The Egyptian Journal of Hospital Medicine (October 2017) Vol.69 (4), Page 2209-2214

Infection with Genital Herpes Virus and Its Treatment in Relation to Preterm Delivery

Ahmad Ayed Derham[1], Hanadi Hezam AL-Thobiati[2], Mohannad ali alghamdi[1], Nasir Ahmad Alsubai[2], Lamees Hatim Aldoobie[1], Razan Hussain Alhasawi[3], Sara Falah Alsahafi[3]

1 King Abdulaziz University, 2 Umm AL-Qura University,

3 Batterjee Medical College for Science and Technology

Corresponding Author: Ahmad Ayed Derham, email: Ahmad_aaasda@hotmail.com

ABSTRACT

Infection with herpes simplex is a standout amongst the most well-sexually transmitted infections. As the infection is common in women of reproductive age it may be contracted and transmitted to the fetus amid pregnancy and the new-born. Herpes simplex virus is a significant cause of neonatal infection, which could lead to death or long-term disabilities. Infrequently in the uterus, as it happens frequently during the transmission delivery.

The most serious danger of transmission to the fetus and the new-born happens in case of an early maternal infection contracted in the second half of pregnancy. The danger of transmission of maternal-fetal-neonatal herpes simplex could be diminished by applying a treatment with antiviral medicines or depending on a caesarean section in some particular cases. The aim of this paper is to provide recommendations on the management of herpes simplex infections in pregnancy and approaches to decrease perinatal transmission of herpes simplex virus.

Keywords: Genital Herpes, Herpes Simplex Virus, Caesarean, Perinatal Transmission.

INTRODUCTION

Genital herpes is a main public- health concern as a result of its recurrent nature, its ability to be transmitted asymptomatically, and its potential for complications [1]. This sexually transmitted disease is initiated by herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), in most cases by HSV-2 [2]. HSV-2 is the reason of most genital herpes and is nearly always sexually transmitted. HSV-1 is generally transmitted in childhood through non-sexual contacts. Nevertheless, HSV-1 has emerged as a principle causative agent of genital herpes in several developed countries [3, 4]. The highest occurrence of HSV infections occurs in women of reproductive age, the danger of maternal transmission of the virus to the foetus or neonate has become a main health concern [5]. Women recently diagnosed with genital herpes will habitually experience psychological distress and concern about future sexual relationships and pregnancy.

Demographically, HSV-2 infection is more typical in women than in men, and in the non-Hispanic black populace, there is an expanded predominance in both genders. Even between people with comparative quantities of lifetime sexual accomplices, this difference between the ethnicities remains [3]. Most individuals with symptomatic genital herpes will encounter repetitive contaminations inside the principal year of the essential disease, and the middle repeat rate is four to six scenes for each year [7]. Pregnant ladies with untreated genital herpes amid the first or second trimester seem to have a more noteworthy than two-overlap danger of preterm conveyance contrasted with ladies not exposed with herpes, especially in connection to premature rupture of membrane and early preterm conveyance (less than or equal 35 week of gestation) [8]. Pregnant women who get antiherpes treatment have a lower danger of preterm conveyance than untreated ladies, and their preterm conveyance chance is like that seen in unexposed women.

The study was approved by the Ethics Board of King Abdulaziz University.

MATERIALS AND METHODS

- **Data sources and search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from January 1, 1980, through February 28, 2017. The following search terms were used: Genital Herpes, Herpes Simplex Virus, Caesarean, Perinatal Transmission, HSV-1, HSV- 2, and Disseminated Herpes Infection.

- **Data extraction**

Two reviewers independently reviewed studies, abstracted data, and resolved disagreements by

Received:30 / 7/2017 DOI : 10.12816/0041518

Accepted: 9/ 8 /2017

consensus. Studies were evaluated for quality. A review protocol was followed throughout.

Transmission of HSV

Components related with transmission incorporate the sort of maternal contamination (primary or recurrent), the nearness of transplacental maternal killing antibodies, the length of break of layers before conveyance, the utilization of fetal scalp electrodes and the method of delivery. The dangers are most noteworthy when a lady procures another disease (essential genital herpes) in the third trimester, especially inside a month and a half of conveyance, as viral shedding may endure and the infant is probably going to be conceived before the advancement of defensive maternal antibodies [9, 10]. Rarely, intrinsic herpes may happen because of the transplacental intrauterine disease. Case reports propose that the skin, eyes and CNS might be influenced and there might be fetal development limitation or fetal death [11, 12].

Disseminated herpes is more mutual in preterm infants and happens almost entirely as a result of primary infection in the mother. Even though recurrent genital herpes is linked with a very low risk of neonatal herpes, recurrent herpes at the time of delivery, which is normally asymptomatic or unrecognised, might cause the localised forms of neonatal herpes: both local CNS disease and skin, eye and mouth infection. Transplacentally attained HSV antibodies do not avert herpes virus spreading to the brain of the neonate [13]. Data from the USA propose that about 2% of women obtain genital HSV infection in pregnancy and most of these maternal infections are asymptomatic or unrecognised [9, 10]. Nonetheless, acquisition in the KSA in pregnancy can vary particularly given differing rates of neonatal herpes between KSA and USA. It may be difficult to differentiate clinically between recurrent and primary genital HSV infections, as several first episodes HSV infections are not true primary infections [14].

Disseminated herpes infection in the mother

Disseminated herpes, which might exist with hepatitis, disseminated skin lesions or a combination of these conditions, is infrequent in adults. However, it has been more frequently reported in pregnancy, particularly in the immunocompromised. The maternal mortality related with this condition is high [15]. All immunocompromised women, for example, those infected with the HIV virus, are at increased danger of more severe and frequent symptomatic recurrent episodes of genital herpes amid pregnancy and of asymptomatic detaching of HSV at term. Since co-infection with HSV and HIV outcomes in an increased replication of both viruses, there are worries that genital reactivation of HSV might increase the danger of perinatal transmission of both HIV and HSV [16, 17].

Neonatal herpes simplex virus infections

The importance of neonatal herpes simplex virus infection differs and depends on the extent of the infection (Table 1). Local infections are the most frequent and benign type. Nonetheless, serious infections may happen and can lead to death or long-term CNS morbidity. Neonatal HSV infections may be categorised as disseminated disease (25%); central nervous system disease (30%); and disease restricted to the eyes, skin or mouth (45%). Mortality has reduced to 30% for disseminated disease and 4% for central nervous system disease over the previous two decades. Nearly 20% of pretentious neonates will have long term neurologic sequelae. Kimberlin et al recommends that neonatal suppression treatment with acyclovir in infants with HSV might improve neurodevelopmental results [18].

Table 1: Types and Sequelae of Neonatal HSV Infection

Disease Type	Incidence %	Mortality %	Long-term Morbidity %*
CNS	35	15	65
Disseminated	20	60-80	40
Localized disease of skin, eye, mouth	45	0	5

*Morbidity includes mental retardation, chorioretinitis, seizures, and other CNS effects.

Antiviral treatment

Acyclovir

Acyclovir, a nucleoside analogue, was the first antiviral treatment accepted for the treatment and prevention of HSV infection. Acyclovir selectively inhibits viral DNA replication of HSV, whereas having little influence on normal cells. Acyclovir is selective

for HSV-infected cells for the reason that it needs phosphorylation by a viral enzyme (thymidine kinase) to acyclovir monophosphate. Phosphorylation does not ensue in uninfected cells, where it residues virtually undetectable. After its conversion to acyclovir monophosphate in infected cells, other cellular enzymes convert it to acyclovir triphosphate, which acts to inhibit HSV-specific DNA polymerase, consequential in termination of the DNA transcript. With primary HSV infection in non-pregnant women, acyclovir decreases the length of local pain, dysuria, and viral shedding, and it reduces the time to crusting and healing of lesions [19]. With day-to-day usage, acyclovir likewise decreases symptomatic recurrences and subclinical viral shedding.

Amid pregnancy, acyclovir crosses the placenta and gathers in the amniotic liquid. Postpartum, acyclovir contemplates in breast milk. Fetal serum focuses are proportionate to maternal serum fixations. A potential disadvantage of acyclovir treatment is deferred and diminished counter acting agent reaction to an essential HSV disease. Regardless of whether this is because of a diminished viral load or to insusceptible concealment is obscure. Acyclovir has been named a classification B drug (no teratogenic impacts were found in examined animal, however no or restricted human investigations are accessible).

Valacyclovir and famciclovir

Since the presentation of acyclovir, more up to date second-age antivirals have been presented (eg, valacyclovir, famciclovir). Valacyclovir is indistinguishable to acyclovir with the exception of the expansion of an ester side chain that expands bioavailability. Once retained, it is changed over to acyclovir in vivo. This takes into consideration higher serum levels with a less-visit dosing plan. Famciclovir is a nucleotide simple that has a more extended intracellular half-life. Likewise with acyclovir, these second-generation agents have been used for treatment of symptomatic primary and recurrent lesions in addition to daily suppression. Both valacyclovir and famciclovir have been labelled category B drugs [20].

The recommended prescriptions of the 3 antiviral agents are as follows:

Table 2: Recommended Dosages of the Antiviral Agents for Genital Herpes Infection

Indication	Acyclovir	Valacyclovir	Famciclovir
First episode	400 mg tid OR 200 mg 5 times/d (for 7-10 d)	1000 mg bid (for 7-10 d)	250 mg tid (for 7-10 d)
Recurrent	400 mg tid (for 3-5 d) OR 800 mg PO tid (for 2 d)	500 mg bid (for 3 d)	1000 mg bid (for 1 d)
Daily suppression	400 mg bid	500 mg qd or 1000 mg qd (if more than 9 recurrences/year)	250 mg bid

Table 3: Recommended Dosages of the Antiviral Agents for Genital Herpes Infection for the pregnant women

Indication	Acyclovir	Valacyclovir
Primary or first-episode infection	400mg TID for 7-10 days	1g orally BID for 7-10 days
Symptomatic recurrent episodes	400mg TID for 5 days OR 800mg orally BID for 5 days	500g orally, BID, for 3 days or 1g orally, daily, for 5 days
Daily suppression	400mg orally, TID from 36 weeks estimated gestational age until delivery	500mg orally, BID, from 36 weeks estimated gestational age until delivery
Severe or disseminated disease	5-10mg/kg, intravenously, every 8 hours for 2-7 days, then orally therapy for primary infection to complete 10 days	

Prevention of postnatal transmission

- In 25% of cases a likely source of postnatal infection is responsible, typically a close relative of the mother [21].
- Efforts to prevent postnatal transmission of HSV are consequently essential and advice should be given to the mother.
- The mother and all those with herpetic lesions who may be in contact with the neonate, including staff, should practice careful hand hygiene.
- People with oral herpetic lesions (cold sores) must not kiss the neonate.

Strategies to prevent HSV transmission

- **Antiviral suppression for gravidas with first-episode infections during pregnancy**

Distinguishing that recurrent infections occur more regularly within the first year after a primary infection, Scott et al randomized 46 gravidas with first genital outbreak amid pregnancy to either acyclovir (400 mg tid) or placebo beginning at 36 weeks' gestation [22]. Women receiving acyclovir experienced a major decrease in the percentage of HSV recurrences at delivery and caesarean deliveries for HSV (36% versus 0%). On the other hand, the decrease in the total number of caesarean deliveries in enrolled women was not statistically noteworthy (40% versus 19%). No patients in this examination had asymptomatic shedding at the season of conveyance, and no new-born child created neonatal HSV contamination or had complexities from acyclovir. No endeavour was made to recognize primary infections, non-primary first-episode infections, or first perceived recurrent infections. This examination was, be that as it may, the first to show the utility of antiviral concealment in diminishing the quantity of repeats at time of delivery.

- **Routine antiviral suppression for gravidas with a history of genital HSV**

In 1998, Brocklehurst and partners played out a twofold visually impaired fake treatment controlled trial that included 63 ladies with a background marked by intermittent HSV disease [23]. These ladies were randomized to either acyclovir (200 mg qid) or placebo, both starts at 36 weeks' development. Non-significant diminishments were found in repetitive HSV flare-ups at conveyance, caesarean conveyances for HSV, and aggregate caesareans in the acyclovir gathering. No new-born child in either assembles created neonatal HSV, and no gravida experienced poisonous quality from acyclovir. The creators reasoned that the example measure was too little to exhibit a critical advantage from acyclovir and suggested that acyclovir be utilized just in clinical trials. Since that time, extra randomized clinical investigations have been played out, each exhibiting non-significant diminishments in caesarean conveyances for intermittent HSV flare-ups and no distinctions in neonatal results.

A meta-analysis in 2003 combined the results of five randomized clinical trials assessing the use of antenatal suppressive acyclovir in 799 gravidas [24]. The results of the meta-analysis are shown in Table 3.

Table 3: Antiviral Trial Results

Outcome	Acyclovir %	Placebo %	OR (95% CI)
Recurrent HSV infection at delivery	3.5	15.5	0.25 (0.15-0.40)
Asymptomatic HSV shedding at delivery	0	3.1	0.09 (0.02-0.39)
Total cesarean deliveries	16.7	25.9	0.61 (0.43-0.86)
Cesarean deliveries for HSV	4	14.7	0.30 (0.13-0.67)

All of the observed results were significantly reduced with suppressive use of acyclovir (no 95% confidence interval comprised the value of 1). No cases of neonatal herpes were stated in any of the 799 infants in all 5 studies, whether in the acyclovir or placebo group. Because of the fewness of neonatal HSV infections, far larger numbers of subjects are necessary to determine a significant difference in this important result.

Recommended regimen for suppressive therapy for pregnant women with recurrent genital herpes

- Acyclovir 400mg orally three times per day
- Valacyclovir 500mg orally twice a day

Identification of seronegative gravidas at risk for primary and non-primary first-episode genital HSV infections

This method is the most aspiring of all strategies to avoid vertical transmission. Its reasoning is based on the observation that most neonatal HSV transmission happens not in gravidas with a history of genital HSV, but somewhat in women who have primary or non-primary first-episode genital infections at the time of labor. If routine serologic screening shows that a woman was at hazard for primary HSV (no antibodies) or non-primary first-episode infection either only HSV-1 or HSV-2, she might be counselled to prevent genital-genital or oral-genital contact in order to avoid new genital infections throughout the third trimester of pregnancy and, therefore, decrease neonatal HSV infections.

An alternate strategy would be to check the serologic status of the sexual partner too and to mention sexual abstinence only if the woman was at risk and the couple was serologically discordant, which happens in 15-25% of couples. Such as, if a woman was seronegative for HSV-2, and her partner was seropositive for HSV-2, the woman's risk of obtaining HSV-2 amid pregnancy would be as high as 20%. Such a couple would, therefore, be advised to abstain from sexual activity amid pregnancy.

Thung and Grobman implemented a decision analysis comparing current routine care (no serology testing); couple screening for susceptible gravidas with counseling for discordant couples; and counselling for discordant couples plus acyclovir prophylaxis for seropositive women to prevent symptomatic and asymptomatic shedding in labor [25]. Out of 100,000 hypothetical women, serology screening would prevent 2 and 3.8 neonatal deaths or neurologic sequelae for strategies 2 and 3, respectively, with respective costs of 5.8 and 4 million dollars for each adverse sequela prevented. Similarity, the decision analysis of HSV-2 screening by Baker and colleagues compared no routine serology screening; routine screening, counseling for HSV-negative gravidas about safe sex, and offering acyclovir prophylaxis to HSV-positive women at 36 weeks; and testing the partners of HSV-negative women and offering suppressive therapy for HSV-positive men starting at 15 weeks [26].

At this time, routine maternal serologic screening is not prevalent. Reasons for this include cost attentions; the unconfirmed value of abstinence counselling in susceptible women; and the psychosocial ramifications of discovering a positive serology, as HSV-2 is mostly a sexually-transmitted disease. Currently, the American College of Obstetricians and Gynecologists has not recognized routine maternal HSV serology screening [27].

CONCLUSION

Because of the high prevalence of genital HSV infections and the potentially devastating consequences of neonatal HSV disease, it is significant that clinicians understand how to distinguish and treat neonatal HSV infections in a timely manner, and how best to decrease mother-to-child transmission. Results for neonatal HSV infections have improved in the past 30 years, but there is continued need for further studies to help maximize the prevention and treatment of this disease.

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