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Herpes Simplex Virus 2 Infection Rate and Necessity of Screening during Pregnancy: A Clinical and Seroepidemiologic Study

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Purpose: This study determined the seroprevalence of herpes virus 2 in gravidas and the differences between herpes virus 2-infected and healthy gravidas. The need to screen gravidas for herpes virus 2 was also evaluated. **Materials and Methods:** A retrospective analysis involving 500 gravidas who underwent herpes virus 2 serologic testing and delivery in our hospital between January 2009 and August 2010 was performed. All patients in the study group were classified as herpes simplex virus 2 (HSV2) positive, and all cases were analyzed with respect to the clinical course of the pregnancy, pregnancy outcome, obstetric complications, and neonatal outcomes. SPSS software (version 14.0) was used for statistical analysis. A chi-square test and Student's t-test were used for statistical analysis. **Results:** In the current study, the herpes virus 2 seroprevalence rate in gravidas was 17%. There was no significant difference in the rates of preterm delivery, premature rupture of membranes, preterm labor, and intrauterine growth restriction between the herpes virus 2-infected gravidas and the healthy control group. The rates of spontaneous abortion and sexually transmitted disease were higher in the herpes virus 2 infection group than the healthy control group. **Conclusion:** After educating gravidas on genital herpes and, if gravidas thereafter consent to herpes virus 2 screening, the risk of neonatal herpes virus 2 infections can be reduced. In addition, examination of gravidas for sexually transmitted diseases would increase as would appropriate treatment.

Key Words: Herpes virus 2, seroprevalence, pregnancy, sexually transmitted disease

INTRODUCTION

Herples simplex virus (HSV) is an enveloped, double stranded DNA virus pertinent to the human herpesvirus family. Although closely related, HSV1 and HSV2 still contain sufficient differences to enable type identification and serodiagnosis, however both viruses are neurotropic,[1] attaching themselves to a host epidermal or mucosal cell and then transporting the enveloped virions via axons to the nuclei of the neuronal cells.[2]

The two viruses, HSV1 and HSV2, spread themselves through different means. The former being via salivary and respiratory contact whiles the latter through genital contact. Cases of HSV1 infections are seen worldwide and do not discriminate by age. A human with a primary infection may manifest orolabial herpes, gingivostomatitis, pharyngitis and genital herpes.[3]

One of the most commonly seen sexually transmitted disease would be an HSV infection of the genital tract. According to serologic test results, there is a 2% incidence of HSV1 or HSV2 infections among women during pregnancy,[4] most of them being asymptomatic, as with non-pregnant women.[1] It has also been observed that while postnatal infections are rare (though possible), neonatal infections are usually acquired *in utero*; during the intrapartum period via exposure to the virus in the genital tract.[5] Long-term neurologic sequelae has been noted in about 20% of neonatal herpes survivors.[6] However neonatal mortality rates have decreased substantially in the last two decades. More specifically, disseminated disease and central nervous system disease mortality rates fell 30% and 4% each.[6]

Herpes virus screening of gravidas reduces neonatal herpes infection rates and the need for antiviral drug treatment at the time of delivery. Thus, we studied the presence of HSV2 infections in gravidas by serological methods, and determined the differences between infected and healthy groups of gravidas. Furthermore, we evaluated the need for herpes virus 2 serologic screening in gravidas.

MATERIALS AND METHODS

A retrospective analysis including 500 gravidas who underwent HSV2 serologic testing and gave birth at our hospital, was carried out between January 2009 and August 2010. The study group was classified as anti-herpes virus 2 antibody-positive, and the following variables were analyzed: clinical course of pregnancy, pregnancy outcome, obstetric complications, and neonatal outcomes. The clinical course and outcomes of pregnancy were assessed for gestational age at delivery and incidence of fetal loss. Obstetric complications were assessed according to rates of intrauterine growth restriction, premature rupture of membranes, preterm deliveries, and preterm labor. Routine prenatal tests included tests of rubella, varicella, and hepatitis B (HB) antibody titers, and human immunodeficiency virus (HIV) and venereal disease research laboratory (VDRL) tests.

Herpes virus 2 serologic tests were performed between 27 and 29 weeks gestation. Gravidas were educated about genital herpes, and, after informed consent for a herpes virus 2 serologic test was granted, a blood sample was obtained. At 38 weeks gestation and at the time of delivery, herpes lesions were confirmed based on genital inspection and answers to questions regarding herpes symptoms. If there were symptoms of vaginosis or abnormal vaginal secretions antepartum, sexually transmitted disease (STD) testing was performed. Human papillomavirus (HPV) testing was performed early during the pregnancy upon request from the gravida.

SPSS software (version 14.0) was used for statistical analysis. The average and standard deviations are shown. A chi-square test and Student's t-test were used for statistical analysis. The significance level for the p-value was set at 0.05.

RESULTS

Comparison of maternal demographic data

The mean age of the gravidas was 31.6±4.6 years in the HSV2 positive group and 30.4±4.2 years in the healthy control group. There was a significant difference in the ages of the gravidas between the two groups ($p<0.05$). The mean gestational age of the gravidas was 38.9±1.4 weeks in the HSV2 positive group and 39.2±1.1 weeks in the healthy control group. Among 85 gravidas in the HSV2 positive group, 56 were primiparas and 29 were multiparas; in the control group, 296 gravidas were primiparas and 119 were multiparas. The gender ratio of neonates were 1 : 1 in both the HSV2 positive group (42 males and 43 females) and the healthy control group (205 males and 210 females). The average birth weight of neonates was 3.2±0.4 kg in the HSV2 positive group and 3.2±0.3 kg in the healthy control group. There were no significant differences in gestational age, ratio of primiparas to multiparas, gender ratio of neonates, and birth weights of neonates between the two groups (Table 1).

Comparison of seropositivity

No gravidas were rubella IgM-positive in either group. Seventy-eight gravidas (91.8%) in the HSV2 positive group and 369 of 415 gravidas (88.9%) in the health control group were rubella IgG-positive. Seventy-eight gravidas (91.8%) in the HSV2 positive group and 386 gravidas (93.0%) in the healthy control group were positive for anti-varicella antibody. Six of the 85 gravidas (7.1%) in the HSV2 positive

Table 1. Comparison of Maternal Demographic Data

	Herpes virus 2 antibody-positive	Control	*p* value
Maternal age (yrs)	31.6±4.6	30.4±4.2	0.014
<20	0 (0)	5 (1.2)	
21-24	4 (4.7)	24 (5.7)	
25-29	27 (31.7)	162 (39.0)	
30-34	30 (35.2)	149 (35.9)	
35-40	20 (23.5)	68 (16.3)	
≥41	4 (4.7)	7 (1.6)	
Gestational age (wks)	38.9±1.4	39.2±1.1	0.076
Primipara-to-multipara ratio	56 : 29	296 : 119	0.317
Gender (M : F)	1 : 1	1 : 1	0.998
Birth weight (kg)	3.2±0.4	3.2±0.3	0.492

Values are presented as the mean±SD or number (%).

Table 2. Comparison of Seropositivity

	Herpes virus 2 antibody-positive	Control	*p* value
Rubella IgM	0	0	
Rubella IgG	78 (91.8)	369 (88.9)	0.437
Varicella antibody-positive	78 (91.8)	386 (93.0)	0.648
HBsAg-positive	6 (7.1)	21 (5.1)	0.434
HBsAb-positive	64 (75.3)	308 (74.2)	0.892

HB, hepatitis B.
Values are presented as a number (%).

group and 21 of 415 gravidas (5.1%) in the healthy control group were HBsAg-positive. Sixty-four gravidas (75.3%) in the HSV2 positive group and 308 gravidas (74.2%) in the healthy control group were HBsAb-positive. There were no significant differences in rubella and varicella antibody titers, as well as the HBsAg-positive, and HBsAb-positive rates between the two groups of gravidas (Table 2).

Comparison of sexually transmitted pathogens

No gravidas were HIV-positive or VDRL-positive in either group. One gravida (1.2%) in the HSV2 positive group and three gravidas (0.7%) in the healthy control group had genital condyloma infections. Four of 14 gravidas (28.6%) in the HSV2 positive group and 13 of 35 gravidas (37.1%) in the healthy control group had HPV infections. There were no significant differences in condyloma and HPV infections between the two groups of gravidas. Twelve of 17 gravidas (70.6%) in the HSV2 positive group and 23 of 49 gravidas (46.93%) in the control group had positive sexually transmitted disease screens (Table 3). There was a significant difference in sexually transmitted disease screening between the two groups (p<0.05).

Comparison of obstetric complications

Thirty-three of 85 gravidas (38.8%) in the HSV2 positive group and 123 of 415 gravidas (29.6%) in the healthy control group had a history of abortions. There was a significant difference in the abortion rates between the 2 groups (p<0.05). Two of 85 gravidas (2.3%) in the HSV2 positive group and 15 of 415 gravidas (3.6%) in the healthy control group had preterm labor. Eighteen gravidas (21.2%) in the HSV2 positive group and 73 gravidas (17.6%) in the healthy control group had premature rupture of membranes. Seven gravidas (8.2%) in the HSV2 positive group and 26 gravidas (6.2%) in the healthy control group had preterm deliveries. Fourteen of 85 gravidas (16.4%) in the HSV2 positive group and 75 of 415 gravidas (18.0%) in the healthy control group were diagnosed with intrauterine growth retardation. Three of 85 newborns (3.5%) in the HSV2 positive group and 6 of 415 neonates (1.4%) in the healthy control group were admitted to the neonatal ICU (Table 4). There were no significant differences in the rates of preterm labor, premature rupture of membranes, preterm delivery, intrauterine growth retardation, and neonatal ICU admission between the two groups.

DISCUSSION

This is the first study to attempt to determine the prevalence

Table 3. Comparison of Sexually Transmitted Pathogens

	Herpes virus 2 antibody-positive	Control	*p* value
HIV	0	0	
VDRL	0	0	
STD	12/17 (70.5)	23/49 (46.9)	0.006
Chlamydia	3	1	
Mycoplasma	2	3	
Trichomonas	1	0	
Ureaplasma	6	19	
HPV	4/14 (28.5)	13/35 (37.1)	0.642
Genotype16	1	5	
Genotype 18	1	1	
Genotype 32	0	1	
Genotype 34	0	1	
Genotype 53	1	0	
Genotype 53.68	1	0	
Genotype 56	0	1	
Genotype 62	0	1	
Genotype 66	0	1	
Genotype 74	0	1	
Genotype 90	0	1	
Condyloma	1 (1.17)	3 (0.72)	0.669

HIV, human immunodeficiency virus; VDRL, venereal disease research laboratory; STD, sexually transmitted disease; HPV, human papillomavirus.
Values are presented as a number (%).

Table 4. Comparison of Obstetric Complications

	Herpes virus 2 antibody-positive	Control	*p* value
Abortion	33 (38.8)	123 (29.6)	0.045
1*	19	86	
2	8	26	
3	3	8	
4	2	2	
5	1	1	
Preterm labor	2 (2.3)	15 (3.6)	0.559
PROM	18 (21.2)	73 (17.6)	0.442
Preterm delivery	7 (8.2)	26 (6.2)	0.528
IUGR	14 (16.4)	75 (18.0)	0.718
NICU	3 (3.5)	6 (1.4)	0.185

PROM, preterm rupture of membrane; IUGR, intrauterine growth retardation; NICU, neonatal intensive care unit.
Values are presented as a number (%).
*The number of abortions a given gravida has had.

of HSV2 infections in gravidas in Korea. In the current study, the HSV2 positive rate was 17% in Korean gravidas. The HSV2 positive rate in gravidas from several countries has been surveyed. The HSV2 positive rate was higher in African countries, such as Uganda (67.2%)[33] and Zimbabwe (49.1%).[34] In contrast, the HSV2 positive rates in Australia (13.6%)[37] and the US (22%)[36] are similar to the rate now shown for Korea (17%) (Table 5).

Compared to women with primary Herpes Virus 2 infections, women with non-primary infections reflect milder symptoms.[7] 75-85% of recurrences of genital infections are asymptomatic in infected women, however individuals infected with herpes virus are generally unaware of the incident; as a mere 5-15% of people report an infection.[8,9] Therefore gravidas, early in pregnancy, should be questioned for signs that may indicate genital herpes, not excluding prodromal symptoms. Suspected herpes virus infections should then be confirmed through viral or serological testing, as clinical presentation alone has a sensitivity of 40%, specificity of 99% and a false positive rate of 20%.[10] Only type-

Table 5. Herpes Virus 2 Antibody-Positive Rate in Gravidas

Investigator	Country	Herpes virus 2 antibody-positive
Nakubulwa, et al.[33]	Uganda	67.2 (168/250)
Munjoma, et al.[34]	Zimbabwe	49.1 (167/340)
Kapranos, et al.[35]	Greece	43.2 (41/95)
Xu, et al.[36]	USA	22.0 (138/626)
Sasadeusz, et al.[37]	Australia	13.6 (186/1371)
Berntsson, et al.[38]	Sweden	10.4 (31/299)
Ozdemir, et al.[39]	Turkey	8.2 (13/158)
Current study	Korea	17.0 (85/500)

Values are presented as a % (number).

specific serologic testing can distinguish between primary, non-primary, and recurrent infections with certainty.[11] About 75% of women with recurring genital herpes virus infections suffer at least one recurrence during pregnancy whiles approximately 14% of them will show prodromal symptoms or clinical recurrence during delivery.[12,13] Thus, women with a history of a herpes virus infection should be examined for genital herpetic lesions during labor and delivery. In the late antepartum period, there may be fever and urinary symptoms associated with herpes virus infections, but often without local symptoms, which results in missed diagnoses.[3]

Serologic testing for herpes virus 2 will identify gravidas with sub-clinical herpes virus 2 infections who were previously undiagnosed.[14] According to The American College of Obstetricians and Gynecologists recommendations, routine HSV screening of gravidas is not recommended. A survey conducted on a sample of 100 gravidas, regarding their knowledge and attitude on genital herpes, showed that 80% of them desired to be tested for HSV and 76% also encouraged their sexual partners to be tested.[15] Based on this study, an examination for herpes virus is readily accepted in gravidas upon receiving education on genital herpes. Ideally, most, if not all gravidas are examined for herpes virus infection in addition to gravidas who are scheduled for a repeat cesarean section. To evaluate the cost-effectiveness of different screening protocols for gravidas, several analyses have been made on how the incidence of neonatal herpes virus infections is reduced by those.[16-20]

As opposed to recurrent infections, primary genital herpes infections present a higher risk for perinatal transmission, as the mean duration of viral shedding for women with intreated primary HSV2 is 15 days.[21] Moreover 90% of women with primary infections also showed cervical shedding by viral culture.[21] However there is a 30-60% risk of vertical transmission to the neonate when there is a primary outbreak during delivery.[22]

Herpes virus 1 accounts to about one-third to a half of cases of neonatal herpes,[22,23] though amongst gravidas who suffer recurrent lesions during delivery, their transmission rate with a vaginal delivery is only of 3%.[17] Beyond this, only 2 out of every 10000 gravidas with a history of recurrent disease, but no visible lesions during delivery, are in risk of transmission.[22,24]

Maternal herpes virus acquisitions during pregnancy are, unfortunately, not addressed by antiviral suppression and cesarean delivery, which fail 70-80% of the time to prevent neonatal herpes infections. In cases in which the herpes virus infections are sub-clinical, nearly 90% of these are not accounted by the methods mentioned above.[4,23]

Increased risk of spontaneous abortion has always been associated with herpes virus, though this has been found to be contradictory to recent studies.[25] In the current study, however, the spontaneous abortion rate was correlated with a statistically significant increase in the herpes virus 2 antibody-positive group, in comparison with the control group. The transplacental passage of the virus is rare, and herpes virus 2 infections are not associated with stillbirths.[26]

Neonatal chorioretinitis, microcephaly and skin lesions are very occasionally associated with primary outbreaks in the first trimester of pregnancy.[27] Neonatal herpes virus infections can fall under 3 different classifications, those being disseminated disease (25%) central nervous system disease (30%), and disease limited to the skin, eyes, or mouth (45%).[5] Though uncommon, neonatal herpes encephalitis is known as severe with a mortality rate of 4-14% and long term neurologic sequelate (56-69%).[1,28-32] According to a large cohort study, gravidas are much less likely to transmit herpes virus infections to their infants when they give birth by cesarean section.[22] Only 1.2% of infants, from gravidas with herpes virus infections detected at the time of delivery, received neonatal herpes infections when delivered by ce-

sarean section as opposed to a 7.7% of those delivered vaginally.[22]

A comparison of the clinical characteristics of HSV2 positive gravidas compared with the healthy control group revealed that there were no significant differences in the rates of preterm delivery, premature rupture of membranes, preterm labor, intrauterine growth restriction, and cesarean section. In this study, the HSV2 positive group did not have higher hepatitis B, varicella, or rubella antibody titers than the healthy control group. However, the HSV2 positive group had a statistically significantly higher rate of positive sexually transmitted disease than the healthy control group. Thus, we recommend sexually transmitted disease screening in HSV2 positive gravidas to help discover the presence of sexually transmitted disease.

A limitation of the current study was that herpes virus infections and herpes virus antibodies were not assessed in infants born to HSV2 positive gravidas.

Educating gravidas on genital herpes and herpes virus 2 screening might reduce the probability of transmitting herpes virus 2 infections to neonates. In addition, educating gravidas on herpes virus 2 infections could facilitate sexually transmitted disease screening and appropriate treatment.

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