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A Call for Spreading Awareness among Parents and Gynecologists on the Danger of Genital Herpes on Neonates - Department of Medicine and Dermatology- King Abdulaziz Hospital and Oncology Center, Jeddah, Saudi Arabia

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ABSTRACT

Background: genital Herpes infection is caused by HSV 1 and HSV2 Virus. It causes distressing symptoms in a significant number of adolescents and adults with over 40 million people sufferers from recurrent HSV genital ulcer disease causes significant disease globally and it is potentially fatal when transmitted to neonates and most maternal infections with risk of transmission are asymptomatic.

Aim of the Study: highlighting the crucial rule of parents' education and awareness on the prevention and management of HSV in neonates (NHSV).

Patients and methods: 112 females and 34 males HSV2 seropositive patients were assigned to fill a questionnaire on their awareness about HSV2 infection and symptoms and its effect on potential neonates. In parallel, there was a questionnaire for the assigned gynecologists to assess the counseling process of the mothers about the history of previous infection. Data was compared to the patients' medical chart and past delivery of defected and treated neonates.

Results: Patients whom were aware with the dangerous effect of the infection of virus had no mortality in their neonatal and had the good treatment for them.

Conclusion: Couple educational and Awareness campaigns on genital Herpes infection have become a compelling need in order to avoid neonates mortality and help in designing preventive measures for neonates morbidity.

Keywords: Genital Herpes, HSV2, NHSV, Acyclovir, Neonates morbidity, pregnant women.

INTRODUCTION

Herpes genitalis is one of the most common sexually transmitted diseases [(1)].

Historically, Herpes infection routes of transmission have been narrowed down to either sexual contact for HSV-2 infection, or oral-to-oral contact for HSV-1 infection causing oro-labial herpes. However, there is an emerging trend of increasing genital HSV-1 infection among young people in many settings [(2)]. Although type-specific serological tests can measure the presence of HSV-1 antibodies, they are unable to determine the site of infection [(3)]. However, recurrences due to genital HSV-1 infection are much less frequent than with genital HSV-2 infection [(4)], and globally most symptomatic genital herpes is due to HSV-2[(5)].

According to 2012 statistical study, there were 417 million people aged 15–49 years (range: 274–678 million) living with HSV-2 infection world-wide (11.3% global prevalence), of whom 267 million were women. The global burden of HSV-2 infection is large, leaving over 400 million people at increased risk of genital ulcer disease, HIV acquisition, and transmission of

HSV-2 to partners or neonates. These estimates highlight the critical need for development of vaccines, microbicides, and other new HSV prevention strategies [(6)].

The incidence of herpes simplex virus (HSV) infection has been increasing steadily in recent decades, and concerns about perinatal HSV infection are growing among women of reproductive age because of the risk of transmission of the virus to their babies during pregnancy, with potentially devastating consequences to the fetus[(7)] . It is potentially fatal when transmitted to neonates, and causes distressing symptoms in a substantial number of adolescents and adults with over 40 million people sufferers from recurrent HSV genital ulcer disease.

Maternal genital HSV cases may be classified as follows [(8)]:

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- Newly acquired
  - First-episode primary infection (mother has no serum antibodies to HSV-1 or -2 at onset);
  - First-episode nonprimary infection (mother has a new infection with one HSV type in the presence of antibodies to the other type).
- Recurrent (mother has pre-existing antibodies to the HSV type that is isolated from the genital tract).
- The most common and important category of NHSV acquisition is intrapartum. Even for HSV-1, >75% of cases of NHSV are acquired during delivery from genital disease that is often newly acquired and asymptomatic [(9)]. Newborns may also acquire HSV infection through in utero or postnatal transmission. Although rare, in utero HSV infection can have teratogenic effects such as skin lesions or scars, central nervous system (CNS) disorders and chorioretinitis[(10)] .Postnatal infection can be acquired from the infant's mother or from nonmaternal sources (e.g. relatives or hospital personnel with orolabial herpes or asymptomatic shedding of HSV-1)[(11)].
- In most cases of NHSV infection, there is no known history of maternal genital HSV because mothers have never had or have never noticed external genital lesions. Studies show that 75% to 90% of individuals who are seropositive for HSV-2 were unaware of their infection [(12)].All infants, therefore, must be considered to be potentially at risk for NHSV infection. Seropositive women intermittently shed HSV in their genital tracts, with 10% to 20% of individuals with HSV-2 shedding on any given day, as detected by polymerase chain reaction (PCR) testing [(13)].
- The category of maternal infection at time of delivery influences the likelihood of NHSV acquisition, presumably because mothers who have had an HSV infection transmit HSV-neutralizing antibodies to their infant across the placenta, provided that their infant is not born before 32 weeks' gestation[(14)] .Thus, infants born to mothers who have a first-episode primary infection at time of delivery are at the highest risk for acquiring HSV, with transmission rates of up to 60%, because their mother had no pre-existing neutralizing antibodies to transmit[(15)] . For infants born to mothers who have first-episode nonprimary infections, the transmission rates are in the order of ≤30% because cross-reactive antibodies are present. The lowest risk of neonatal transmission occurs with maternal recurrent infection (at <2%) because type-specific antibodies are present [(16)].
- Delivery by elective cesarean section markedly reduces but does not eliminate the risk for newborn infection [(17)] .Women with recurrent genital HSV are commonly prophylaxed with acyclovir (ACV) or valacyclovir from 36 weeks' gestation until delivery. In this context, antiviral therapy near the end of pregnancy can lower recurrence of genital HSV and shedding at delivery [(18)] .however, it is not clear whether this prophylaxis translates to a reduced risk for NHSV infection. Guidelines regarding the role of Cesarean delivery and the indications for acyclovir are published [(19)], but are not specifically addressed in the present statement.

PATIENTS AND METHODS

Study Setting and Design

This study was conducted at the Gynecology Inpatient and Outpatient Clinics of King Abdulaziz Hospital for 112 mother patients and 34 husbands.

*Study Population a*nd *Inclusion Criteria:*

- Mothers with a childbearing age (18-49 years old) who were tested positive for HSV2 and given birth over a period of two years (March 2014 to April 2016)
- Fathers tested positive for HSV 2
- Couples with a neonate with Localized or disseminative disease triggered by NHSV (tested positive for HSV).
- Gynecologists who witnessed an HSV2 infected mother delivery.

Clinical examination and laboratory investigations were carried out for the study subjects to exclude other causes of fetal wastage, such as hypertension, diabetes mellitus, syphilis, Rh (rhesus) incompatibility, physical causes of abortion, and consanguinity. Subjects with known causes of fetal wastage were excluded from the study. All of them were interviewed to ascertain age, medical and obstetric information.

Study Design and Timeline

An informed consent was obtained from the previously mentioned hospitals and healthcare centers, following this, the Study staff administered a baseline interview with the patients.

1. Retesting

*D*iagnosis confirmation for symptomatic and asymptomatic patients was done by an assigned study nurse who obtained a blood sample from the participant for HSV-2 type-specific serologic testing. Patients were able to receive results by calling the clinic's results line. Patients tested positive for HSV-2 were provided standardized counseling by experienced study staff in the presence of the study conductors. Two follow-up telephone interviews were conducted 1 week (follow-up 1) and 3 months (follow-up 2) after a participant received his or her test results.

Laboratory Methods

Anti-HSV-1 and anti-HSV-2 IgG and IgM antibodies were determined using type-specific ELISA.

2. Psychosocial Morbidity

The questionnaire collected information on demographics, sexual behavior, mental health and perception of genital herpes. We modified 2 questionnaires to assess mental health and sexual attitudes. We assessed mental health using a modified version of the Rand Mental Health Inventory 5 item version (MHI-5). The MHI-5 evaluates emotional well-being, anxiety, depression, and behavioral/emotional control [(20)]. We modified the 6-point scale (1 all of the time or always; 6 none of the time or never) to a 5-point scale (1 never; 5 always) that allowed participants to pick a neutral response (3 sometimes). The Multidimensional Sexual Self-Concept Questionnaire (MSSCQ) is a comprehensive100-item survey that explores 20 aspects of sexual self-concept [(21)]. To assess sexual attitudes for this study, we took 10 questions from the survey that only assessed sexual anxiety, sexual optimism, sexual self-monitoring, sexual satisfaction, sexual fear/apprehension, and sexual depression. We also revised the 5-point scale responses from "not at all characteristic of me" (1) and "very characteristic of me" (5) to "strongly disagree" (1) and "strongly agree." (5) Finally, we evaluated perception of genital herpes by administering an instrument from the American Social Health Association (ASHA) that assessed perceived trauma associated with genital herpes; responses were on a 4-point scale ranging from "not traumatic at all" (1) to "very traumatic" [(21)].

Collection of Data

Subjects screened using a predesigned pretested schedule considering the inclusion and exclusion criteria and data collection was pulled from the outcome of the following methods:

a. Patients' Medical Chart

a complete record of a patient's key clinical data and medical history, such as demographics, vital signs, diagnoses, medications, treatment plans, progress notes, problems, immunization dates, allergies, radiology images, and laboratory and test results, neonates mortality and morbidity.

b. Patients' questionnaire

A detailed questionnaire allowing retrospective diagnosis of clinically probable genital HSV infection. The questionnaire was designed to collect detailed information on (a) socio-demographic characteristics (b) lifestyle and habits (c) medical history. The sociodemographic and lifestyle variables considered to be of importance included: age, nationality, consanguinity, education level, education level of husband, monthly family income, occupation, number of family members, number of children below five years and past history of sexually transmitted infections.

c. Colleague questionnaire

Colleague questionnaire was administrated to be filled out by the assigned gynecologists involved in the treatment of the test patients for providing supporting information for appraisal and revalidation.

Questionnaires sought information on the awareness of the patients of their infection, experience during labor, abnormal clinical findings and patients' response to the gynecologist's advice as well as effect of education on the patients' condition and precautious behavior during pregnancy.

Ethics approval of research

The study was done after approval of ethical board of King Abdulaziz University and an informed written consent was taken from each participant in the study.

RESULTS

Retesting confirmed the seropositivity of all of the 146 symptomatic and asymptomatic patients: 71% of cases were Symptomatic versus 29% of asymptomatic infection, Subclinical shedding rates were higher in persons with symptomatic infection compared with asymptomatic infection However, the amount of HSV detected during subclinical shedding episodes was similar.

23 males and 91 females out of 146 (78%) eligible clinic attendees, over one year period, completed the questionnaire. Nineteen of those who did not participate said they did not think they needed it, and the remainder thirteen did not give a reason. All questionnaires were suitable for analysis and sufficient to draw a valid statistical trend, although data were missing in a few of the questions.

Questionnaires results showed that patients' awareness about HSV2 infection and preventive measures was 36% among parents; only 38% of females and 26% of males were aware of HSV2 infection implication on neonates (Figure 1).while gynecologists who felt the necessity of questioning the parents about previous HSV infection and history of morbidity with a proper induction and education to the parents recorded only 68%(Figure 2).

91 neonates birth condition and status were traced along with the treatment protocol followed and results were illustrated in **Table 1.**

Clinical findings based on data collection and patient history and medical charts: In the pre-antiviral era, 67% of patients with disseminated neonatal HSV disease died by 1 year of age, as did 50% of patients with CNS neonatal HSV disease. Evaluations of Vidarabine and of a lower dose of Acyclovir (30 mg/kg/day for 10 days) documented that both of these antiviral drugs reduce mortality to comparable degrees, with mortality rates from disseminated disease and from CNS disease at 1 year decreasing to 58% and 12%, respectively. Despite its lack of therapeutic superiority, the lower dose of acyclovir quickly supplanted vidarabine as the treatment of choice for neonatal HSV disease due to its favorable safety profile and its ease of administration. Unlike acyclovir, vidarabine had to be administered over prolonged infusion times and in large volumes of fluid**.** With utilization of a higher dose of acyclovir (60 mg/kg per day for 21 days), 12 month mortality is further reduced to 22% for disseminated neonatal HSV disease and to 8% for CNS HSV disease .Differences in mortality at 24 months among patients treated with the higher dose of acyclovir and the lower dose of acyclovir are statistically significant after stratification for disease category (CNS vs. disseminated) Lethargy and severe hepatitis are associated with mortality among patients with disseminated disease, as are prematurity and seizures in patients with CNS disease (Table1).

DISCUSSION

Historically, disseminated HSV infections have accounted for approximately one-half to two-thirds of all children with neonatal HSV disease. However, this figure has been reduced to about 25% since the development and utilization of antiviral therapy, probably the consequence of recognizing and treating SEM infection before its progression to more severe disease [(23)]. Encephalitis is a common component of this category of infection, occurring in about 60 to 75% of infants with disseminated disease [(24)]. While the presence of a vesicular rash can greatly facilitate the diagnosis of HSV infection, over 20% of neonates with disseminated HSV disease do not develop cutaneous vesicles during the course of their illness [(23)]. Events associated with disseminated neonatal HSV infection which actually result in death relate primarily to the severe coagulopathy, liver dysfunction, and pulmonary involvement of the disease.

CNS Disease

Almost one-third of all neonates with HSV infection are categorized as having CNS disease (with or without SEM involvement) [(23)]. Clinical manifestations of CNS disease include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, and bulging fontanelle. Between 60 and 70% of babies classified as having CNS disease have associated skin vesicles at some point in the disease course [(25)]. In infants with CNS disease, mortality is usually caused by devastating brain destruction, with resulting acute neurologic and autonomic dysfunction.

Skin, Eyes and Mouth disease (SEM) Disease

SEM disease has historically accounted for approximately 18% of all cases of neonatal HSV disease. With the introduction of early antiviral therapy, this frequency has increased to approximately 45% [(23)]. Systematic application of PCR to blood samples from babies with neonatal HSV disease will probably demonstrate that these disease classifications are really more of a spectrum than absolute differences in disease manifestations [(26)] with SEM disease having more limited viral dissemination but without visceral (liver, lung, etc.) involvement as detected biochemically (e.g., elevated transaminase levels) or clinically (e.g., pneumonitis).

In the present study, there was a decrease in the mortality and the infection of neonatal treated with acyclovir. The notable safety profile of acyclovir relates to its initial activation by the viral-induced enzyme thymidine kinase.

Acyclovir is most active against HSV; activity against VZV also is substantial but approximately ten-fold less. Epstein Barr virus (EBV) is only moderately susceptible to acyclovir because EBV has minimal thymidine kinase activity. Activity against CMV is poor because CMV does not have a unique thymidine kinase, and CMV DNA polymerase is poorly inhibited by acyclovir triphosphate. Acyclovir is the most frequently prescribed antiviral agent [(27)].

In the present study, there was a decrease also in mortality and the infection of neonatal whom treated with vidarabine.

Vidarabine is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). The inhibitory activity of Vidarabine is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts Vidarabine into Vidarabine monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *in vitro*, Vidarabine triphosphate stops replication of herpes viral DNA. When used as a substrate for viral DNA polymerase, Vidarabine triphosphate competitively inhibits dATP leading to the formation of 'faulty' DNA. This is where Vidarabine triphosphate is incorporated into the DNA strand replacing many of the adenosine bases. This results in the prevention of DNA synthesis, as phosphodiester bridges can longer to be built, destabilizing the strand[(28)].

Vidarabine stops replication of herpes viral DNA in 2 ways: 1) competitive inhibition of viral DNA polymerase, and consequently 2) incorporation into and termination of the growing viral DNA chain. This drug is a nucleoside analog and therefore has to be phosphorylated to be active. Vidarabine is sequentially phosphorylated by kinases to the triphosphate ara-ATP. This is the active form of vidarabine and is both an inhibitor and a substrate of viral DNA polymerase. When used as a substrate for viral DNA polymerase, ara-ATP competitively inhibits dATP leading to the formation of 'faulty' DNA. This is where ara-ATP is incorporated into the DNA strand replacing many of the adenosine bases [(28)].

CONCLUSION

Awareness campaigns and educational efforts focusing on the early diagnosis of HSV2 in couples for an implicit understanding of the biology and natural history of HSV in the gravid woman and the neonate should be systematically undertaken which should be leveraged to save neonates lives.

Furthermore, for gynecologists, a continuous medical education is essentially required.

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Table 1: Mortality and morbidity outcomes among 91 infants with neonatal HSV infection.

Extent of disease	Untreated	Vidarabine	Acyclovir , 30 mg/kg/day	Acyclovir, 60 mg/kg/day
	***SEM disease**			
Total	4	10	14	5
Dead	0 (0)	0 (0)	0 (0)	0 (0)
Alive	4 (100)	10 (100)	14 (100)	5 (100)
Normal	3 (75)	7 (70)	12 (86)	1 (20)
Abnormal	1 (25)	1 (10)	0 (0)	0 (0)
Unknown	0 (0)	2 (20)	2 (14)	4 (80)
	CNS disease			
Total	4	9	8	13
Dead	2 (50)	1 (11)	1 (13)	1 (8)
Alive	2 (50)	8 (89)	7 (88)	12 (92)
Normal	1 (50)	3 (38)	3 (43)	2 (17)
Abnormal	1 (50)	4 (50)	4 (57)	5 (42)
Unknown	0 (0)	1 (13)	0	5 (42)
	Disseminated disease			
Total	3	7	5	9
Dead	2 (67)	4 (57)	3 (60)	2 (22)
Alive	1 (33)	3 (43)	2 (40)	7 (78)
Normal	0 (0)	1 (33)	1 (50)	41 (57)
Abnormal	1 (100)	2 (66)	1 (50)	1 1 (14)
Unknown	0 (0)	0 (0)	0 (0)	21 (29)

( ):%, *SEM =Skin, Eyes and Mouth disease

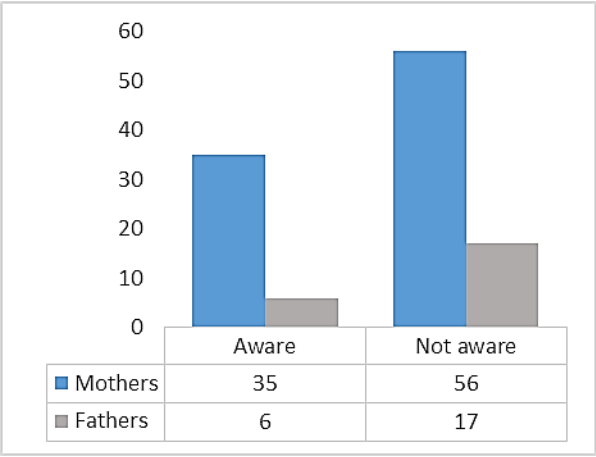

Figure 1: shows the awareness Level of 114 patients on HSV2 danger on neonates and pregnancy precautions presented by the number of patients split between “Aware” and “Not aware” based on the questionnaire results which turned out to be 38% in mothers and 26% in fathers.

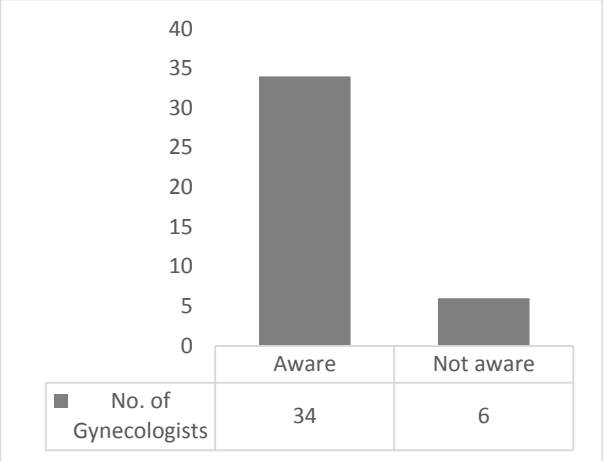

Figure 2: shows the awareness Level of 50 gynecologists on the significance of investigating the couples’ history and medical chart during the pregnancy of the mother presented by the number of doctors split between “Aware” and “Not aware” based on the questionnaire results which turned out to be 68%