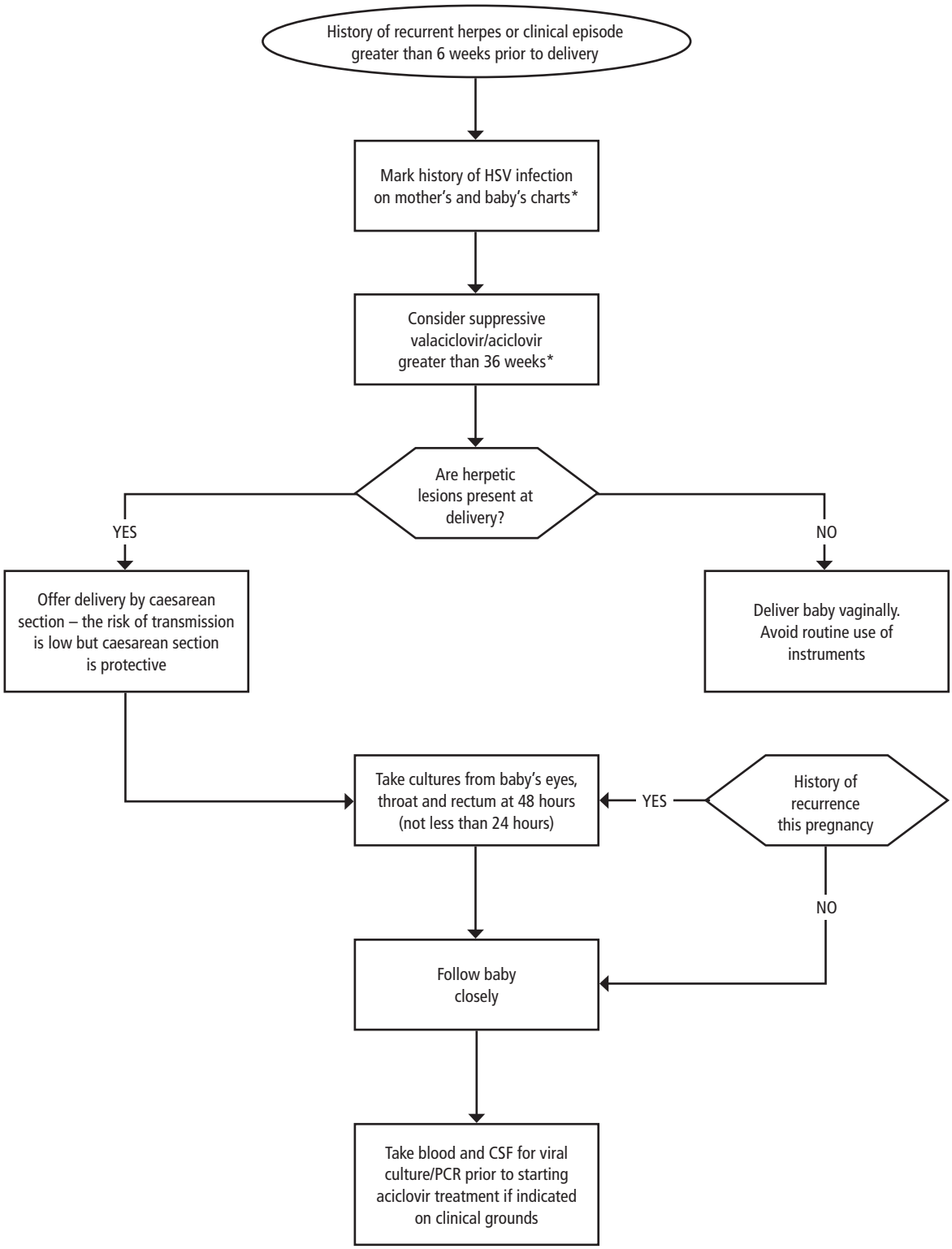
Management of women with suspected genital herpes in pregnancy
(in consultation with a specialist)



* 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 caesarean section.
Effects on neonate have still to be determined.

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

Management of women with history of genital herpes 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 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 33.

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 1,234 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:

- Valaciclovir.
- 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.
- 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.[76]