Diagnosis and treatment of herpes simplex I virus infection in pregnancy

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Abstract

A nulliparous woman presented at 21 weeks' gestation with a 72-h history of a rash on her left arm. Initially isolated to the forearm, it had quickly spread, becoming multiple itchy fluid-filled blisters. Blood tests showed mild neutrophilia and raised CRP. Skin swabs demonstrated the presence of herpes simplex virus type I (HSV1) DNA. There was no history of previous HSV1 exposure. There is scant literature on uncomplicated cutaneous HSV1 since the majority is oral/genital. The incidence of transmission varies and is dependent on site of infection and immunological status. Type-specific serological testing is recommended to identify a primary first episode infection due to the 30–60% vertical transmission rate. Infection is associated with morbidity and mortality for both mother and fetus including maternal encephalitis, acute retinal necrosis, pneumonia and hepatitis. Neonatal disease can be congenital (cutaneous lesions, microcephaly, hydranencephaly, intracranial calcifications, chorioretinitis, microphthalmia and optic nerve atrophy) or acquired (skin, eyes and mouth disease or central nervous system disease or disseminated disease). Prophylactic aciclovir reduces the number of women with active genital lesions at the time of delivery. If primary infection occurs outside of the first trimester and active genital lesions are present, then vaginal delivery should be avoided. If infection has occurred in the first trimester, vaginal birth can be attempted even in the presence of active lesions. There is no available guidance on prophylactic treatment of non-genital HSV1 in pregnancy.

Keywords

Immunology, infection, infectious diseases, maternal–fetal medicine, perinatal medicine

Date received: 7 February 2016; accepted: 10 December 2016

Clinical scenario

The patient was a 30-year-old nulliparous farmer with a BMI of 28 and a history of irritable bowel syndrome. A primigravida, all her booking bloods and routine antenatal screening tests (UK screening includes: hepatitis B surface antigen, HIV testing, syphilis antibodies and rubella IgG) were unremarkable. She had an uneventful first trimester and was assigned to a low-risk care pathway. She was at 21 weeks' gestation, when she presented one evening to her local Accident and Emergency department with a rash on her left forearm (Figure 1). The rash had appeared that morning. The patient said that initially it had been a cluster of white pimples but she had noticed it start to spread and become itchy and red. The Accident and Emergency Doctor described the rash to be a 5 × 5 cm erythematous area with numerous fluid filled blisters on the left forearm. Blood tests showed a mild neutrophilia and mildly raised CRP. She was directed to attend her GP for a dermatology referral.

Two days later, she was seen by a dermatology specialist. The rash had spread to the upper left arm but was of a similar character (see Figure 1). Skin swabs were taken and the differential diagnoses were infected nettle rash or phytophotodermatitis. She was commenced on oral flucloxacillin and aciclovir. The skin swabs showed evidence of herpes simplex virus type 1 (HSV1) DNA. An obstetric opinion was sought and at 23 weeks' gestation the patient was seen by a fetal medicine consultant. Since there was no personal history of previous HSV1 infection, the patient was counselled of the low risks associated with fetal development and HSV1 infection. The patient requested ultrasound surveillance of her fetus and delivered a live male infant at term by normal vaginal delivery. After paediatric review, the child was found to have been unaffected by the maternal cutaneous HSV1.

Literature review – Herpes simplex I in pregnancy

Herpes simplex belongs to the family of *Herpesviridae*. It is a double-stranded DNA virus encapsulated in a lipid and glycoprotein envelope.¹ Herpes simplex can be further divided into type I (HSV1) and

type II (HSV2), identifiable by specific glycoproteins I and II, respectively.¹ Other than humans, no other organism is known to be a latent carrier of herpes simplex. Once the virus has been acquired, and after the primary infection, it moves to the sensory ganglia and lies dormant. Lifelong infection is characterised by periods of latency and reactivation.¹ Historically, HSV1 has been associated with oral lesions and HSV2 with genital lesions, but more recently, there has been a change in aetiology and HSV1 is now responsible, in some populations, for around 80% of genital herpes infections.^{2,3}

HSV1 and HSV2 have significant structural similarities resulting in immunological cross-reactivity. Each virus stimulates production of type-specific IgM and IgG and so it is possible to determine the infective agent. Maternal IgM is produced in response to a current infection and in greater amounts at the first exposure to a particular antigen. After two or three days, antigenic stimulation provokes ongoing type-specific IgG production (the only immunoglobulin to cross the placenta, providing some passive immunity to the fetus). Therefore, the presence of IgG indicates a previous infection.³ The absence of HSV1 IgM and the presence of HSV1 IgG in a woman's serology suggest a recurrent manifestation of disease which confers much lower risk to the fetus and neonate. Checking a pregnant woman's booking blood test for the presence of HSV1 IgM and IgG will further clarify the infection status. If a woman is IgG positive in her booking bloods, then she has historically been exposed to the herpes virus and is manifesting a recurrence. Infections can be classified as 'primary first episode infection' (a woman who has never been infected with either HSV1 or HSV2), and 'non-primary first episode' infection' (a woman who has been previously infected with HSV1 or HSV2 and has contracted the other viral type during this pregnancy).

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Figure 1. Lesions of the left forearm.

HSV1 can be horizontally transmitted through mucosal membranes, abraded skin or through sexual contact.⁴ Around 90% of women test positive for HSV1 antibodies by the age of 50, and around 53% of pregnant women would test positive for the presence of HSV1 IgG indicating past infection.^{3,5} It is thought that only 0.5–2% of first episode maternal HSV1 infection occurs during pregnancy.⁶ Currently, screening is not advised, partly because serum screening is only 80% sensitive and partly because culturing asymptomatic women does not predict genital lesions at the time of delivery; it is only in the presence of genital lesions that management would be altered (i.e. caesarean section would be the recommended mode of delivery).^{1,5} The prevalence of HSV1 is higher in patients with altered immunity (i.e. pregnancy), women under 25 years, those of lower socioeconomic group, women with a sexual partner who is less than 20 years old and women whose partner has a positive history of oral herpes lesions.^{3,4,7} Additionally, the period of latency is shorter, and the severity of symptoms stronger in patients with altered immunity.¹

The risk of vertical transmission of HSV varies and is dependent on the immunological status of the pregnant woman. The risk of transmission to the fetus or neonate is higher in women who have a primary first episode infection (30 to 60%), as compared to 25% in non-primary first episode infections, and 1% in women with a recurrent infection.^{1,3,5,8,9} Around 61% of cases of maternal HSV infection occur in the third trimester.¹⁰ Maternal HSV infection can present in a number of ways, but most commonly as cold-type symptoms (headaches, chills) and classic vesicular lesions in the infected area.^{1,10} It is acknowledged that it can be difficult to diagnose herpetic skin lesions in pregnancy due to the prevalence of 'non-pathological skin eruptions' commonly related to the expected hormonal changes.¹ Less commonly, HSV can present with fever, neurological symptoms, reduced consciousness, hemiparesis, aphasia and seizures, all of which are associated with a rare complication of maternal HSV infection – encephalitis.^{2,10} Although encephalitis is a rare complication of maternal HSV infection, HSV is a relatively common cause for sporadic encephalitis in an adult.^{2,10} Even with rapid diagnosis through PCR of the cerebrospinal fluid and aggressive treatment with intravenous acyclovir, HSV encephalitis is associated with poor long-term prognosis and often leaves survivors with significant long-term morbidity.^{1,2} Additionally, acute retinal necrosis, pneumonitis and hepatitis have also been seen in association with maternal HSV infection.^{5,11}

For HSV1 infection at any site, the mainstay of treatment is oral antiviral therapy and aciclovir is the recommended drug of choice in pregnancy.^{1,5,8,9} There is evidence that aciclovir is not associated with any congenital abnormalities and is safe when breastfeeding, but is associated with transient neonatal neutropenia.^{5,10,8,9,12}

Treatment with aciclovir has been shown to reduce the duration and severity of the symptoms of infection in the pregnant woman, and the duration of viral shedding.⁸ A Cochrane review in 2008 demonstrated that viral suppression using prophylactic aciclovir in pregnant women with known HSV of the genital tract reduced the number of women with active genital lesions at the time of delivery and also reduced the number of women undergoing delivery by caesarean section.^{5,12} There is no available advice on prophylactic treatment of non-genital HSV1 in pregnancy. In the case of first episode genital infection occurring during pregnancy, current guidance from the Royal College of Obstetricians and Gynaecologists and The Centre for Disease Control is to treat at the time of infection with 7–10 days of 400 mg oral aciclovir three times a day, followed by a suppressive dose of 400 mg of aciclovir once a day from 36 weeks' gestation until delivery in an attempt to suppress viral load, and reduce the likelihood of active genital lesions and the need for delivery by caesarean section.^{3,8,9} The recommendation is that any woman with active genital HSV lesions at the time of delivery should be offered caesarean section before rupture of membranes (including those with recurrent disease), although it should be clear that this does not completely eliminate the risk of transmission.^{1,3,5,8,9} Women presenting with serologically proven recurrent disease and active lesions can be advised that the rate of vertical transmission during vaginal birth is low (0–3%), but caesarean section should still be recommended.^{1,5,8,9} If spontaneous rupture of membranes does occur, caesarean section should still be the recommended mode of delivery.³ Vaginal birth can be recommended for women without active genital lesions who are taking the described suppressive aciclovir regime and have either serologically proven recurrent HSV or were infected before 36 weeks' gestation.^{3,8}

Herpes simplex may rarely cause congenital fetal infection via vertical transmission in utero, by the virus undergoing hematogenous spread to the placental bed and passing through to the fetal circulation (5%).^{3,13} Hematogenous spread can occur from any site of infection including cutaneous, oral and genital.^{3,13} HSV can also cause neonatal infection in utero (85%) as the neonate comes into contact with the virus in the birth canal. Postpartum infection of the neonate is uncommon (10%) and all described cases relate to transmission via contact with oral herpetic lesions of the parent or family member.^{3,14} The Royal College of Obstetricians and Gynaecologists do not distinguish between congenital and neonatal infection but suggest UK rates of neonatal herpes are 1.65–3/100,000 live births, and attribute 50% of those infections to HSV1.⁸

If transmission occurs in utero during the first trimester, the majority of fetuses will spontaneously abort.² Second or third trimester infection manifest as macroscopic physical signs such as cutaneous lesions,

microcephaly, hydranencephaly, intracranial calcifications, chorioretinitis, microphthalmia and optic nerve atrophy, as well as microscopic changes including inflammatory changes to the infected tissues.^{3,5,14,15} Any pregnant woman with suspected primary first episode HSV1 infection should undergo molecular testing by swabbing any lesions.⁸

Around 85% of vertical transmission occur intrapartum during vaginal delivery. This rate increases in the presence of active genital lesions.^{2,7-9} Evidence suggests that the use of invasive fetal testing (fetal blood sampling) or monitoring (fetal scalp electrode), and to a lesser degree the use of instrumental delivery are associated with an increased risk of transmission.^{3,5,8} If infected intrapartum, the neonate will usually manifest symptoms within the first four weeks of life, typically around 10 days old. Infection can be identified though PCR testing of vesicle fluid, blood or cerebrospinal fluid. The presence of viral IgM is diagnostic of congenital infection but is often not detectable until 15 days of life.^{2,7} Manifestation of HSV infection in the neonate is commonly classified into three categories: skin, eye, and mouth disease (45%), central nervous system disease (30%) and disseminated disease (25%).^{8,16} Neonates with disseminated HSV infection have a poor prognosis with a 30% mortality rate and 20% significant morbidity rate.¹⁶ Diagnosing neonatal HSV infection early and treating it with high-dose intravenous aciclovir is associated with slightly lower rates of mortality and less long-term neurological impairment.⁷

Acknowledgements

I would like to extend my gratitude to the patient with whom the journey started and to Mrs Manju Nair for her support.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Written consent was gained from the patient for the use of an image and description of her case.

Guarantor

RH

Contributorship

This article was researched and written by Dr RL under the supervision and guidance of MN.

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