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Neonatal Herpes Simplex Virus Infections: Diagnosis, Treatment, and Prevention

Review

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Abstract – Neonatal herpes simplex infection (HSV) is a ruinous disease in infants, related with broad morbidity and mortality. The utilization of PCR for HSV identification of infected new born and acyclovir for treatment has considerably further developed Acyclovir anticipation for affected new borns. The resulting utilization of suppressive therapy with oral acyclovir following completion of parenteral treatment of acute disease has also worked on the long term prognosis for these new borns.
This review will discuss the study of disease transmission, risk factors and routes of acquisition, clinical presentation, and assessment of neonates thought to have the infection, and treatment of proven neonatal HSV disease.

Keywords – Herpes Simplex Virus (HSV); Neonate; Pregnancy; Acyclovir.

INTRODUCTION

HSV-1 and HSV-2 are individuals from the alpha herpes infection subfamily of the family Herpes viridae. HSV virions comprise of a centre containing a solitary straight, double stranded DNA particle around 152 kilo base pairs long; an icosahedral capsid comprised of 162 capsomeres encompassed via an amorphous, tightly adherent tegument; and a lipid bilayer envelope containing viral glycoprotein spikes encompassing the capsid-tegument complex. These glycoprotein spikes intervene connection and passage into host cells and are responsible for evoking the host response. [1]

HSV DNA comprises of two covalently connected parts, designated simply as lengthy (L) and short (S), each comprising of unique regions (UL and US) flanked with the inverted repeats.[2] The genomes of HSV-1 and HSV-2 offer around 50% homology, resulting in significant cross-reactivity between antigenically related glycoproteins of each HSV types.[3] Type-explicit glycoproteins, like glycoprotein G, do happen (gG-1 and gG-2 for HSV-1 and HSV-2, respectively), allowing for differentiation of the two infection types by utilizing antigen-specific antibody reaction. HSV type differentiation can also be executed via restriction endonuclease fingerprinting and DNA sequencing. [4,5]

HSV infection is portrayed by utilizing short reproductive cycles, host cell destruction at some stage in active replication, and the virus' ability to set up long lasting latency in sensory neural ganglia. [6] Within a HSV-infected cell, key stages in viral replication comprise of cell surface attachment, entry of the viral genome into the nucleus, transcription, DNA synthesis, capsid assembly, DNA packaging, and envelopment as new virions pass through the trans-Golgi network.

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I. EPIDEMIOLOGY

Humans are the exclusively natural reservoir of HSV, and seroprevalence studies bring up that HSV-1 and HSV-2 infections are common around the world, in each developed and undeveloped countries. [7] Acquisition of HSV results in life long infection, with intermittent clinical or subclinical viral reactivation. Predominance of HSV antibodies will increment with age, however prior obtaining of infection is considered with HSV-1 as opposed to HSV-2, and in individuals of socioeconomic status for each HSV-1 and HSV-2. [8,9] More than 90% of adults have acquired HSV-1 disease through their fifth decade of life, despite the fact that exclusively a minority develop clinically apparent disease at the hour of acquisition. [10]

Past studies demonstrated a developing seroprevalence of HSV-2 in developed countries, [11,12]. In particular, while the seroprevalences of HSV-1 and HSV-2 in the United States had been around 58% and 17%, separately, in individuals aged 14 to 49 years for the span of 1999 to 2004, a follow-up finds out about from 2005 to 2010 affirmed that HSV-1 seroprevalence had brought down to 54%, though HSV-2 seroprevalence had not apparently altered (anywhere near 16%).[13,14] Further assessment of HSV-1 seroprevalence inside a large study about population recommends that the greatest decrease in HSV-1 seropositivity came to pass for in the 14-to 19-year-old group.

HSV-1 and HSV-2 can both cause genital infection, with HSV-1 being more noteworthy generally related with orolabial sores and HSV-2 being the extra continuous intention of genital lesions. However, HSV-1 has become the overwhelming infection incurring genital herpes, responsible for up to 80% of genital herpes in certain populations of young women.[15,16] When respected close by the decreasing HSV-1 seroprevalence in adolescents and young adults, these attributes infer that a developing assortment of more young people are without protecting HSV-1 antibodies at the time of their sexual debut.[17] Risk factors for acquiring HSV genital disease include: female gender, low income, minority ethnic gathering, longer time of sexual activity, earlier records of various genital infections, and number of sexual partners.[18]

Somewhere in the range of 20% and 30% of pregnant women are seropositive for HSV-2.[19,20] In pregnant female who report an earlier records of genital herpes, 75% have something like one recurrence over pregnancy.[21,22] Women missing antibodies to each HSV-1 and HSV-2 have a practically 4% risk of acquiring HSV-1 or HSV-2 for the course of their pregnancy, though female with exclusively HSV-1 antibodies have a 2% chance of getting HSV-2 all through pregnancy.[23] As with nonpregnant women, up to 66% of pregnant women who acquire genital HSV infection have asymptomatic or subclinical infections and are not appropriately diagnosed. This is consistent with research showing that 60% to 80% of women who have vertically transmitted HSV to their infants really do not record a prior history of genital herpes. [24-26]

Regardless of the high seroprevalence of HSV-1 and HSV-2, neonatal HSV infection stays intriguing, occurring in around 1 out of 3200 deliveries in the United States. [27] Most neonatal HSV diseases in a many parts of the world are currently caused by HSV-1, which is reliable with the increasing proportion of HSV-1 genital infections. [28,29]

1.1 Maternal genital herpes

Seroprevalence rates of HSV-1 and - 2 vary extensively depending on age, sex, race, and geographic distribution. HSV-2 prevalence has been referenced to be highest in areas of Africa, noticed through bringing down rates in North America, northern Europe and western and southern Europe, with the least frequency referenced from Asia.[30,31] While HSV-2 customarily has been the dominating serotype incurring genital and neonatal herpes in the United States, HSV-1 currently reasons most of genital herpes and perchance neonatal herpes in the United States and a few European nations, essentially because of adjusting sexual inclinations.[31-35] HSV -2 reactivates extra in the genital tract than HSV-1, therefore developing the probabilities of transmission to the neonate.[36]

HSV-2 seroprevalence among pregnant women is assessed to be 20-30%, and around 10% of HSV-2 seronegative women have a seropositive partner and thusly are at risk for acquisition of genital HSV-2 during pregnancy. [37] Among discordant couples, women seronegative for each HSV-1 and HSV-2 have an expected 3.7% risk for seroconversion, while the risk for female currently seropositive for HSV-1 to seroconvert to HSV-2 is assessed to be1.7%. [38]

A larger part of genital diseases incited with the guide of HSV-1 or - 2 are asymptomatic (clinically unapparent), with 66% of female who acquire genital HSV infection at some stage in being pregnant being either asymptomatic or having nonspecific symptoms. Among young women with earlier history of genital herpes, 75% will have no less than one recurrence for the span of pregnancy and 14% will have prodromal symptoms or lesions at the time of delivery. [39,40] For peripartum neonatal

transmission to occur, women must shed the infection in their genital tracts symptomatically or asymptomatically round the time of delivery. Somewhere in the range of 0.2% and 0.39% [41] of all pregnant women shed HSV in the genital tract round the time of delivery independent of earlier history of HSV, and shedding will increment to 0.77-1.4% among women with earlier history of recurrent genital herpes. [42,43]

The risk of transmission of HSV to the neonate remains significantly more noteworthy with dominating maternal diseases got closer to the time of delivery interestingly, with recurrent infections (50-60% with primary infections versus 3% for recurrent infections), generally no doubt because of absence of transplacentally acquired antibodies in the neonate of women with primary infection as appropriately as exposures in the birth canal of these women to large quantities of infection for longer duration of time.[44] Fortunately, most genital herpes infections during pregnancy are recurrent and therefore are associated with low risk of transmission to the neonate.

1.2 Neonatal HSV

Herpes simplex infection (HSV) disease of the neonate is uncommon with different rates all through the world due to varying rates of birth and HSV seroprevalence. Both HSV-1 and HSV2 have been identified to cause neonatal herpes infection. Studies have reported rates of 1.65 per 100,000, 1.6 per 100,000, 3.2 per 100,000 and 8.4 per 100,000 live births in the British Isles, Switzerland, the Netherlands, and Israel, respectively.[45-48] In the United States, the frequency rates are expressed to be more prominent with 5-33 for each 100,000 live births, resulting in an expected 1500 cases yearly throughout the country.[49,50] Though neonatal HSV stays an uncommon disease and does not need required announcing, the incidence is more prominent than reportable congenital infection like syphilis, toxoplasmosis, and rubella,[51] and may likewise be increasing.[52] The widespread pace of neonatal HSV, dependent absolutely upon seroprevalence, birth rates and infections in pregnancy is assessed to be 10 for every 100,000 live births, with a best rate of 14,000 cases annually.[53] This study marks the first attempt to evaluate the world burden of neonatal HSV.[54]

1.3 Risk factors

At the point when an individual with no HSV-1 or HSV-2 antibody obtains either infection in the genital tract, a first-episode primary infection results (Table 1). If a person with prior HSV-1 gets HSV-2 genital infection (or vice versa), a first-episode non-primary infection results. Viral reactivation delivers a recurrent infection. The chance of neonatal acquisition of HSV is significantly more prominent with first-episode primary and first-episode non-primary maternal infections conversely, with recurrent genital infections. In a large study, the risk of neonatal transmission was assessed as 57% with first-episode primary infection conversely, with 25% with first-episode non-primary infection and 2% with recurrent genital HSV infections. Other significant risk factors for transmission of HSV to the neonate had been isolated of HSV-1 from genital lesions versus HSV-2 and utilization of invasive monitoring strategies like fetal scalp electrodes. [50]

Table 1 – Risk factors for HSV transmission to neonate

1. Type of maternal infection (first-episode primary first-episode non-primary or recurrent)
2. Maternal HSV serostatus
3. Mode of delivery (vaginal or C-section)
4. Duration of rupture of membranes
5. Disruption of cutaneous barrier (use of fetal scalp electrodes and other instrumentation)
6. HSV serotype (HSV-1 or HSV-2)

The earliest antiviral agents effective against HSV included 5iodo-2′-doexyuridine and 1-β-D-arabinofuranosyl cytosine, but have been found to be too toxic for human use. Despite the fact that caesarean delivery has been confirmed to be successful in preventing the transmission of HSV to the neonate,[55] neonatal HSV examples have occurred despite caesarean delivery before rupture of membranes.[37] The American College of Obstetricians and Gynaecologists (ACOG) suggests caesarean section in the

presence of lesions suggestive of herpes at the time of delivery, while the Royal College of Obstetricians and Gynaecologists (RCOG) suggests caesarean delivery exclusively with primary genital herpes infections within 6 weeks of estimated delivery.[56] Evidence additionally exists for prolonged rupture of membranes[57] and interruption of mucocutaneous membrane via the utilization of fetal scalp electrodes and other instrumentation to expand the probabilities of acquisition of neonatal HSVdisease.[50,58] While it has been demonstrated that the potential outcomes of acquisition of HSV-1 are brought down in women seropositive for HSV-2, transmission of HSV-1 to the neonate has been recorded to be high regardless of primary or recurrent infection.[50].

Table 2 Types of HSV acquisition by the new born (59)

Mode of transmission of neonatal HSV	
In utero	*5%*
Peripartum	*85%*
Postnatal	*10%*

1.4 Clinical presentation

Neonatal HSV can be gained in-utero (5%), in the peripartum period (85%), or in the post-natal period (10%). For the later 2 modes of acquisition, extent of disease can be classified into the following categories:

1. SEM infection (skin, eye, and /or mouth)
2. CNS disorder (focal sensory system)
3. Disseminated disease

This classified is predictive of morbidity and mortality related with this neonatal HSV. [60-64]

1.4.1 SEM infection

In infants with Skin, Eyes and Mouth disease (SEM) disease, infection is confined to the skin, eye, or potentially mouth of infants other than any involvement of CNS or visceral organs. New born children with SEM disease historically represented 20% of cases of neonatal herpes disease anyway have increased to 45% with the presentation of antiviral treatment, as less infant's progress from a SEM to a disseminated extent of involvement. [37] Infants with SEM disease present at 10-12 days of life and 80% of these infants have a vesicular rash on physical examination. [64]

1.4.2 CNS infection

Close to 33% of cases of neonatal herpes infection present as encephalitis and are categorized as CNS disease, regardless of skin involvement.8 Neonates normally existing at 16-19 days of life, despite the fact that it is doable to have disease manifestations start at any time within the first month of life. Infants existing with focal/generalized seizures, lethargy, irritability, poor feeding, temperature instability, and protruding fontanel. Altogether, 60-70% of these infants have skin lesions at some point for the course of the disease. [64]

1.4.3 Disseminated disease

In the era of effective antiviral therapy directed towards HSV, disseminated disease represents ~25% of all neonatal herpes infections. [37] Affected infants existing around days 10-12 of life. Newborns with disseminated disease existing with respiratory and hepatic failure with disseminated intravascular coagulation (DIC). Disease incorporates several organs, comprising of CNS, lungs, liver, adrenal, skin, eye, and additionally mouth. 66% of infants have concurrent encephalitis and ~40% of infants never develop vesicular rash throughout the entire disease. [37,64] Death from disseminated disease is usually due to severe coagulopathy and extensive hepatic and pulmonary involvement.

Table 3 Clinical manifestations of neonatal HSV (65)

	Proportion	Age at onset	Clinical signs
SEM disease	20-45%	7-14 days	Vesicular lesions (confined to the skin, eyes and mucosa)
CNS disease	30-35%	14-21 days	CNS involvement (lethargy, poor feeding, tremor, seizures)
Disseminated disease	25%	5-12 days	Multiple organ involvement (lung and liver, coagulopathy)

II. ASSESSMENT OF THE NEONATE WITH SUSPECTED HSV INFECTION

2.1 Viral culture

The conclusive methodology of diagnosing neonatal HSV is by means of separation of HSV in tissue culture. Surface culture swabs (swabs from conjunctivae, nasopharynx, mouth, and anus), cerebrospinal liquid (CSF), or blood from affected new borns are inoculated into cell culture systems and checked for cytopathic effect. [66]

2.2 Polymerase chain response

The utility of PCR to CSF samples has upset the diagnosis of CNS neonatal herpes disease. [67-70] The overall sensitivities of CSF PCR in neonatal HSV disorder have ranged from 75% to 100%, with widespread specificities going from 71% to 100%. [68,69] A negative PCR result from the CSF in all actuality does presently not all by itself preclude neonatal HSV CNS disease, as the investigate can likewise be negative in early stages of the infection. In correlation, blood PCR in neonatal HSV has been assessed less significantly and in smaller cohorts, but is by all accounts a successful tool in the examination of neonatal HSV infections. [69-71] A positive CSF PCR for HSV DNA characterizes that confirmed individual as having CNS involvement (arranged both as CNS Disease, or as Disseminated Disease with CNS involvement). A positive blood PCR for HSV DNA affirms infection anyway does define infection classification, when you think about that all clinical disease categories (SEM, CNS, and disseminated) can have viremia and DNAemia. [67,69] Blood PCR can be positive for long time, with the clinical significance of this (if any) unknown. [72] Currently, no data exist to assist utilization of serial blood PCR assay to monitor response to treatment. Samples to obtain from new born before initiating antiviral treatment.

Before initiation of empiric parenteral antiviral treatment, the following specimens should be collected to aid in the diagnosis of neonatal HSV disease or to determine if antiviral therapy may also be discontinued assuming HSV has been excluded:

1. Swab for viral culture from the base of vesicles, suspicious areas, and mucous membrane lesions for viral culture (if accessible) or PCR.
2. Swab from mouth, nasopharynx, conjunctiva, and rectum

(surface cultures) for viral culture (if accessible) or PCR.

3. CSF for indices, HSV DNA PCR, and bacterial culture.
4. Whole blood for HSV DNA PCR.
5. Blood to measure Alanine aminotransferase (ALT) level.

When did maternal HSV infection occur?	Overall transmission risk	Delivery details (if rupture of membranes, ROM, timing is unknown – assume to be >4hrs)	Risk
Primary: pre-pregnancy	<1%	No lesions within six weeks of delivery Any mode of delivery Any duration of ROM Any fetal monitoring Any gestation	LOW
Recurrent HSV in this pregnancy* Or Primary HSV infection within six weeks before delivery	~3%	No lesions at delivery, any gestation, any mode of delivery	LOW
		Lesions at delivery & Caesarean with ROM <4hrs, any gestation	LOW
		Lesions at delivery, >37 weeks & any of Vaginal delivery, or caesarean section after ROM >4hrs or fetal blood sampling	MEDIUM
		Lesions at delivery, <37 weeks** & any of Vaginal delivery, or caesarean section after ROM >4hrs or fetal blood sampling	HIGH
Primary HSV infection within six weeks of delivery*	40-50%	Caesarean with ROM <4hrs pre-delivery and no fetal blood sampling, any gestation	LOW
		Caesarean with ROM >4hrs OR vaginal delivery OR fetal blood sampling, any gestation	HIGH
		Vaginal delivery	HIGH
Unknown (mother presenting in labour/late pregnancy with lesions)	Swab lesion urgently and send for HSV PCR. Discuss with virologist for processing of PCR and retrieval/testing of maternal booking sample for specific HSV serology. It is not likely to be available in time to affect management Manage as primary infection		
Maternal HSV identified in two weeks post delivery	Maternal lesions should be swabbed for HSV PCR and history sought Baby should be examined and risk stratified as above (recurrent/primary lesion at delivery). If high risk or primary or unknown infection, baby should be discussed with neonatal, paediatric infectious disease or virology consultant – likely to need clinical assessment and management as per high risk group		

Fig. 1 Local guidance on risk stratification according to timing of HSV infection in the mother and the labour and delivery details. (73) *Although antenatal acyclovir suppressive therapy reduces maternal HSV shedding, it does not change risk stratification. **It is unknown at what gestation HSV Ig transfer is adequate for protection. Note that 28 weeks is the cut off used in UK guidance for protection from varicella-zoster virus infection. (74)

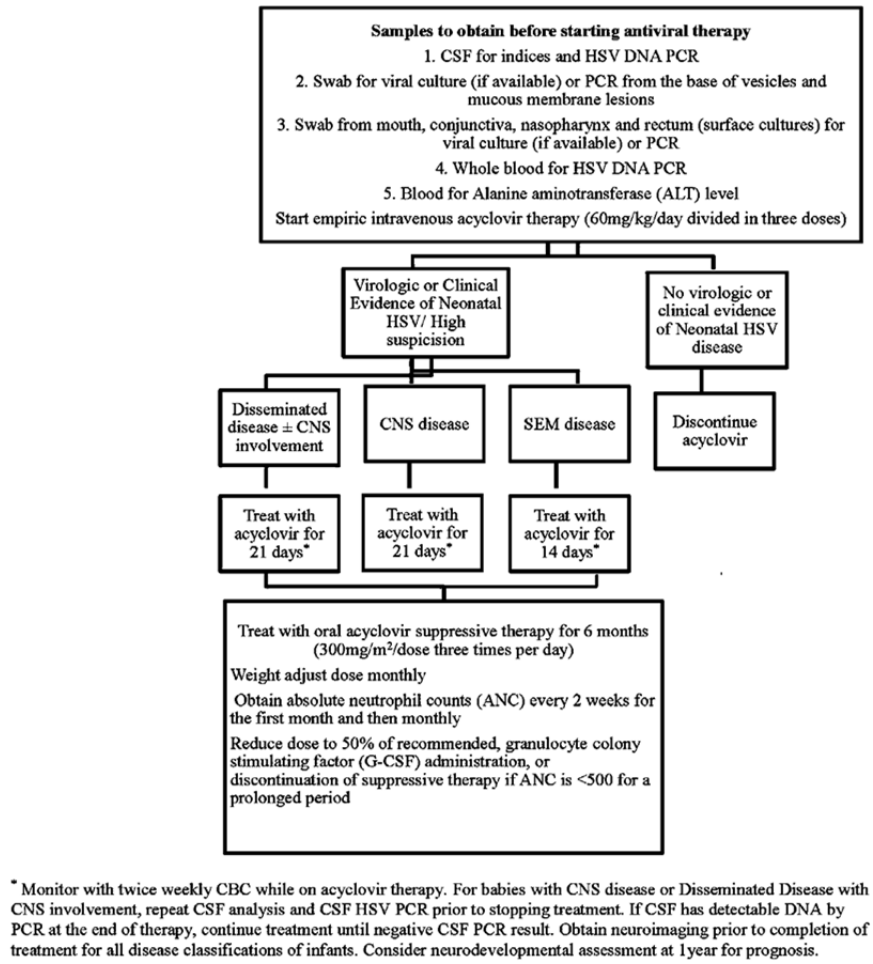
III. Treatment of Neonatal HSV

The earliest antiviral agents effective against HSV included 5iodo-2′-doexyuridine and 1-β-D-arabinofuranosylcytosine, but were found to be too toxic for human use. Vidarabine was once authorized for use in cases of life threatening HSV disease in the United States in 1977. During the 1980s, lower dose acyclovir (30 mg/kg/day administered three times a day for 10 days) used to be found effective for neonatal herpes disease [61] and used to the treatment of choice because of its safety and ease of

administration. Hence, a higher dose of acyclovir (60 mg/kg/day divided in three dosages for 14-21 days) used to be confirmed to improve mortality and morbidity associated with neonatal HSV disease. [63]

The state of the art tips is to manage all neonates with HSV disease parenterally with acyclovir given at 60 mg/kg/day divided every eight hours. [63,66] Duration of treatment is 14 days for neonates with SEM disease and 21 days for CNS and disseminated disease presentations. [64] All neonates with CNS involvement should have repeat CSF PCR near the end of 21 days of treatment for report negative CSF PCR result and for CSF indices. HSV DNA recognized in CSF at or after completion of acyclovir therapy has been associated with poorer outcomes. [66] In these rare neonates with positive CSF PCR at the end of treatment, antiviral therapy should be persisted till PCR negativity is achieved. [64,66,68] Since the significance of blood DNA PCR positivity on disease results remains obscure, serial measurements of blood DNA PCR for assessing response to therapy is presently not supported at this time. [64]

Adverse effects of high-dose acyclovir treatment include neutropenia, thrombocytopenia, and in elevated creatinine levels. [63,75,76] There have been no reported cases of renal failure and most cases of neutropenia settled aside from intervention or dose decrease. Sequential absolute neutrophil count (ANC) determination must be made somewhere around two times week after week while on high-dose acyclovir treatment. Diminishing the acyclovir dose or regulating granulocyte province colony-stimulating factor should be considered for persistent neutropenia. [63]



* Monitor with twice weekly CBC while on acyclovir therapy. For babies with CNS disease or Disseminated Disease with CNS involvement, repeat CSF analysis and CSF HSV PCR prior to stopping treatment. If CSF has detectable DNA by PCR at the end of therapy, continue treatment until negative CSF PCR result. Obtain neuroimaging prior to completion of treatment for all disease classifications of infants. Consider neurodevelopmental assessment at 1year for prognosis.

Fig. 2 – Evaluation and management of neonatal HSV disease

IV. PROGNOSIS

In the pre-antiviral period, 85% of neonates with disseminated disease and 50%of neonates with CNS disease died by 1 year of age, while50% of survivors with disseminated disease and 33% of neonates with CNS disease grew normally at 12months of age.[60] Altered mental status, DIC, prematurity, and pneumonitis in neonates with disseminated disease have been associated

with increased mortality, though increased rates of morbidity had been associated with encephalitis, DIC, seizures, and infection with HSV-2.[63] Currently, with the use of the higher dose of acyclovir (60 mg/kg/day divided in three dosages for 21 days), 1 year mortality has been diminished to 29% for disseminated disease and 4% for CNS disease,33 while 83% of neonates with disseminated disease and 31% with CNS infection improve usually at a 12months of age.[60,63] Seizures preceding or at the time of initiation of antiviral therapy has been associated with extended risk of morbidity in neonates with disseminated disease and CNS disease.[63] None of the neonates with SEM disease in the high-dose acyclovir study develop developmental disabilities at a 12months age.[63]

4.1 Antiviral suppressive therapy after treatment

The consequence of neonatal herpes disease relies upon on the extent of disease. Approximately 20% of survivors with disseminated disorder have been proven to have neurologic sequelae comparing with 70% of neonates with CNS disease. [63] A placebo-controlled study carried out via the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) documented that use of oral acyclovir suppressive therapy for 6 months after completion of parenteral acyclovir remedy for neonatal HSV disorder improves outcomes. Neonates with CNS disease stratified to the treatment arm have been determined to have better neurodevelopmental outcomes and to have fewer cutaneous recurrences in contrast to placebo group, and neonates with SEM disease have been located to have much less everyday recurrence of skin lesions whilst receiving suppressive therapy. [77] The present day suggestion is to deal with oral acyclovir at 300 mg/m2/dose, 3 times a day for 6 months. Absolute neutrophil counts ought to be monitored at two and four weeks and month-to-month thereafter following initiation of suppressive therapy. [66] Infection with acyclovir resistant lines or improvement of resistance after prolonged exposure to acyclovir has been reported, [78–80] however is rare. Persistence of signs notwithstanding strict adherence to remedy or clinical worsening whilst on appropriate therapy ought to alert the clinician to think about infection with a resistant strain or development of resistance for the duration of treatment. Approach to neonates exposed at delivery to active HSV lesions in the course of maternal primary or recurrent genital HSV infection.

The latest guidance encouraged by using the American Academy of Pediatrics (AAP) offers evidence-based tips on the management of neonates born to women with active genital herpetic lesions. [81] The suggestions take into consideration the presence of genital lesions at the time of delivery, the route of delivery, and maternal serological status. The tips are relevant solely to establishments that have get access to PCR services with a quick time, and solely to neonates exposed to HSV from maternal genital lesions existing at the time of delivery. They are no longer relevant to conditions with asymptomatic maternal shedding of HSV.

All women with genital lesions attribute of HSV at the time of delivery must have viral culture and PCR sent off from the lesions. Further characterization of the virus as HSV-1 or HSV-2 is required for correlation with serology to decide status of maternal infection (primary vs recurrent).

Management of new borns to women with lesions at delivery and history of genital herpes prior to pregnancy

- For women with history of genital herpes prior to pregnancy, the probability of lesions at delivery being recurrent are excessive and consequently the risk of transmission to new born is low (3%).
- Collect following samples from new born about 24 hours after delivery:

(a) surface cultures (conjunctiva, mouth, nasopharynx, rectum, and scalp electrode web site when present)

(b) blood DNA PCR

- It is acceptable to discharge new borns who proceed to be clinically well at 48 hours with guidelines to caregivers for very close monitoring and immediately clinical attention with development of any findings concerning neonatal HSV.
- If the surface and blood virological studies are negative at 5 days, similarly comparison of the new born is endorsed solely with the development of any signs and symptoms suggestive of neonatal HSV in the next 6 weeks.
- If the surface and blood virological studies are positive, suggesting HSV infection, a full evaluation (CSF for indices and HSV PCR, serum ALT level) is recommended to decide presence and extent of HSV disease. Therapy with intravenous acyclovir need to be started in these neonates as quickly as possible.

o If the outcomes of this evaluation are negative (normal CSF indices and negative CSF HSV PCR, normal ALT level), suggestive of neonatal HSV infection that has not progressed forward to HSV disease, pre-emptive remedy for 10 days with parenteral acyclovir ought to be administered to prevent the progression of HSV infection to HSV disease.

o If this assessment is suggestive of neonatal HSV disease (abnormal CSF indices with HSV CSF PCR þ or elevated serum ALT), therapy with acyclovir ought to be endured for 21 days for CNS or disseminated neonatal HSV disease or for 14 days for SEM disease, observed via oral suppressive remedy with acyclovir for 6 months. Management of new borns born to women with lesions at delivery and no history of genital herpes prior to pregnancy

• In women without a history of genital herpes prior to pregnancy, the presence of genital lesions in the during labour should simulate most primary infection (450% risk of transmission to neonate), non-primary infection (25% risk of transmission to neonate), or recurrent infection (3% risk of transmission).

• At about 24 hours after birth, the following samples have to be collected:

(a) surface cultures (mouth, eye, nasopharynx, and rectum)

(b) blood for HSV DNA PCR

(c) CSF to determine indices and HSV PCR

(d) serum for ALT level

• Due to greater risk, empiric therapy with intravenous acyclovir ought to be initiated.

• If the maternal serology and virological studies are suggestive of a recurrent infection and the neonate remains asymptomatic with no evidence of HSV infection/disease (negative end result on surface cultures, blood DNA PCR, and CSF PCR; and normal ALT level), discontinuation of parenteral acyclovir with directions for close monitoring and re-evaluation with the development of any new symptoms is recommended.

• If the maternal studies are suggestive of a primary or nonprimary genital infection and the neonate stays asymptomatic and lacks evidence of HSV infection/disease, remedy with 10 days of parenteral acyclovir is endorsed (pre-emptive therapy) due to the fact the neonate's risk of developing neonatal HSV disease is so high (25% to 450%).

• In neonates with evidence of HSV infection or HSV disease, the approach method is comparable to these outlined in the method to a new born to a mother with history of genital herpes prior to pregnancy: 10 days of parenteral acyclovir for HSV infection (pre-emptive therapy), 14 days of parenteral acyclovir for neonatal SEM disorder, and 21 days of parenteral acyclovir treatment for CNS or disseminated disease.

V. Prevention of HSV in the New Born

5.1 Caesarean delivery

Delivery by utilizing caesarean section diminishes anyway does not prevent HSV transmission to the neonate. Transmission of HSV has been documented in circumstances where caesarean section used to be performed before rupture of membranes.[37,73] This method of delivery in women with active genital lesions can diminish the newborn's risk of acquiring HSV[50,57] and is recommended when genital lesions or prodromal symptoms are existing at the time of delivery.[55] Caesarean delivery is extra perhaps to be effective when performed preceding rupture of membranes, but in conditions where rupture of membranes has happened and genital lesions are observed on physical examination, caesarean delivery is recommended to limit exposure of HSV to the neonate.[55] This intervention is not generally recommended for women with a prior history of genital herpes anyway no active lesions/prodromal symptoms at the time of delivery.[55,81]

5.2 Antiviral suppressive therapy for the length of pregnancy

In women with recurrent genital herpes, commencement of antiviral suppressive therapy with acyclovir/valacyclovir at 36 weeks of gestation is associated with brought down likelihood of genital lesions at the time of delivery and decreased viral detection through culture/PCR. This intervention is as of now suggested with the guide of ACOG. [55] However, subclinical viral shedding is not generally completely suppressed and the utility of such a practice in preventing neonatal HSV disease is not generally well

characterized. A recent multicentre case series reported eight cases of infants with neonatal HSV disease acquired from mothers' despite getting antiviral suppressive beyond 36weeks of gestation. [84]

5.3 HSV antibody

Presently, no vaccine has approved for preventing infection of HSV-1 or HSV-2. A HSV-2 gD subunit vaccine, adjuvant with alum, initially used to be found to be effective in preventing HSV-1 or HSV-2 genital herpes (~75% vaccine efficacy) and HSV-2 infection, but the efficacy used to be restricted exclusively to women who had been HSV-1 and HSV-2 seronegative.[85] In a resulting randomized, double blind trial assessing the adequacy of the same HSV-2 gD subunit vaccine in women seronegative for HVS-1 and HSV-2, the vaccine used to be seen to have an efficacy of 58% for preventing HSV-1 genital herpes but lack the efficacy for preventing HSV-2 genital herpes.[86]

5.4 Avoidance of post-natal acquisition

Approximately, 10% of cases are acquired in the postpartum period with the guide of exposure to the infection from symptomatic lesions or asymptomatic shedding of caretakers, alongside following Jewish ritual circumcision including oro-genital contact. [87] The guidance for infected household contacts and family members is to avoid contact with the new born. The idea for infected healthcare personnel with active herpetic whitlow sores is currently not to provide direct care for neonates. [66]

VI. Conclusion

HSV-1 and HSV-2 are highly prevalent viruses of establishing lifelong infection that is accentuated with episodic reactivation. Genital HSV infection in women of childbearing age represent a significant risk for MTCT (mother-to-child transmission) of HSV. Albeit neonatal exposure to HSV around the time of delivery is not uncommon, neonatal infections remain uncommon. Primary and first-episode genital HSV infections represent the greatest risk for MTCT.

Neonatal HSV infection is sorted as SEM, disseminated or CNS disease, and these groupings are predictive of morbidity and mortality. The advent of parenteral acyclovir as antiviral therapy for neonatal HSV infection has prompted significant overall improvement in disease outcomes, but long term neurodevelopmental outcomes in CNS disease remain unacceptability poor. Further studies are needed to improve the clinician's ability to identify infants at increased risk for HSV infection and prevent MTCT, as to propel novel antiviral agents with increased efficacy in new borns with HSV infection.

VII. Conflict Of Interest

All authors declare no conflicts of interest.

VIII. Authors Contribution

Authors have equally participated and shared every item of the work.

References

[1] Akhtar, Jihan, and Deepak Shukla. "Viral entry mechanisms: cellular and viral mediators of herpes simplex virus entry." *The FEBS journal* 276.24 (2009): 7228-7236.

[2] Roizman, Bernard, and Richard J. Whitley. "An inquiry into the molecular basis of HSV latency and reactivation." *Annual review of microbiology* 67 (2013): 355-374.

[3] Mocarski, Edward S., and Bernard Roizman. "Structure and role of the herpes simplex virus DNA termini in inversion, circularization and generation of virion DNA." *Cell* 31.1 (1982): 89-97.

[4] Buchman, Timothy G., et al. "Restriction endonuclease fingerprinting of herpes simplex virus DNA: a novel epidemiological tool applied to a nosocomial outbreak." *Journal of Infectious Diseases* 138.4 (1978): 488-498.

[5] Umene, Kenichi, and Takashi Kawana. "Divergence of reiterated sequences in a series of genital isolates of herpes simplex virus type 1 from individual patients." *Journal of general virology* 84.4 (2003): 917-923.

[6] Steiner, Israel. "Herpes simplex virus encephalitis: new infection or reactivation?" *Current opinion in neurology* 24.3 (2011): 268-274.

[7] Smith, Jennifer S., and N. Jamie Robinson. "Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review." *The Journal of infectious diseases*186.Supplement_1 (2002): S3-S28.

[8] Nahmias, ANDRÉ J., FRANCIS K. Lee, and S. U. S. A. Beckman-Nahmias. "Sero-epidemiological and-sociological patterns of herpes simplex virus infection in the world." *Scand J Infect Dis Suppl* 69 (1990): 19-36.

[9] Tunbäck, Petra, et al. "Prevalence of herpes simplex virus antibodies in childhood and adolescence: a cross-sectional study." *Scandinavian journal of infectious diseases* 35.8 (2003): 498-502.

[10] Belova, Anastasiya V., et al. "Genital herpes and pregnancy." *VF Snegirev Archives of Obstetrics and Gynaecology* 4.3 (2017): 124-130.

[11] Corey, Lawrence, et al. "The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 35.5 (2004): 435-445.

[12] Fleming, Douglas T., et al. "Herpes simplex virus type 2 in the United States, 1976 to 1994." *New England Journal of Medicine* 337.16 (1997): 1105-1111.

[13] Xu, Fujie, et al. "Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States." *Jama* 296.8 (2006): 964-973.

[14] Patton, Monica E., et al. "Seroprevalence of herpes simplex virus types 1 and 2 among pregnant women and sexually active, nonpregnant women in the United States." *Clinical Infectious Diseases* 67.10 (2018): 1535-1542.

[15] Bernstein, David I., et al. "Epidemiology, clinical presentation, and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women." *Clinical infectious diseases* 56.3 (2013): 344-351.

[16] Roberts, Craig M., John R. Pfister, and Scott J. Spear. "Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students." *Sexually transmitted diseases* 30.10 (2003): 797-800.

[17] Slutsker, Jennifer Sanderson, and Julia A. Schillinger. "Assessing the burden of infant deaths due to herpes simplex virus, human immunodeficiency virus, and congenital syphilis: United States, 1995 to 2017." *Sexually Transmitted Diseases*48.8 Suppl (2021): S4.

[18] Stephenson-Famy, Alyssa, and Carolyn Gardella. "Herpes simplex virus infection during pregnancy." *Obstetrics and Gynaecology Clinics* 41.4 (2014): 601-614.

[19] Kulhanjian, Julie A., et al. "Identification of women at unsuspected risk of primary infection with herpes simplex virus type 2 during pregnancy." *New England Journal of Medicine*326.14 (1992): 916-920.

[20] Kucera, Pavel, et al. "Seroepidemiology of herpes simplex virus type 1 and 2 in pregnant women in Switzerland: an obstetric clinic based study." *European Journal of Obstetrics & Gynaecology and Reproductive Biology* 160.1 (2012): 13-17.

[21] Sheffield, Jeanne S., et al. "Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial." *Obstetrics & Gynaecology* 108.1 (2006): 141-147.

[22] Watts, D. Heather, et al. "A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and caesarean delivery." *American journal of obstetrics and gynaecology* 188.3 (2003): 836-843.

[23] Brown, Zane A., et al. "The acquisition of herpes simplex virus during pregnancy." *New England Journal of Medicine* 337.8 (1997): 509-516.

[24] Yeager, Anne S., and Ann M. Arvin. "Reasons for the absence of a history of recurrent genital infections in mothers of neonates infected with herpes simplex virus." *Pediatrics* 73.2 (1984): 188-193.

[25] Whitley, Richard J. "Herpes simplex virus infections of the central nervous system." *Neuroinflammation and Neurodegeneration* (2014): 263-290.

[26] Whitley, Richard J., et al. "Changing presentation of herpes simplex virus infection in neonates." *Journal of Infectious Diseases* 158.1 (1988): 109-116.

[27] Brown, Zane A., et al. "Effect of serologic status and caesarean delivery on transmission rates of herpes simplex virus from mother to infant." *Jama* 289.2 (2003): 203-209.

[28] Kropp, Rhonda Y., et al. "Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study." *Pediatrics* 117.6 (2006): 1955-1962.

[29] Jones, Cheryl A., Camille Raynes-Greenow, and David Isaacs. "Population-based surveillance of neonatal herpes simplex virus infection in Australia, 1997–2011." *Clinical infectious diseases* 59.4 (2014): 525-531.

[30] Smith, Jennifer S., and N. Jamie Robinson. "Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review." *The Journal of infectious diseases*186.Supplement_1 (2002): S3-S28.

[31] Malkin, Jean-Elie. "Epidemiology of genital herpes simplex virus infection in developed countries." *Herpes: the journal of the IHMF* 11 (2004): 2A-23A.

[32] James, Scott H., and David W. Kimberlin. "Neonatal herpes simplex virus infection." *Infectious Disease Clinics* 29.3 (2015): 391-400.

[33] Berntsson, Matilda, et al. "Decreasing prevalence of herpes simplex virus-2 antibodies in selected groups of women in Sweden." *Acta dermato-venereologica* 89.6 (2009).

[34] Mertz, Gregory J., Susan L. Rosenthal, and Lawrence R. Stanberry. "Is herpes simplex virus type 1 (HSV-1) now more common than HSV-2 in first episodes of genital herpes?" *Sexually transmitted diseases* 30.10 (2003): 801-802.

[35] James, Scott H., and David W. Kimberlin. "Neonatal herpes simplex virus infection." *Infectious Disease Clinics* 29.3 (2015): 391-400.

[36] Kimberlin, David W. "The scarlet H." *The Journal of infectious diseases* 209.3 (2014): 315-317.

[37] Whitley, Richard J. "Herpes simplex virus infections of the central nervous system." *Drugs* 42.3 (1991): 406-427.

[38] Brown, Zane A., et al. "Effect of serologic status and caesarean delivery on transmission rates of herpes simplex virus from mother to infant." *Jama* 289.2 (2003): 203-209.

[39] Baker, David A. "Consequences of herpes simplex virus in pregnancy and their prevention." *Current opinion in infectious diseases* 20.1 (2007): 73-76.

[40] Watts, D. Heather, et al. "A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and caesarean delivery." *American journal of obstetrics and gynaecology* 188.3 (2003): 836-843.

[41] Brown, Zane A., et al. "Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labour." *New England Journal of Medicine* 324.18 (1991): 1247-1252.

[42] Arvin, Ann M., et al. "Failure of antepartum maternal cultures to predict the infant's risk of exposure to herpes simplex virus at delivery." *New England Journal of Medicine* 315.13 (1986): 796-800.

[43] Pinninti, Swetha G., and David W. Kimberlin. "Maternal and neonatal herpes simplex virus infections." *American journal of perinatology* 30.02 (2013): 113-120.

[44] Sullender, Wayne M., et al. "Type-specific antibodies to herpes simplex virus type 2 (HSV-2) glycoprotein G in pregnant women, infants exposed to maternal HSV-2 infection at delivery, and infants with neonatal herpes." *Journal of Infectious Diseases* 157.1 (1988): 164-165.

[45] Tookey, Pat, and Catherine S. Peckham. "Neonatal herpes simplex virus infection in the British Isles." *Paediatric and perinatal epidemiology* 10.4 (1996): 432-442.

[46] Pascual, A., et al. "Neonatal herpes simplex virus infections in Switzerland: results of a 6-year national prospective surveillance study." *Clinical microbiology and infection* 17.12 (2011): 1907-1910.

[47] De Jong, E. P., et al. "Is routine TORCH screening warranted in neonates with lenticulostriate vasculopathy?" *Neonatology*97.3 (2010): 274-278.

[48] Schillinger, Julia A., and Susan Blank. "Julia A. Schillinger, MD, MSc." (2013).

[49] Samies, Nicole L., Scott H. James, and David W. Kimberlin. "Neonatal Herpes Simplex Virus Disease: Updates and Continued Challenges." *Clinics in Perinatology* 48.2 (2021): 263-274.

[50] Brown, Zane A., Anna Wald, and Lawrence Corey. "Caesarean delivery and risk of herpes simplex virus infection." *Jama*289.17 (2003): 2208-2209.

[51] Corey, Lawrence, and Anna Wald. "Maternal and neonatal herpes simplex virus infections." *New England Journal of Medicine* 361.14 (2009): 1376-1385.

[52] Pinninti, Swetha G., and David W. Kimberlin. "Neonatal herpes simplex virus infections." *Seminars in perinatology*. Vol. 42. No. 3. WB Saunders, 2018.

[53] Pittet, Laure F., and Nigel Curtis. "Postnatal Exposure to Herpes Simplex Virus: To Treat or Not to Treat?" *The Pediatric Infectious Disease Journal* 40.5S (2021): S16-S21.

[54] Patel, Chaya D., et al. "Maternal immunization confers protection against neonatal herpes simplex mortality and behavioural morbidity." *Science translational medicine* 11.487 (2019): eaau6039.

[55] Samies, Nicole L., and Scott H. James. "Prevention and treatment of neonatal herpes simplex virus infection." *Antiviral research* 176 (2020): 104721.

[56] Hill, James B., et al. "Intrapartum fetal surveillance: review of three national guidelines." *American journal of perinatology*29.07 (2012): 539-550.

[57] Nahmias, AndréJ, et al. "Perinatal risk associated with maternal genital herpes simplex virus infection." *American journal of obstetrics and gynaecology* 110.6 (1971): 825-837.

[58] Anzivino, Elena, et al. "Herpes simplex virus infection in pregnancy and in neonate: status of art of epidemiology, diagnosis, therapy and prevention." *Virology journal* 6.1 (2009): 1-11.

[59] Pinninti, Swetha G., and David W. Kimberlin. "Preventing herpes simplex virus in the new born." *Clinics in perinatology*41.4 (2014): 945-955.

[60] Whitley, R. J. "Neonatal herpes simplex virus infections." *Journal of medical virology* 41. S1 (1993): 13-21.

[61] Whitley, Richard, et al. "A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection." *New England Journal of Medicine* 324.7 (1991): 444-449.

[62] Whitley, Richard, et al. "Predictors of morbidity and mortality in neonates with herpes simplex virus infections." *New England Journal of Medicine* 324.7 (1991): 450-454.

[63] Kimberlin, David W., et al. "Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections." *Pediatrics* 108.2 (2001): 230-238.

[64] James, Scott H., and David W. Kimberlin. "Neonatal herpes simplex virus infection." *Infectious Disease Clinics* 29.3 (2015): 391-400.

[65] Pittet, Laure F., and Nigel Curtis. "Postnatal Exposure to Herpes Simplex Virus: To Treat or Not to Treat?" *The Pediatric Infectious Disease Journal* 40.5S (2021): S16-S21.

[66] Rellosa, Neil. "İnfectious etiologies of cerebral palsy." *Cerebral Palsy* (2020): 45-54.

[67] Corey, Lawrence, and Anna Wald. "Maternal and neonatal herpes simplex virus infections." *New England Journal of Medicine* 361.14 (2009): 1376-1385.

[68] Kimberlin, David W., et al. "Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease." *Journal of Infectious Diseases*174.6 (1996): 1162-1167.

[69] Kimura, Hiroshi, et al. "Detection of viral DNA in neonatal herpes simplex virus infections: frequent and prolonged presence in serum and cerebrospinal fluid." *Journal of Infectious Diseases* 164.2 (1991): 289-293.

[70] Malm G, Forsgren M. Neonatal herpes simplex virus infections: HSV DNA in cerebrospinal fluid and serum. Arch Dis Child Fetal Neonatal Ed. 1999;81:F24–F29.

[71] James, Scott H., and David W. Kimberlin. "Quantitative herpes simplex virus concentrations in neonatal infection." *The Journal of Pediatrics* 166.4 (2015): 793-795.

[72] James, Scott H., and David W. Kimberlin. "Quantitative herpes simplex virus concentrations in neonatal infection." *The Journal of Pediatrics* 166.4 (2015): 793-795.

[73] Arend-Trujillo, Monica, and Lauren Dhugga. "Neonatal herpes simplex virus infection: maternal risk stratification and management of at-risk neonates." *Infant* 18.1 (2022).

[74] UK Health Security Agency. Varicella: the green book, chapter 34. 2019 online at: www.gov.uk/government/publications/varicella-the-green-b

[75] Ramgopal, Sriram, Paria M. Wilson, and Todd A. Florin. "Diagnosis and management of neonatal herpes simplex infection in the emergency department." *Pediatric emergency care* 36.4 (2020): 196-202.

[76] Hanna, Mina H., David J. Askenazi, and David T. Selewski. "Drug induced acute kidney injury in neonates." *Current opinion in pediatrics* 28.2 (2016): 180.

[77] Kimberlin, David W., et al. "Oral acyclovir suppression and neurodevelopment after neonatal herpes." *New England Journal of Medicine* 365.14 (2011): 1284-1292.

[78] Kakiuchi, Satsuki, et al. "Neonatal herpes encephalitis caused by a virologically confirmed acyclovir-resistant herpes simplex virus 1 strain." *Journal of clinical microbiology* 51.1 (2013): 356-359.

[79] Bacon, Teresa H., et al. "Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy." *Clinical microbiology reviews* 16.1 (2003): 114-128.

[80] Kakiuchi, Satsuki, et al. "Neonatal herpes encephalitis caused by a virologically confirmed acyclovir-resistant herpes simplex virus 1 strain." *Journal of clinical microbiology* 51.1 (2013): 356-359.

[81] MAAKS, DAWN LEE GARZON. "Principles of developmental management of children." *Burns' Pediatric Primary Care E-Book* (2019): 63.

[82] Chudnovets, Anna, et al. "Role of inflammation in virus pathogenesis during pregnancy." *Journal of virology* 95.2 (2020): e01381-19.

[83] Roberts, Scott W., et al. "Genital herpes during pregnancy: no lesions, no caesarean." *Obstetrics & Gynaecology* 85.2 (1995): 261-264.

[84] Rogan, Sarah C., and Richard H. Beigi. "Management of Viral Complications of Pregnancy: Pharmacotherapy to Reduce Vertical Transmission." *Obstetrics and Gynaecology Clinics*48.1 (2021): 53-74.

[85] Stanberry, Lawrence R., et al. "Glycoprotein-D–adjuvant vaccine to prevent genital herpes." *New England Journal of Medicine* 347.21 (2002): 1652-1661.

[86] Belshe, Robert B., et al. "Efficacy results of a trial of a herpes simplex vaccine." *New England Journal of Medicine* 366.1 (2012): 34-43.

[87] Slutsker, Jennifer Sanderson, and Julia A. Schillinger. "Assessing the burden of infant deaths due to herpes simplex virus, human immunodeficiency virus, and congenital syphilis: United States, 1995 to 2017." *Sexually Transmitted Diseases*48.8 Suppl (2021): S4.