Clinical Guideline

GENITAL HERPES IN PREGNANCY AND THE NEWBORN, MANAGEMENT OF

SETTING	**Maternity and Neonatal services for University Hospitals Bristol**
FOR STAFF	**Midwives, Obstetricians, Neonatologists**
PATIENTS	**Pregnant women with past or present history of genital herpes; Infants born to mothers with history of genital herpes**

GUIDANCE

Referral to a genitourinary physician should be made and management of the woman should be in line with her clinical condition, which will involve a five-day course of oral aciclovir in standard doses - 400 milligrams three times daily for 5 days. If new lesions occur from day 4 then a longer course of treatment may be advisable. Individual cases can be discussed with the Consultant Microbiologist/Virologist.

- Daily suppressive aciclovir from 36 weeks gestation may prevent genital herpes recurrences at term (400milligrams three times daily until the birth).

- Caesarean section is recommended for all women presenting with first-episode genital herpes lesions at the time of delivery, but is not indicated for women who develop first episode genital herpes lesions during the first or second trimesters. For women who present with first-episode genital herpes lesions within six weeks of the expected date of delivery or onset of preterm labour, elective caesarean section should be considered the optimum mode of delivery, and the neonatologists should be informed.

- For women who develop first-episode genital herpes lesions within six weeks of delivery and who opt for a vaginal birth, invasive procedures should be avoided.

- For women who develop first-episode genital herpes lesions at or within six weeks of delivery, intravenous aciclovir given intrapartum to the mother and subsequently to the neonate, may reduce the risk of neonatal herpes.

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

- For women presenting with recurrent genital herpes lesions at the onset of labour, the risks to the baby of neonatal herpes are small and should be set against the risks to the mother of caesarean section. A recurrent episode of genital herpes occurring at any other time during pregnancy is not an indication for delivery by caesarean section.

- Management of patients with primary herpes in preterm prelabour rupture of membranes should be guided by the multidisciplinary team discussion and will depend on the gestation that PPROM occurred. If decision is for immediate delivery then anticipated

benefits of caesarean section will remain. If there is initial conservative management, the mother should be recommended to receive intravenous aciclovir 5mg/kg every 8 hours until the decision for delivery is made

- Women who are HIV antibody positive and have a history of genital herpes should be offered daily suppressive oral aciclovir 400mgs three times daily from 32 weeks gestation to reduce the risk of transmission of HIV infection.

- All women should be asked at their first antenatal visit if they or their male partner have ever had genital herpes. Female partners of men with genital herpes, who themselves give no history of genital herpes, should be advised about reducing their risk of acquiring this infection.

- Identifying women susceptible to acquiring genital herpes in pregnancy by means of type-specific antibody testing has been evaluated in the UK in terms of costs and benefits and is not indicated, except in the context of further research.

- Healthcare workers and family members with active Herpes Simplex Virus (HSV) infection should avoid direct contact between lesions and the neonate. This includes covering the lesions and using aciclovir treatment. Health care workers should follow the Trust infection control procedures.

- Case by case discussion with virologists and paediatric infectious diseases team is encouraged (see contact details below).

- Where HSV infection is suspected in an unwell infant, the baby should be admitted, investigated and immediately commenced on aciclovir pending results.

- Breastfeeding is recommended unless the mother has herpetic lesions around the nipples.

- If it is not known whether the mother has a past history of genital herpes, or has an unknown HSV antibody status, the mother and the baby should be treated as if the mother had a primary HSV infection and maternal HSV type specific serology needs to be taken at the earliest opportunity to establish maternal immune status.

- If HSV is detected in skin swabs the baby will require isolation. In all other instances please consult the infection control policies and alert the team.

Neonatal Herpes - Background

Neonatal herpes is a severe systemic viral infection with a high morbidity and mortality, which is most commonly acquired at or near the time of delivery. Congenital herpes is extremely rare and occurs by infection transmitted in-utero. Incidence of neonatal herpes in the UK is about 1.6 per 100,000, this is probably underestimated

30% of neonatal herpes infection involve;

- Disease localized to skin, eye or mouth

70% of neonatal herpes infection involve;

- Local central nervous disease (CNS) disease with or without
- Disseminated infection with multi organ involvement

Almost all cases of neonatal herpes occur as a result of direct contact with infected maternal secretions during birth, although cases of postnatal transmission have been described. Neonatal herpes may be caused by herpes simplex type 1 (HSV-1) or herpes simplex type 2 (HSV-2), as either viral type can cause genital herpes.
The risk of transmission is greatest when a woman acquires a new infection (primary genital herpes) during late pregnancy, so that the baby is delivered before the development of protective maternal antibodies.

Risk of mother to child transmission:

- Up to 50% for a primary infection acquired around labour or within 6 weeks from delivery;
- Up to 20% for first episode non-primary HSV infection, defined as a new infection from HSV1 in a mother already infected with HSV 2 (or viceversa);
- About 2% for reactivations (recurrent episodes)

Other factors associated with transmission include duration of rupture of membranes before delivery, use of fetal scalp electrodes, prematurity and mode of delivery. Most of these maternal infections are asymptomatic or unrecognized and it may be difficult to distinguish clinically between recurrent and primary genital HSV infections

Since the severe consequences of neonatal herpes infection are well established, obstetricians need to be aware of interventions that may reduce the risk of perinatal transmission.

Obstetrics - Management

First clinically recognised episode of genital herpes during first or second trimester (until 27+6 weeks of gestation)

- Refer to the genitourinary medicine (GUM) clinic
- A five-day course of oral aciclovir in standard doses should be prescribed
- Referral to the obstetric consultant.
- Paracetamol and topical lidocaine 2% gel can be offered as symptomatic relief
- Providing that the delivery doesn't ensue within the next six weeks, pregnancy should be managed expectantly and vaginal delivery anticipated.
    - Prescribe daily suppressive aciclovir 400mgs three times daily from 36 weeks of gestation

Any woman with suspected first-episode genital herpes should be referred to the GUM clinic, who will confirm or refute the diagnosis using viral PCR (polymerase chain reaction), advise on management and arrange a screen for other sexually transmitted infections. Treatment for all women who develop a first episode of genital herpes in pregnancy should not be delayed while awaiting the referral. Use of oral aciclovir (or intravenous if disseminated maternal infection) in

standard doses of 400mgs three times a day for 5 days should be prescribed. The use of aciclovir is associated with reduction in the duration and severity of symptoms and decrease in duration of viral shedding.
Suppressive aciclovir from 36 weeks onwards reduces the detection of genital herpes recurrences at term and hence the need for delivery by caesarean section may be reduced. It has not been shown whether giving suppressive aciclovir in this way improves neonatal outcome.

First recognised clinical episode of genital herpes during third trimester (from 28 weeks of gestation)

- For women presenting with first episode of genital herpes in the third trimester, particularly in the last 6 weeks of pregnancy, type specific HSV antibody testing, Immunoglobulin G (IgG) antibodies to HSV 1 and HSV 2, is advisable. 15% of women presenting with first episode of genital herpes have evidence of prior infection.
- Caesarean section is recommended for all women presenting with first-episode genital herpes lesions in the third trimester particularly those developing symptoms within 6 weeks of delivery as the risk of neonatal transmission of HSV is very high at 41%.
- The benefit of Caesarean section is reduced if membranes have been ruptured for greater than 4 hours but there may be some benefit in performing a caesarean section even after this time interval.

There is some evidence of increased perinatal morbidity (low birth weight and preterm labour). Treatment with oral aciclovir with 400mgs (or if disseminated infection suspected with iv aciclovir) five times a day should be started without delay. In the third trimester, treatment will usually continue with daily suppressive aciclovir 400mgs three times daily until delivery.

- For women who develop first-episode genital herpes lesions within six weeks of delivery and who opt for a vaginal birth, avoid invasive procedures such as fetal blood sampling, fetal scalp electrode, and artificial rupture of membranes and/or instrumental delivery.
- Intravenous aciclovir (5mg/kg every 8 hours) given intrapartum to the mother and subsequently to the neonate (20mg/kg every 8 hours) may be considered, however it is unknown whether intrapartum aciclovir reduces the risk of neonatal transmission.

Recurrent genital herpes

- Daily suppressive aciclovir 400mgs three times daily should be considered from 36 weeks.
- Vaginal delivery should be recommended to women with recurrent genital herpes at the onset of labour. In view of low transmission rates of 0-3% in pregnant women with recurrent genital herpes, invasive procedures like fetal blood sampling, fetal scalp electrode, and artificial rupture of membranes and/or instrumental delivery may be used if required.

Women with recurrent genital herpes should be informed that the risk of neonatal herpes is low,

even if lesions are present at the time of the delivery (0-3% for vaginal delivery). Most recurrent episodes of genital herpes are short lasting and may resolve within 7-10 days without antiviral treatment. Supportive treatment measures using saline bathing and analgesia with standard doses of Paracetamol will usually suffice, however acyclovir can also be used safely.

There is no increased risk of preterm labour, preterm prelabour rupture of membranes or fetal growth restriction with women seropositive for HSV.

There is no evidence to guide the management of women with spontaneous rupture of membranes at term, but consider expediting delivery in an attempt to minimize the duration of potential exposure of the fetus to HSV.

Genital herpes in preterm prelabour rupture of membranes (PPROM)

Primary genital herpes with (PPROM)

- Management should be guided by the multidisciplinary team discussion involving obstetricians, neonatologists and genitourinary medicine physicians and will depend on the gestation that PPROM occurred.
- If decision is for immediate delivery then anticipated benefits of caesarean section will remain.
- If there is initial conservative management, the mother should be recommended to receive intravenous aciclovir 5mg/kg every 8 hours. Prophylactic steroids should be considered to reduce the implications of preterm delivery upon infant.
- If delivery is indicated within 6 weeks of primary infection, delivery by caesarean section may still offer some benefit despite the PPROM.

Recurrent genital herpes in PPROM

- < 34 weeks: There is evidence to suggest that expectant management is appropriate, including oral aciclovir 400mgs three times daily for the mother.
- >34 weeks: Management should be undertaken in accordance with the departmental guideline on PPROM and should not influenced by the presence of recurrent genital herpes infection

The risk of neonatal transmission in women with recurrent genital infections who have encountered PPROM is very small and maybe outweighed by the morbidity and mortality associated with preterm delivery.

Management of HIV positive women with HSV infection

Primary HSV infection

HIV positive women with primary genital HSV infection should be managed according to the

recommendations for all women with primary genital HSV infection.

Recurrent HSV infection

There is some evidence that HIV antibody positive women with genital HSV ulceration in pregnancy are more likely to transmit HIV infection, independent of other factors. Women who are HIV antibody positive and have a history of genital herpes should be offered daily suppressive oral aciclovir 400mgs three times daily from 32 weeks gestation to reduce the risk of transmission of HSV infection. Starting therapy at an earlier gestation is considered in view of increased possibility of preterm labour in HIV positive women. The mode of delivery should be in line with departmental HIV in pregnancy guideline recommendations according to obstetric factors and HIV parameters such as HIV viral load.

Neonatal Management

When maternal genital herpes has been identified in advance of labour, a plan for management of the neonate must be available in the relevant notes. Case by case discussion with virologists and paediatric infectious diseases team is encouraged

Management of babies born to mothers with primary HSV infection in the last trimester of pregnancy born from vaginal delivery – HIGHEST RISK GROUP

Although in primary HSV infection a C section is recommended this may not be acceptable to the mother or not possible and vaginal birth occurs, as this is high risk for neonatal HSV infection, the following actions are recommended

- If the baby is well, a neonatal examination, HSV blood PCR, urine PCR and swabs of the skin, conjunctiva, nose, oropharynx and rectum should be sent for herpes simplex PCR when the baby is at least 24 hours old. HSV PCR blood, urine and swabs should be repeated between day 3 and 5, together with CSF PCR. Acyclovir 20mg/kg every 8 hours should be started, without delay for acquisition of samples, until evidence of active infection is ruled out on sample sets from day 1 and day 3- 5.
- If the baby is unwell, immediately isolate, perform blood and LP for HSV PCR and swabs of the skin, nose, conjunctiva, oropharynx and rectum when the baby is at least 24 hours old and if negative again on day 3-5. Acyclovir 20mg/kg every 8 hours should be initiated, without delay for acquisition of samples, until evidence of active infection is ruled out.
- See the treatment section for duration of treatment if HSV infection confirmed.

Babies born by caesarean section in mothers with primary HSV infection and babies born to mothers with recurrent HSV infection in pregnancy with or without active lesions at delivery are at low risk of vertically transmitted HSV infection so conservative management is recommended.

Management of babies born by planned caesarean section in mothers with primary HSV infection in the third trimester (from 28 weeks to term)

If baby is born by planned C section with rupture of membranes less than 4 hours, they are at relatively low risk of vertically transmitted HSV infection

- If the baby is well, normal postnatal care of the baby, neonatal examination by a doctor and HSV PCR (blood) and swabs of the skin, conjunctiva, oropharynx and rectum for herpes simplex PCR after at least 24 hours from birth should be taken.
- If results are negative the baby can be discharged. Parents should be given the parent information leaflet and advised to seek medical help if they have concerns regarding their baby. In particular, they should be advised to look for:
  – skin, eye and mucous membrane lesions, lethargy/irritability, poor feeding, spontaneous bleeding.
- If results are positive the baby should be kept in or re-admitted to Bristol Royal Children Hospital, LP for HSV PCR and LFTs performed and acyclovir 20mg/kg every 8 hours, started immediately.
- If the baby is unwell the differential diagnosis of HSV should be kept in consideration and the baby should have a full septic screen, surface swabs as above and be started on iv and acyclovir 20mg/kg every 8 hours and antibiotics.
- If the caesarean section occurs after 4 or more hours of rupture of membranes the same advice as per vaginal delivery should be followed.

Management of babies born to mothers with recurrent HSV infection in pregnancy or primary acquisition of HSV in first or second trimester, with or without active lesions at delivery - LOW RISK CATEGORY

- If the baby is well, born by planned C section with no rupture of membrane or rupture of membranes less than 4 hours
- Normal postnatal care. Surface swabs of the baby are not indicated. Give parent information leaflet and explain the signs to look for.
- If there is evidence of maternal genital lesions at time of delivery and baby born by vaginal delivery or by C section with rupture of membranes greater than 4 hours and the baby is well
    - HSV PCR (blood, urine) and swabs for herpes simplex PCR of the skin, conjunctiva, nose, oropharynx and rectum at 24 hours of age
    - The baby can be discharged from the hospital if well and feeding is established. Parents should be given the parent information leaflet (link) and advised to seek medical help if they have concerns. In particular, they should be advised to look for:
      – skin, eye and mucous membrane lesions, lethargy/irritability, poor feeding, spontaneous bleeding.
    - HSV PCR results should be available within 96 hours. If the baby is discharged prior to this, the details should be entered into the postnatal tests log and it is the responsibility of the requesting team to follow up the results. As a failsafe, the duty virologist will inform the on call neonatal registrar (bleep 2935) of an abnormal result when it is identified.
    - If results of PCR are negative the parents/carers are notified by the neonatal team. If results are positive the parents/carers of the baby should be advised to

attend the emergency department at Bristol Royal Hospital for Children, from where they will be admitted, and a full septic screen, including LP should be performed; LFTs should be taken and intravenous acyclovir 20 mg/Kg every 8 hours started immediately.

Management of PREMATURE babies born to mothers with primary or recurrent HSV infection in pregnancy with or without active lesions at delivery

In case of a premature neonate (<37 weeks), particularly less than 28 weeks gestation

- If baby is clinically well, take surface swabs (skin, conjunctiva, rectum and oropharynx), blood PCR and LFT. LP and treatment should be considered in discussion with the virologists or the paediatric infectious diseases team.
- If the baby is unwell a full septic screen is necessary, surface swabs, blood and CSF should be sent for HSV PCR. These babies will need to be started on antibiotics in adjunct to Intravenous aciclovir (20 mg/kg every 8 hours).

Genital herpetic lesions developing in the mother within 7 days after delivery

- If primary infection is suspected, take neonatal HSV PCR (blood) and swabs and start intravenous aciclovir in the baby (20 mg/kg every 8 hours) while evidence of active infection is ruled out. Test the mother to confirm by vaginal swab and do maternal serology. The post –delivery lesions may appear anytime from day 1 to 7 in this scenario affecting the relevance of the neonatal samples- e.g. if taken more than three days after birth then the negative is reliable as exposure to the baby will only have occurred at birth.
- If recurrent maternal infection, take neonatal HSV PCR (blood) and swabs (skin, conjunctiva, nose, rectum and oropharynx). Start iv aciclovir only in a well baby if tests return a positive result; if baby unwell start iv aciclovir immediately, but also consider bacterial sepsis.

Note that 2/3 of women that acquire primary herpes in pregnancy are asymptomatic or not diagnosed. Therefore **maternal HSV may not be recognised in pregnancy**: when a neonate is unwell with clinical evidence of sepsis, HSV infection should be considered. Deranged LFTs or poor response to antibacterial treatment should alert the clinician (HSV can also present as a rash/conjunctivitis/pneumonitis). If HSV is suspected:

- Take the maternal history, if in doubt obtain maternal HSV type specific serology.
- Take blood, CSF, viral swabs (nose, eye, mouth, any skin lesion swabs) and urine for Herpes PCR from the baby.
- Start intravenous aciclovir (20 mg/kg every 8 hours) pending the results.

Prevention of postnatal transmission

In 25% of cases a possible source of postnatal infection is usually a close relative of the mother. Carers with HSV infection should be educated regarding good hand hygiene to reduce risk of postnatal infection. If lesions are in exposed areas (e.g. cold sores) they should also be

recommended to cover them. Antivirals should be considered for the carers if lesions are detected early or they develop new lesions.

Neonatal drugs, doses and duration

- Treatment: Acyclovir 20 mg/kg every 8 hours (increased dosing interval if renal impairment present – consult BNFC)
- Duration:
    - Virus detected in blood or CSF: 21 days minimum,
        - If positive CSF repeat LP so that a result is available 1 or 2 days before the planned date of stopping iv aciclovir,
        - Prophylaxis with oral aciclovir 300mg/m^2 3 times/day for 6 months should be started after intravenous treatment
    - Unwell baby, virus isolated from a surface swab but no lesions evident and negative blood and CSF discuss duration with the virology or infectious diseases team.

Well or unwell babies with evidence of vesicles and virus detected from the skin and/or mucous membrane sites only is SEM disease (skin and mucosal disease) the recommended duration is generally 14 days but discuss with virology or infectious diseases team.

- The babies can be referred to the OPAT team for home treatment is a 3fr PICC line is inserted.

What laboratory samples

- Skin, conjunctival, rectal, nose and oropharyngeal swab specimens needs to be sent in viral media. Plain urine in sterile container.
- Blood PCR is collected on EDTA and CSF is collected in a plain universal container. Please alert virology laboratories about the incoming specimens

Contact number for virology and paediatric infectious diseases and neonatology:
Virology: Dr Matthew Donati; Dr Peter Muir; Dr Javeed Ahmed accessed via virology service clinical advice line 25551 or via switchboard

Paediatric infectious diseases: Dr Jolanta Bernatoniene x20207; Adam Finn x20168, Marianne Roderick x20158, Stefania Vergnano x 27534 or bleep3997

Neonatology: Neonatal consultant on call x21852 (0800-2200) or via switchboard; Neonatal registrar on call x21853, Bleep 2935

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Consultation: Antenatal Working Party, CDS Working party, NICU Clinical Governance group

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References

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- European guideline for management of genital herpes(2010)
- BASHH guidance on management of genital herpes (http://www.bashh.org/documents/HSV%20Final%20guidelines%20with%20ref%20sorted.pdf (2014)
- RCOG green top guideline on management of genital herpes in pregnancy (2007)
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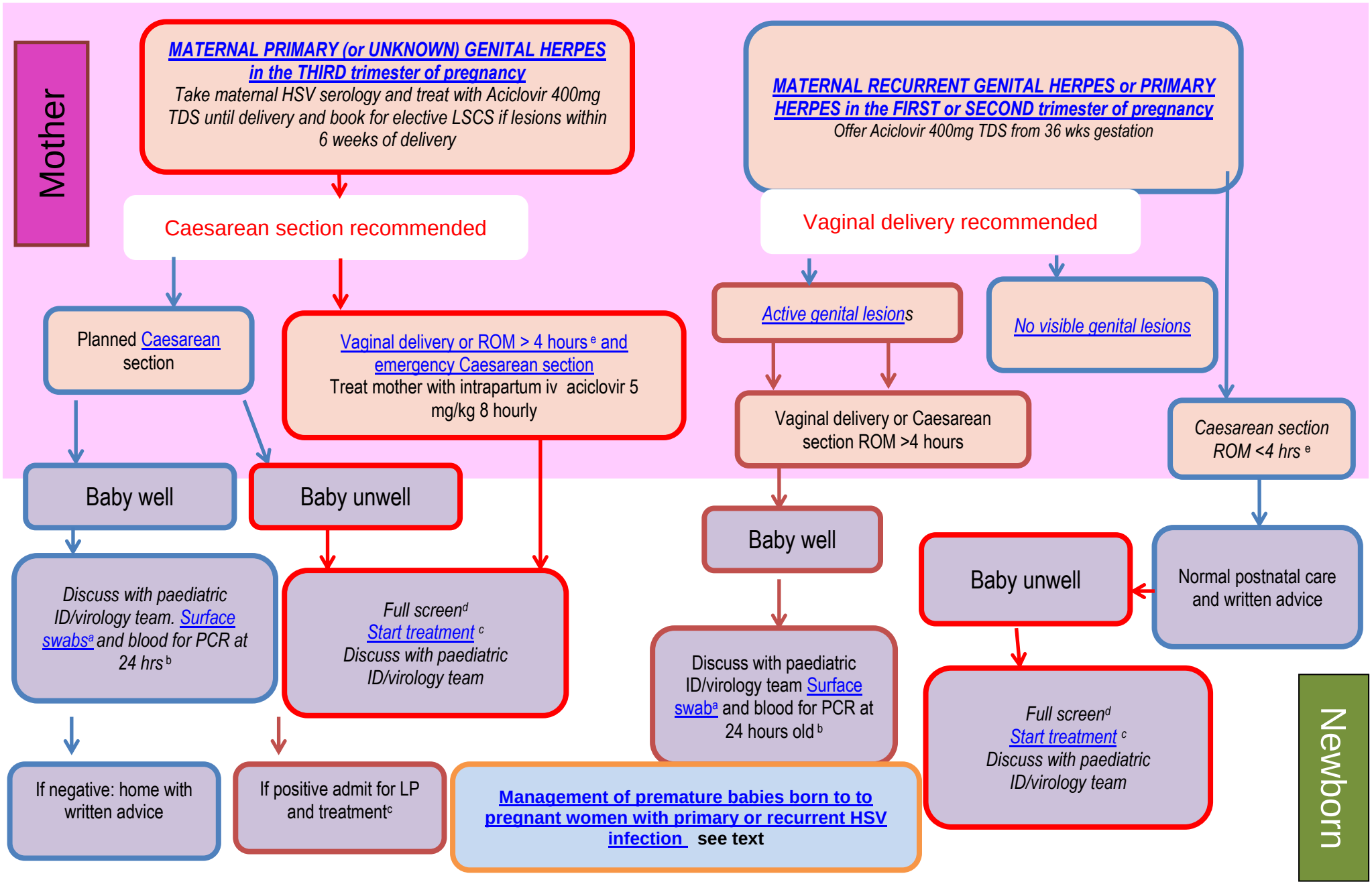
Mother
MATERNAL PRIMARY (or UNKNOWN) GENITAL HERPES in the THIRD trimester of pregnancy
Take maternal HSV serology and treat with Aciclovir 400mg TDS until delivery and book for elective LSCS if lesions within 6 weeks of delivery
Caesarean section recommended
Planned Caesarean section
Vaginal delivery or ROM > 4 hours e and emergency Caesarean section
Treat mother with intrapartum iv aciclovir 5 mg/kg 8 hourly
Baby well
Baby unwell
Discuss with paediatric ID/virology team. Surface swabs a and blood for PCR at 24 hrs b
Full screen d
Start treatment c
Discuss with paediatric ID/virology team
If negative: home with written advice
If positive admit for LP and treatment c
MATERNAL RECURRENT GENITAL HERPES or PRIMARY HERPES in the FIRST or SECOND trimester of pregnancy
Offer Aciclovir 400mg TDS from 36 wks gestation
Vaginal delivery recommended
Active genital lesions
No visible genital lesions
Vaginal delivery or Caesarean section ROM >4 hours
Caesarean section ROM <4 hrs e
Baby well
Baby unwell
Normal postnatal care and written advice
Discuss with paediatric ID/virology team Surface swab a and blood for PCR at 24 hours old b
Full screen d
Start treatment c
Discuss with paediatric ID/virology team
Management of premature babies born to to pregnant women with primary or recurrent HSV infection see text
Newborn