

Herpes Simplex Virus Perinatal Management

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Abstract

Aim

Herpes Simplex Virus (HSV) is a double stranded deoxyribonucleic acid (DNA) virus with 2 serotypes, HSV-1 and HSV-2. Neonatal HSV infection is uncommon due to evidence-based interventions for pregnancy, delivery and the newborn. The study assessed whether pregnant women with a history of genital HSV and their infants were managed according to best practice recommendations.

Methods

A retrospective analysis of pregnancies between January 2018 and December 2021. Included were women with documented HSV – either diagnosed, treated, or with positive laboratory testing.

Results

234 women with 261 pregnancies were identified. Mean maternal age was 32 (SD =/- 5.2). 110 (42%) pregnancies had visible lesions. 2 (0.07%) cases of primary HSV occurred within 6 weeks of delivery. 11 (4.2%) had lesions at labour onset – all were recurrences. Prophylaxis was prescribed in 178 (68%) pregnancies. 14 (5%) infants required evaluation, with only one yielding a positive swab requiring full acyclovir treatment.

Discussion

Genital HSV prevalence in this population was 0.07% (2 cases), with incidence of 0.003% (1 case) of infant requiring treatment throughout this timeframe. Primary infection within 6

weeks of delivery was rare, with no cases at labour onset. Recurrent lesions were reported in under 50% (110 pregnancies). Requirement for infant evaluation was low (5%, 14 infants).

Introduction

Herpes Simplex Virus (HSV) is a double stranded deoxyribonucleic acid (DNA) virus with 2 main serotypes, HSV-1 and HSV-2. Identification of pregnant women with active or historic genital HSV can be difficult as outbreaks can be mild or misdiagnosed¹. However, it is important to do so as infant exposure to active HSV lesions at delivery may be associated with neonatal infection and disease. Identification of at-risk mother-infant dyads allows maternal perinatal treatment with acyclovir, which may reduce active lesions at delivery and hence reduce the number of infants needing intervention in the newborn period.

Neonatal HSV disease is clinical manifestation of infection and can be categorised as: [1] disease limited to skin, eyes and/or mouth (SEM disease). [2] central nervous system disease, with or without skin lesions; and [3] disease involving multiple organs (disseminated disease)². Almost all neonates with HSV disease present within the first 4 weeks of life¹. The risk of mortality for treated neonatal HSV disease is 40-50% but exceeds 80% in untreated infants³.

Neonatal HSV infection and disease is largely uncommon due to evidence-based preventative recommendations for pregnancy, delivery and newborn care, combined with diagnostic advances leading to improved infant outcomes⁴. Acyclovir prophylaxis in pregnancy does not eliminate infant HSV infection risk, but reduces the frequency of viral shedding, genital lesions near term and thus the need for delivery by caesarean section and invasive infant evaluation⁵.

Up-to-date, evidence-based recommendations for best practice are key to prevent serious neonatal infection and disease. Current local guidelines are risk-based and depend on distinguishing primary (first episode) from recurrent genital lesions, and whether lesions are present at the onset of labour. Care and prophylaxis is offered by the obstetric and midwifery teams in close collaboration with the specialist midwife and Consultant in infectious diseases, who will generally provide an in-person review to facilitate individualized advice.

All women with genital ulceration during pregnancy should be offered a swab for HSV polymerase chain reaction (PCR) testing, and blood sampling for HSV Immunoglobulin G (IgG) type-specific antibodies.

Pregnant women with a first episode of genital herpes within 6 weeks of birth or full term gestation are the highest risk for infant transmission^{6, 7, 8}. These women should receive antiviral treatment until lesions regress, and continue antiviral prophylaxis until delivery^{7, 8}.

Vaginal birth can be offered if there is a gap of more than six weeks since first occurrence and there are no visible genital lesions at labour onset^{6, 7, 8}.

It is also recommended that prophylaxis from 32 weeks (or earlier if preterm birth is anticipated) is offered to women with a history of HSV without recurrence during pregnancy to minimise the risk of recurrent lesions at the onset of labour^{6, 7}. Any recurrence in pregnancy should be actively treated with antiviral treatment⁵.

Infant management depends on maternal history of infection and the presence or absence of visible maternal genital lesions at delivery. Infant risk for HSV infection may be categorised as high, intermediate or low risk, and their management tailored appropriately. Infants born to women with a first episode HSV within 6 weeks of delivery are high risk for infection, and should have evaluation including HSV-PCR swabs from skin (if lesions present), conjunctivae, nostrils, oropharynx and rectum, as well as blood HSV-PCR. Intravenous (IV) acyclovir should commence, and continue until PCR results are available. Infants with a positive PCR should have cerebrospinal Fluid (CSF) for HSV-PCR, as should infants who are clinically unwell. Treatment duration is determined by infant CSF results⁶.

Infants born to women with recurrent visible HSV lesions at delivery are categorised as being at intermediate risk for HSV infection, regardless of mode of delivery. Mucosal swabs and blood PCR are recommended, and treatment commenced only if PCR is positive from swabs or blood. Infants born to women with a history of recurrent HSV who do not have visible lesions at delivery do not require specific evaluation⁶.

The aim of this study was to determine whether pregnant women with a history of genital HSV and their infants were managed according to local guidelines at a tertiary referral maternity unit with over 8000 births annually in Dublin, Ireland.

Methods

This was a 4-year retrospective chart review of pregnancies registered between January 2018 and December 2021, with births occurring up to September 2022. Inclusion criteria comprised women with a history or laboratory evidence of HSV exposure, including those with clinical HSV (first episode or recurrence in pregnancy), women with a known history of HSV, and women with evidence of HSV on laboratory testing (Table 1).

Description	Value (n)
Number of women	234
Number of pregnancies	261
Mean maternal age (years)	32
Number of pregnancies with HSV lesions	110
Maternal Genital HSV Infections	
2018	28
2019	24
2020	45
2021	13
Risk Category of Maternal Genital HSV Infection	
High Risk	2
Intermediate risk	10
Low risk	98
Infants evaluated	
High risk	2
Intermediate risk	8
Low risk	4
Infants requiring full treatment course	
High risk	1
Intermediate risk	0
Low risk	0

Table 1. Characteristics of pregnant women with HSV and infant outcomes

Results

42,679 infants weighing greater than 500g were born over a 5-year period. 234 women who fulfilled the inclusion criteria for this study had 261 pregnancies during this period. Mean maternal age was 32 years. 42% of these women had active HSV lesions during their pregnancy (110 pregnancies).

There were 2 cases of maternal primary HSV infection within 6 weeks of delivery (0.07% of pregnancies) and these infants were assigned to high risk management.

10 (3.8% of pregnancies) had lesions at labour onset, but none represented primary infection. Eight of these 10 women had prophylaxis prescribed from 32 weeks. Of the two not prescribed prophylaxis one was scheduled to have planned caesarean section (CS) but had an earlier rapid vaginal birth prior to the date of caesarean section, the other patient did not disclose a history of HSV antenatally.

Acyclovir prophylaxis from 32 weeks gestation was prescribed in 178 (68%) pregnancies. For those not prescribed prophylaxis reasons included: patient declined, planned CS, or low risk stratification based on lack of recurrences or prolonged time interval from the last outbreak.

261 pregnancies yielded 261 liveborn infants. 14 (5.4%) infants required evaluation with HSV-PCR, 2 were born to women with primary HSV within 6 weeks of delivery and deemed high risk. One infant yielded a positive nasal swab with negative blood and CSF HSV-PCR and received 10 days of intravenous acyclovir. The second had negative swab and blood PCRs, and treatment was discontinued when results were available. Both infants had normal outcomes.

8 infants were designated intermediate risk and evaluated with PCRs (swabs and blood). All PCRs were negative and thus none required treatment. A further 4 infants were tested for HSV-PCR as part of general sepsis management as the infants were unwell and due to maternal HSV history commenced on antiviral. HSV-PCRs were negative in all and treatment discontinued.

2 other infants identified in this study were designated as low risk but on review met criteria for evaluation as intermediate risk. Neither experienced an adverse outcome.

There were three pre-term infants included in the study. One born at 26 weeks, therefore no prophylaxis had been prescribed or taken. She was, however, treated with acyclovir peripartum due to a history of lesions in pregnancy (albeit not at delivery). The remaining two delivered after 32 weeks and had commenced prophylaxis. One of the infants was evaluated with HSV PCR swabs due to concern for early onset sepsis and maternal history of HSV.

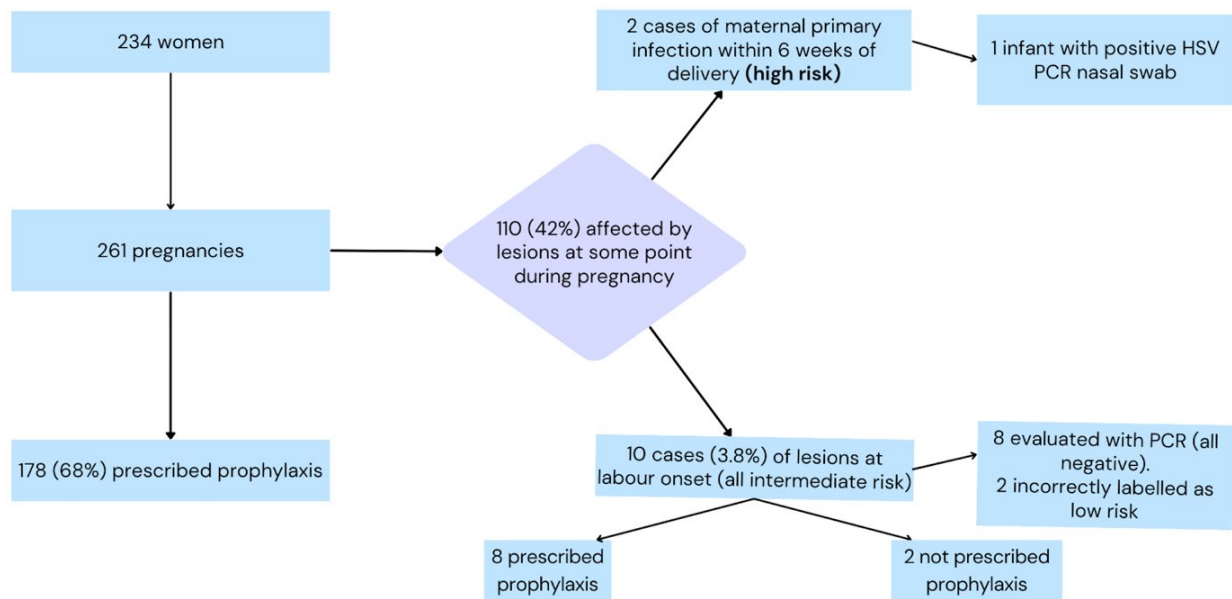


Figure 1. Illustration of cases

Discussion

This study demonstrates that most pregnant women in the studied cohort with a history of genital HSV were at low risk of infant HSV transmission. Amongst women with a known history, the rate of recurrent HSV lesions in pregnancy was low.

The prevalence of neonatal herpes infection in the cohort studied was 0.003% and there were no cases of disseminated neonatal HSV disease. This is lower than previously described in the United Kingdom (UK) with 1.65 cases of neonatal herpes infection per 100,000 births between 1986 and 1991, a subsequent doubling of incidence between 2004 and 2006, and more recent British Paediatric Surveillance Unit (BPSU) data revealing 6.9 cases per 100,000 live births between 2019 and 2022^{8, 9, 10}. Global data reports higher incidences of 10 cases per 100,000 live births, with lower incidence in Europe than the Americas^{11, 12}.

Prophylactic maternal acyclovir was prescribed in 68% of women who met criteria for doing so, with reasons as previously stated for not prescribing antivirals in the remaining 32%.

80% (8 of 10) of patients with lesions at labour onset had been prescribed prophylaxis. Although recurrence rates without prophylaxis are low, it is important to highlight this issue antenatally and integrate adequate awareness of neonatal risk into patient education in those opting out of prophylactic antiviral treatment in pregnancy. Although current guidelines in use in Ireland align closely with those of the Centre for Disease Control (CDC) guideline, the

rate of neonatal HSV in North America is reported as 1,500 cases per 4,000,000 births, significantly higher than reported numbers in this cohort studied².

HSV transmission risk is mainly determined by timing of maternal first episode, presence of lesions at labour onset or delivery, duration of rupture of membranes and mode of delivery. Establishing the type of maternal infection is essential for risk stratification of infants to high, intermediate or low risk. It is important to recognise maternal primary infection within 6 weeks of delivery and discuss elective CS in this scenario, as prolonged genital HSV shedding may increase transmission risk to the infant⁸.

Compliance with recommendations for neonatal management was 100% in the small high risk group and 80% in the intermediate risk group. One could advocate for merging the management plan of high and intermediate risk infants, particularly with access to rapid turnaround HSV-PCR results. However, this is not available in all centres nationally, and thus could lead to over treatment of intermediate risk infants with associated delayed discharge and additional healthcare costs.

As this is the first study of maternal and neonatal HSV in Ireland, little is known about prior incidence rates of maternal and neonatal HSV. Although prophylaxis prescription rates were recorded, it is difficult to fully ascertain the rates of compliance with acyclovir prophylaxis in a retrospective study of this nature.

This study demonstrates that the number of infants exposed to primary maternal infection is much lower than those exposed to recurrent lesions at delivery. However, maternal primary HSV infection within six weeks of delivery poses a high risk of transmission to the infant with potential adverse outcomes, and appropriate antenatal advice and strict adherence to existing guidelines is required in this group.⁵

In the cohort studied, the majority of women were categorised as low risk. 3.8 % of women in the cohort studied had lesions at onset of labour, all of which represented recurrences and the high risk category were a minority. Compliance with infant recommendations was 100% for both the high and low risk group and 80% for the intermediate risk group. Two high risk infants were treated with IV acyclovir pending PCR results, one of which required a ten day course of IV Acyclovir due to positive nasal swab but remained asymptomatic. Eight intermediate risk infants had negative HSV-swab and blood PCRs and did not require any treatment.

The 98 remaining HSV exposed infants were categorised as low risk and did not require interventions.

This study highlights the importance of education, early identification, and risk stratification of pregnant women with HSV for timely interventions to yield best possible infant outcome.

Declarations of Conflicts of Interest:

None declared.

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