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REVIEW ARTICLE

Herpes in Pregnancy

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Abstract Herpes simplex virus infection (predominantly HSV2) in pregnancy can be a cause of maternal morbidity. The more serious cause of concern is perinatal transmission of infection resulting in neonatal morbidity and mortality. Genital HSV infection can be primary, non-primary first episode or recurrent infection. Clinical and laboratory diagnosis in pregnant women is similar to non-pregnant women. Direct viral testing (PCR) from lesion's and type specific serology are required to classify type of infection. Vertical transmission occurs during labor and delivery. The risk is higher in primary and non-primary first episode near the time of delivery. Antiviral treatment with Acyclovir or Valacyclovir is recommended for acute episode to reduce lesion duration and viral shedding. Acyclovir as suppressive therapy from 36 weeks onwards reduces clinical recurrences and need for caesarean delivery. Caesarean section reduces but does not eliminate the risk of vertical transmission and is recommended for a woman has an acute infection episode at the time of labor or within 6 weeks before delivery. Clinical management of preterm premature rupture of membranes in a woman with HSV infection should be individualized. All neonates born to these mothers should be carefully handled and monitored for development of neonatal herpes.

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Introduction

Herpes simplex virus (HSV) is an enveloped and double stranded DNA virus of the Herpesviridae family, transmitted across mucosal membranes and non-intact skin and migrates into nerve tissues to persist in a latent state. HSV-1 typically found in the trigeminal ganglia, causes orolabial lesions, whereas HSV-2 which predominates in genital lesions, is most commonly found in the lumbosacral ganglia.

Herpes simplex virus (HSV) infection is prevalent among reproductive age women. The rate of HSV-2 seroconversion during pregnancy is estimated to be 0.2–4%. 36% of pregnant women harbour a prior infection with either HSV-1 or HSV-2 [1, 2]. The seroprevalence of HSV-1 and HSV-2 in pregnant women was found to be 59 and 21%, respectively [3]. In the last 4–5 years, overall prevalence of HSV-1 and HSV-2 among pregnant women has declined, leaving a large seronegative fraction of reproductive-age women who may be at risk for acquiring HSV-1 or HSV-2 during pregnancy [4, 5].

The major concern of genital HSV infection during pregnancy is maternal to fetal transmission and also neonatal infection; both result in serious morbidity and mortality. Although both HSV-1 and HSV-2 may cause neonatal herpes, HSV-2 is responsible for 70% of cases. Neonatal herpes infection affects 1 per 1700 to 12,500 live births across various populations. The prevalence of neonatal HSV infection has, however, remained stable [6, 7]. In the recent past, HSV-1 infection cases have increased, especially among young women, which may

explain why the rate of neonatal HSV infection has not decreased along with the decrease in maternal HSV-2 prevalence.

Genital herpes simplex virus (HSV) infection can be classified as

- *Primary*: First occurrence of a genital HSV lesion in a patient with no pre-existing HSV-1 or HSV-2 antibodies.
- Non-primary first-episode: First occurrence of a genital HSV lesion in a patient with pre-existing HSV antibodies of different types. Eg:
  - HSV-2 genital lesion in a patient with pre-existing HSV-1 antibodies but no HSV-2 antibodies. This is commonly seen in patients with a history of orolabial herpes.
  - HSV-1 genital lesion in a patient with pre-existing HSV-2 antibodies but no HSV-1 antibodies. This is a rare occurrence.
- *Recurrent*: The HSV type of genital lesion is the same as pre-existing antibodies in the patient. The recurrence may sometimes be the first clinically recognized episode of genital herpes in a patient with previous asymptomatic episode of genital lesion.

Both type-specific serology and virus isolation are usually required for accurate classification, except in cases of well-documented recurrent HSV previously confirmed by culture or polymerase chain reaction (PCR) [8]. Type-specific antibodies develop within the first 12 weeks of infection and persist indefinitely [9].

It is important to accurately classify the HSV infection in pregnancy because primary or non-primary first-episode around the time of delivery is a major risk factor for neonatal herpes. Recurrent genital HSV infection, however, has a much lower risk of vertical transmission [10, 11].

Clinical Presentation

The clinical manifestations of genital herpes simplex virus (HSV) depends upon whether the infection is primary, nonprimary first episode, or recurrent. Clinical findings are similar in pregnant and nonpregnant women.

Primary genital infection can be severe, presents with painful genital ulcers, pruritus, dysuria, fever, tender inguinal lymphadenopathy, and headache. Rarely patient can have hepatitis, pneumonia or encephalitis. However, most patients have only mild symptoms or remain asymptomatic. In a study on HSV seronegative pregnant women, only one-third who seroconverted had symptoms of genital HSV infection [12].

The nonprimary first-episode tends to be milder than primary infection, but cannot be classified based on the clinical picture alone. It requires both virus isolation and serology.

Recurrent infections have mild prodromal symptoms, such as pruritus, burning, or pain, before few localized nontender or atypical in appearance lesions are visible. There are no systemic findings. The duration of lesions and viral shedding is shorter than in a primary episode.

Diagnosis

The clinical diagnosis of genital HSV infection is made by the presence of vesicular or ulcerated lesions. It should be confirmed by laboratory testing. Diagnostic tests include: polymerase chain reaction (PCR), viral culture, direct fluorescent antibody testing, and type-specific serologic tests. Based on clinical presentation, the diagnostic approach to the patient can be as follows:

- Women without a history of genital HSV + an active genital lesion/ulcer during pregnancy:
  (a) Direct viral test on the lesion (vesicle is unroofed and a swab from vesicular fluid and ulcer base should be sent for HSV DNA by real-timePCR) (1b, A)
  (b) type-specific serologic testing. (III, B)

During pregnancy, PCR is more sensitive and is preferred test for diagnosis than cell culture [13–16]. Direct immunofluorescence assay, enzyme immunoassay, Papanicolaou tests and Tzanck tests are poor HSV-screening tests. (1b, A).

Genital HSV infection is diagnosed by a positive viral test. Type-specific HSV serology at the time of initial presentation is necessary for classifying maternal infection as primary, nonprimary, or recurrent [17].

- Women with genital ulcers + high clinical suspicion for HSV infection + negative tests for virus detection and for antibody:
  Repeat serology 3–4 weeks later.

If this repeat testing demonstrates seroconversion of either type-specific antibody, the diagnosis of primary infection (or nonprimary first-episode, if the other type-specific antibody was positive at baseline) can be made.

If there is no seroconversion, the genital ulcers are unlikely to represent HSV infection.

- Woman with history of laboratory confirmed genital HSV do not warrant further testing.

- Woman with history of genital ulcers but not laboratory confirmed diagnosis + an active genital ulcer during pregnancy:
  Do virus isolation (PCR) from the lesion to confirm recurrent HSV (PCR has greater sensitivity in recurrent infection than viral culture). However, if the clinical picture suggests HSV infection, a negative virus test does not rule out the diagnosis of HSV infection. If a definitive diagnosis is desired in this situation, serology can be performed to confirm HSV infection.

Neonatal Herpes: In new-borns with suspected disease, cultures of the skin lesions, mouth, eyes, urine, blood, stool, rectum, and CSF should be obtained. PCR can be used to detect HSV in the spinal fluid.

Vertical Transmission

The key principles for vertical transmission of HSV infection are as follows [18] (Fig. 1)

- The highest risk (90%) of transmission of HSV to the neonate is during labor and delivery due to direct contact with virus shed from infected sites i.e. cervix, vagina, vulva and perianal area. Some pregnant women do not have clinically evident genital herpes and yet new-borns acquire perinatal HSV infection [19].
- The risk is highest with a primary or nonprimary first-episode genital infection, because of the absence of maternal type-specific anti-HSV antibodies and greater viral exposure (both load and duration of viral shedding). The type-specific antibodies to HSV generally take 12 weeks to develop after infection and persist indefinitely [9]. So, those who have a primary or nonprimary first-episode genital infection early in pregnancy and develop type-specific HSV antibodies before the onset of labor appear to be at low risk of vertical transmission (similar to women with recurrent infection) [12].

Herpetic infection acquired within 28 days of birth in a new born, who otherwise appears normal at birth, is perinatally acquired neonatal Herpes.

There is 70% risk of neonatal dissemination which manifest as 3 distinct syndromes. The first and most common (45%) is localized skin, eye, or mouth (SEM) disease. The second (30%) is central nervous system disease, (meningitis or encephalitis) with evidence of HSV DNA in the cerebrospinal fluid. The third (25%) manifests as disseminated disease involving multiple organs.

The risk is slightly lower(< 10%) in women with nonprimary first-episode genital infection, and substantially reduced in women with recurrent HSV due to a protection by already existing HSVspecific maternal antibodies and less viral shedding during reactivation [20].

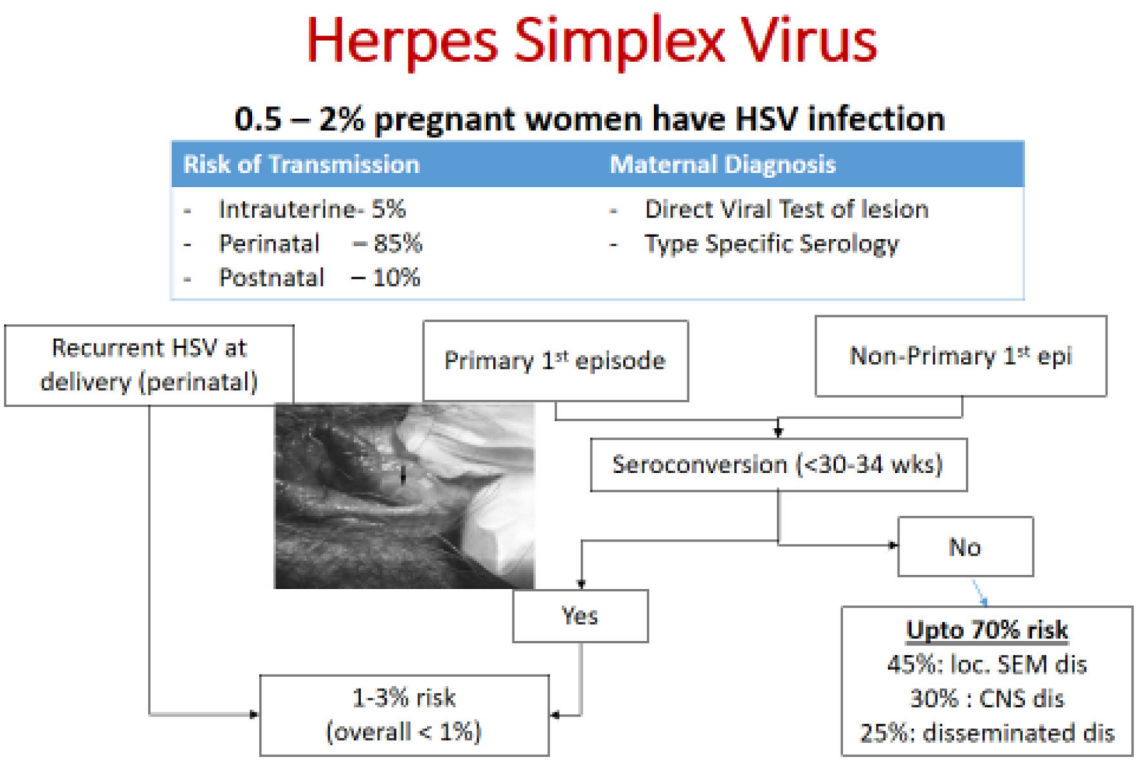

Fig. 1 Vertical transmission of Herpes infection in pregnancy

Studies have quoted the frequency of neonatal infection in culture positive women on admission in labor as 40–45% in primary infection, 25–30% in non-primary first episode genital HSV and 1–3% in recurrent infection [10, 11]. Viral shedding can occur in the absence of maternal symptoms and lesions [16, 18, 21, 22].

- The frequency of viral shedding is higher in HSV-2 than HSV-1 infection and so is the risk of neonatal transmission and sequelae, but this does not change the clinical management of the pregnancy.
- Rarely in utero primary HSV infection from maternal viremia via transplacental route can occur and result in miscarriage, congenital anomalies, preterm birth, and/or fetal growth restriction [12, 23–25]. In utero acquisition of infection should be considered in cases of early neonatal HSV infection despite prelabor cesarean delivery and intact fetal membranes [10, 26]. Congenital infection manifests as a classic triad of skin vesicles, ulcerations, or scarring, eye damage; and severe CNS manifestations, including micro or hydranencephaly. Recurrent HSV is not associated with these outcomes [27].
- Use of invasive fetal monitoring and preterm birth increase the risk of neonatal infection in patients with viral shedding [10].

Pregnancy Management

Two major strategies to reduce the risk of vertical transmission include

- Suppressive antiviral therapy starting at 36 weeks to reduce the risk of recurrence at labor,
- Cesarean delivery for select women

However, neither intervention fully eliminates the risk of neonatal herpes.

Antiviral Therapy [28]

Treatment of primary or nonprimary first-episode genital infection—Start empiric antiviral therapy upon clinical diagnosis while awaiting reports of virus isolation to reduce the duration of active lesions, symptoms, and viral shedding. (*Grade 1A*) This also decreases the risk of other complications of primary infection (central nervous system disease, end-organ disease, disseminated HSV) [28]. *Acyclovir* (400 mg orally three times daily) for 7 to 10 days is the treatment of choice for the first episode. Subsequently, antiviral therapy is restarted at 36 weeks till labor for suppression.

Those developing a primary or nonprimary first-episode lesion during the third trimester should continue antiviral therapy without interruption from the time of treatment initiation through delivery. Although there is no data to support a strong recommendation for this approach, the rationale is the possibility of preterm delivery before 36 weeks, the potential for prolonged viral shedding with a first-episode HSV infection, and the relatively high risk of vertical transmission with preterm labor and rupture of membranes. The decision should be individualized. Although most obstetricians prefer cesarean delivery for women with a primary or nonprimary first-episode genital infection acquired during the latter weeks of pregnancy, this approach may particularly benefit women who insist on vaginal delivery.

Symptomatic treatment includes Analgesics, sitz bath, and topical acyclovir to help relieve fever, vulvar pain, dysuria, and other local symptoms.

Recurrent infection—Most recurrent episodes are short-lived and do not require treatment unless because of severe symptoms or frequent recurrences.

Suppressive therapy at 36 weeks—Initiating suppressive therapy at 36 weeks of gestation until labor and delivery is recommended for all women with a genital HSV lesion anytime during pregnancy, primary, nonprimary first-episode, or recurrent infection. (*Grade 1A*) Acyclovir 400 mg three times daily is used as suppressive therapy.

This reduces the frequency of symptomatic HSV recurrence at the onset of labor, and thus the need for cesarean delivery. It also reduces viral shedding and thus vertical transmission. Women with recurrent symptomatic genital HSV infections during pregnancy are most likely to benefit than those HSV seropositive women without active genital lesions [29, 30].

Although suppressive therapy markedly reduces the frequency of both symptomatic disease and asymptomatic viral shedding, the effect on the incidence of neonatal herpes is not known [9]. Suppressive therapy does not completely eliminate viral shedding [31].

Drugs

Acyclovir: This nucleoside analog is a selective inhibitor of viral replication and is the most commonly prescribed anti-Herpes medication in the dose of 400 mg orally three times a day or 200 mg five times a day for 7 to 10 days, or longer if lesions have not healed. It also prevents recurrences. For suppressive therapy, it is given from 36 weeks of gestation until delivery. Both animal and human data are reassuring regarding Acyclovir exposure and safety during pregnancy, including the first trimester [32].

Valacyclovir: This is a relatively expensive alternative for acute episode and suppressive therapy, with fewer

safety and efficacy data, although patient compliance is better because of twice-daily dosing (500 mg b.d) [32].

Famcyclovir: Human data is limited on its usual dose (250 mg three times a day) and safety in pregnancy.

Safety and monitoring—Antiviral treatment is generally safe, well-tolerated and does not require clinical or laboratory monitoring.

Weekly cultures or PCR testing for genital HSV in late pregnancy is *not* recommended because it cannot predict shedding at the time of delivery [9, 28]. Maternal HSV infection is not an indication for antepartum fetal monitoring (nonstress test, biophysical profile) since the fetus and placenta are not typically infected.

Antepartum obstetric procedures—Transcervical procedures (e.g., cerclage, chorionic villus sampling) should be avoided in women with genital lesions to reduce the risk of infecting the placenta or membranes, but may be performed in asymptomatic patients. Transabdominal procedures (e.g., amniocentesis, fetal blood sampling) are not contraindicated in women with active genital disease [33].

Route of delivery—(Recommendations from the CDC and ACOG).

Offer Cesarean delivery at onset of labor/rupture of membranes:

1. In women with a history of genital HSV and either of the following (*Grade 1B*) [9, 28, 33]:
   - Active genital lesions (including crusted lesions)
   - Prodromal symptoms (pain, burning)

No studies have established an interval after rupture of membranes when cesarean delivery has clear benefit [24, 28, 33].

2. In women with no active lesions or prodromal symptoms, decisions on route of delivery depend on the type and timing of the HSV infection:

   2a. Primary or nonprimary first-episode in current pregnancy

The optimal approach to route of delivery is unclear because viral shedding can be prolonged and maternal antibodies may not have developed before delivery. In the absence of obstetric indications for cesarean delivery, the decision depends on the woman's choice after an informed discussion about the uncertainty of the magnitude of the transmission risk, particularly as the duration of time between the infection and delivery increases, and the evidence that cesarean delivery decreases but does not completely eradicate that risk [26].

2b. Primary or nonprimary first-episode in the latter weeks of pregnancy:

Offer cesarean delivery as the risk of neonatal transmission is high [25]. But, women who do not wish cesarean delivery may do so in the absence of prodromal signs or HSV lesions. RCOG recommends cesarean delivery for all women with a first-episode genital herpes infection in the third trimester, particularly within 6 weeks of expected delivery (*Grade 2C*) [34]. While women with genital infection occurring in early pregnancy may also opt for cesarean to mitigate any possible risk of neonatal transmission.

2c. History of recurrent HSV but no active lesions or prodromal symptoms:

The risk of neonatal HSV is too low (about 2/10,000) to warrant cesarean delivery [35].

Cesarean delivery is not indicated in women with active nongenital HSV lesions (e.g., back, buttock, and thigh); although the risk of genital shedding is higher than in asymptomatic women, the risk of neonatal transmission is still not high enough to warrant caesarean. The nongenital lesions do not pose a risk of transmission in the absence of direct contact [28], and so, it should be covered with an occlusive dressing during labor and delivery.

Labor management—Avoid the use of fetal scalp electrodes, vacuum or forceps delivery in laboring women with a history of HSV infection to prevent neonatal herpes. External fetal heart rate monitoring is preferred as long as adequate information can be obtained.

Postpartum Management

- Parents and caretakers with active lesions, regardless of site, should be careful while handling the infant. Lesions should be covered and hands should be washed before touching the baby. 5–15% of neonatal herpes is acquired after birth from a family member [36].
- Breastfeeding is not contraindicated as long as there are no lesions on breast. Acyclovir and Valacyclovir are not contraindicated during breastfeeding [37].
- HSV PCR samples should be lifted from all the babies born to mothers with first episode genital herpes at labor onset to allow early identification of infected babies. Neonates with possible perinatal exposure to HSV should be monitored for clinical evidence of HSV infection (lethargy, fever, poor feeding, or lesions).

Special Consideration

Preterm premature rupture of membranes—Clinical decision-making for patients with PPROM and active HSV infection requires weighing the risks associated with

prematurity (gestational age) versus the risk of fetal/neonatal HSV infection (type of infection).

- In women with PPROM and recurrent HSV infection, Expectant management is recommended remote from term (*Grade 2C*) along with course of glucocorticoids for fetal lung maturation and intravenous Acyclovir (5 mg/kg every 8 h) to shorten the duration of active lesions in the mother and to decrease viral burden.
- Optimum management of women with PPROM and primary or first-episode genital nonprimary HSV infection is not known. Before 28 to 32 weeks, the risks of prematurity are high and may outweigh the fetal/neonatal infection risk of expectant management. So expectant treatment including Acyclovir and antenatal glucocorticoids may be given to reduce the morbidity and mortality related to preterm birth. After 32–34 weeks immediate cesarean delivery is preferable.

Antenatal Screening

Universal screening is not recommended as it does not meet usual criteria for an effective preventive strategy [10, 28, 38–40].

If a couple requests to be screened, type-specific glycoprotein G (gG)-based assays for HSV antibodies should be requested. Pregnancy management is based upon the serologic findings:

- If both partners are seronegative, care is routine (in monogamous couples).
- If the woman is seronegative for HSV-2 or HSV-1 and the partner is seropositive, use condom in the first and second trimesters. Avoid intercourse and oral-genital contact in the third trimester [9, 41].
- Use of Valacyclovir (500 mg/daily) by infected male partner in monogamous couples discordant for HSV-2 and probably HSV 1 can lower the risk by 48 percent [16].
- HSV vaccine is under development
- In women seropositive for HSV-2 or HSV-1 without history of genital herpes lesions, suppressive antiviral therapy is not offered [9].

Conclusion

Vertical transmission of HSV infection can cause serious harm to the neonate. In order to reduce the incidence of neonatal HSV infection, obstetricians and researchers should focus on the prevention and recognition of asymptomatic primary genital HSV infections. Since HSV vaccines are still under research, prevention of maternal infection, early detection and early initiation of antiviral therapy are main strategies for the prevention of mother-to-child transmission. Prevention of maternal infection should focus on the prevention of new infections in late pregnancy. At present, suppressive standardized antiviral therapy from 36 weeks onwards and caesarean section are advised to reduce neonatal herpes infection. The neonates should be handled carefully and monitored closely in postpartum period.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bernstein DI, Bellamy AR, Hook EW 3rd, et al. Epidemiology, clinical presentation, and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women. Clin Infect Dis. 2013;56:344.
2. Amar OAO, Bajaj HK, Gupta N, Singla A, Masih H. Prevalence of herpes simplex virus in pregnant women from gangetic plain region of Allahabad, India. Adv Microbiol. 2015;5:404–8. https://doi.org/10.4236/aim.2015.56041.
3. Patton ME, Bernstein K, Liu G, et al. Seroprevalence of herpes simplex virus types 1 and 2 among pregnant women and sexually active, nonpregnant women in the United States. Clin Infect Dis. 2018;67:1535.
4. McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of herpes simplex virus type 1 and type 2 in persons aged 14–49: United States, 2015–2016. NCHS Data Brief, no 304. Hyattsville, MD: National Center for Health Statistics. 2018.
5. Krupp K, Bochner A, Ravi K, et al. The epidemiology of herpes simplex virus type-2 infection among pregnant women in rural Mysore Taluk, India. Sex Transm Infect. 2013;89:A160–1.
6. Morris SR, Bauer HM, Samuel MC, et al. Neonatal herpes morbidity and mortality in California, 1995–2003. Sex Transm Dis. 2008;35:14.
7. Kropp RY, Wong T, Cormier L, et al. Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study. Pediatrics. 2006;117:1955.
8. Hensleigh PA, Andrews WW, Brown Z, et al. Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. Obstet Gynecol. 1997;89:891.
9. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep. 2015;64:1.
10. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA. 2003;289:203.
11. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. N Engl J Med. 1991;324:1247.
12. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med. 1997;337:509.
13. Cone RW, Hobson AC, Brown Z, et al. Frequent detection of genital herpes simplex virus DNA by polymerase chain reaction among pregnant women. JAMA. 1994;272:792.

14. Hardy DA, Arvin AM, Yasukawa LL, et al. Use of polymerase chain reaction for successful identification of asymptomatic genital infection with herpes simplex virus in pregnant women at delivery. J Infect Dis. 1990;162:1031.
15. Boggess KA, Watts DH, Hobson AC, et al. Herpes simplex virus type 2 detection by culture and polymerase chain reaction and relationship to genital symptoms and cervical antibody status during the third trimester of pregnancy. Am J Obstet Gynecol. 1997;176:443.
16. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11.
17. Kimberlin DW, Baley J, Committee on infectious diseases, Committee on fetus and newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics. 2013;131:e635.
18. Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. N Engl J Med. 2000;342:844.
19. Pinninti SG, Kimberlin DW. Maternal and neonatal herpes simplex virus infections. Am J Perinatol. 2013;30:113.
20. Johnston C, Magaret A, Selke S, et al. Herpes simplex virus viremia during primary genital infection. J Infect Dis. 2008;198:31.
21. Wald A, Corey L, Cone R, et al. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. J Clin Investig. 1997;99:1092.
22. Tronstein E, Johnston C, Huang ML, et al. Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. JAMA. 2011;305:1441.
23. Brown ZA, Benedetti J, Selke S, et al. Asymptomatic maternal shedding of herpes simplex virus at the onset of labor: relationship to preterm labor. Obstet Gynecol. 1996;87:483.
24. Nahmias AJ, Josey WE, Naib ZM, et al. Perinatal risk associated with maternal genital herpes simplex virus infection. Am J Obstet Gynecol. 1971;110:825.
25. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med. 1987;317:1246.
26. Stone KM, Brooks CA, Guinan ME, Alexander ER. National surveillance for neonatal herpes simplex virus infections. Sex Transm Dis. 1989;16:152.
27. Harger JH, Amortegui AJ, Meyer MP, Pazin GJ. Characteristics of recurrent genital herpes simplex infections in pregnant women. Obstet Gynecol. 1989;73:367.
28. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. No. 82 June 2007. Management of herpes in pregnancy. Obstet Gynecol. 2007;109:1489.
29. Watts DH, Brown ZA, Money D, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. Am J Obstet Gynecol. 2003;188:836.
30. Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. Cochrane Database Syst Rev. 2008;23:CD004946.
31. Pinninti SG, Angara R, Feja KN, et al. Neonatal herpes disease following maternal antenatal antiviral suppressive therapy: a multicenter case series. J Pediatr. 2012;161:134.
32. Briggs GG, Freeman RK, Yaffe, SJ. Acyclovir. In: Drugs in Pregnancy and Lactation: a reference guide to fetal and neonatal risk. (E-book) 8th edition, Philadelphia (PA): Lippincott Williams & Wilkins; 2008.
33. Westhoff GL, Little SE, Caughey AB. Herpes simplex virus and pregnancy: a review of the management of antenatal and peripartum herpes infections. Obstet Gynecol Surv. 2011;66:629.
34. Royal College of Obstetricians and Gynaecologists (2014) Management of genital herpes in pregnancy. https://www.rcog.org.uk/globalassets/documents/guidelines/management-genital-herpes.pdf. Accessed 23 May 2016.
35. Vontver LA, Hickok DE, Brown Z, et al. Recurrent genital herpes simplex virus infection in pregnancy: infant outcome and frequency of asymptomatic recurrences. Am J Obstet Gynecol. 1982;143:75.
36. Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. Pediatr Infect Dis J. 2008;27:425.
37. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Acyclovir. [Updated 2018 Oct 31]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501195
38. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Serologic screening for genital herpes infection: US Preventive Services Task Force recommendation statement. JAMA. 2016;316:2525.
39. Thung SF, Grobman WA. The cost-effectiveness of routine antenatal screening for maternal herpes simplex virus-1 and -2 antibodies. Am J Obstet Gynecol. 2005;192:483.
40. Tita AT, Grobman WA, Rouse DJ. Antenatal herpes serologic screening: an appraisal of the evidence. Obstet Gynecol. 2006;108:1247.
41. Delaney S, Gardella C, Daruthayan C, et al. A prospective cohort study of partner testing for herpes simplex virus and sexual behavior during pregnancy. J Infect Dis. 2012;206:486.