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Serological study of herpes virus infection in female patients with bad obstetric history

***Haider M, Rizvi M, Khan N, Malik A**
Department of Microbiology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh 202002, India.

***Corresponding Author:** mehvashaider@gmail.com

Abstract
Primary Herpes Simplex Virus-2 (HSV-2) infection has been inconclusively linked with abortions. This study is aimed to evaluate the role of HSV-2 infection in patients with bad obstetric history which implies previous unfavourable fetal outcome in terms of two or more consecutive spontaneous abortions, history of intrauterine fetal death, intrauterine growth retardation, still births, early neonatal death and/or congenital anomalies. A retrospective study was conducted on 450 randomly selected patients with bad obstetric history. ELISA was performed to detect anti HSV-2 IgM antibodies. Detailed history and clinical examination was done. Of the 450 cases screened for anti HSV-2 IgM antibodies, 76 (16.8%) tested positive. Of these 76 HSV positive patients, 68 (89.4%) had history of abortion, 5 (6.5%) had disseminated herpes infection, 2 (2.6%) had neonatal cholestasis and 1 (1.3%) had eye complaints. Although some studies show inconclusive evidence of HSV-2 infection with abortion, our study showed significant correlation between HSV infection and abortion. HSV-2 being a preventable and treatable sexually transmitted disease should be actively looked for in symptomatic and asymptomatic patients with bad obstetric history. This is especially important considering the wide prevalence of sexually transmitted diseases in India.

Keywords: Herpes simplex virus-2; HSV-2; Pregnancy; Bad obstetric history.

Introduction

The first trimester of pregnancy is an important period often fraught with complications like bleeding and pain, leading to severe apprehension in the mother (Florence et al., 1999). Pregnancy loss has been attributed to several factors involved in human reproduction. Genetic and uterine abnormalities, endocrine and immunological dysfunctions, infectious agents, environmental pollutants, psychogenetic factors and endometriosis are most important causes (Rock and Zacur, 1983; Dicker et al., 1992) of spontaneous abortion. Some maternal infections, especially during the early gestation, can result in fetal loss or malformations because the ability of the fetus to resist infectious organisms is limited and the fetal immune system is unable to prevent the dissemination of infectious organisms to various tissues (Mladina et al., 2002). The fetus and/or neonate are infected predominantly by viral but also by bacterial and protozoal pathogens. Infections with various pathogens cause miscarriage or may lead to congenital anomalies in the fetus while others are associated with neonatal infectious morbidity.

Bad obstetric history (BOH) implies previous unfavourable fetal outcome in terms of two or more consecutive spontaneous abortions, early neonatal deaths, stillbirths, intrauterine fetal deaths, intrauterine growth retardations and congenital anomalies.

Recurrent pregnancy wastage due to maternal infections transmissible *in utero* at various stage of gestation can be caused by a wide array of organisms which include the TORCH complex (*Toxoplasma gondii*, Rubella virus, Cytomegalovirus, Herpes simplex virus) and other agents like *Chlamydia trachomatis*, *Treponema pallidum*, *Niesseria gonorrhoeae*, HIV, etc.

Toxoplasmosis acquired during pregnancy may cause damage to the fetus (Sharma et al., 1997). Sero-epidemiological studies have shown that 10-20% of women in childbearing age in India are susceptible to Rubella infection (Seth et al., 1985). Infection with Rubella during pregnancy may lead to congenital malformation in 10-54% of cases (Peekham, 1985). The infection caused by CMV in adult is usually asymptomatic but its significance is many times increased when it occurs during pregnancy. However, the rate of primary CMV infection is significantly higher for pregnant women from low socioeconomic group (Stagno, 1986). The mother is the usual source of transmission of HSV to the fetus or newborn. Primary HSV infection during first half of pregnancy is associated with increased frequency of spontaneous abortion, stillbirth, and congenital malformation (Plotskin, 1999).

During the past decade, the detection and treatment of TORCH infections has improved (Stagno, 1986; Plotskin, 1999; Cullen et al., 1998) although it is still a problem in

industrializing countries. Most of the TORCH infections cause mild maternal morbidity but can have serious fetal consequences, and treatment of maternal infection frequently has no beneficial effect for the fetus. Infants with congenital infection due to one of the TORCH agents may result in low birth weight, cardiac defects, ocular lesions, hearing defects, central nervous system defects, neonatal purpuras, and hepatosplenomegaly.

These maternal infections with adverse outcome are initially unapparent or asymptomatic and are thus difficult to diagnose on clinical grounds. Therefore, diagnosis of acute TORCH infection in pregnant women is usually established by demonstration of sero-conversion in paired sera or by demonstration of specific IgM antibodies.

Herpes simplex virus (HSV) types 1 and 2, ubiquitous DNA viruses, contribute to considerable morbidity and mortality among humans. The two serotypes exhibit approximately 50% nucleotide homology and share several important biologic characteristics, notably the capacity to establish latent infections and to reactivate periodically, causing mucocutaneous or neurological disease. Usually transmitted non-sexually, HSV-1 causes stomatitis, keratitis, skin lesions, and encephalitis. By contrast, HSV-2 is typically transmitted sexually, causing genital lesions. Either virus can infect the neonate (Corey and Spear, 1986).

The incidence of neonatal infection ranges from 1 in 2,500 to 1 in 20,000 live births and two-thirds of cases are caused by HVS-2. Neonatal disease is most common acquired intrapartum or postnatally and can result from primary or recurrent maternal infection (Corey and Spear, 1986). Manifestations of congenital HSV include skin lesions and scars, chorioretinitis, microcephaly, and hydranencephaly. Neonates with HSV infection can deteriorate rapidly as a result of respiratory distress, shock, disseminated intravascular coagulopathy, or encephalitis. Infants who survive neonatal HSV encephalitis have high rates of neurological sequelae, consisting of seizure disorders, mental retardation, and visual or motor deficits (Stamos and Rowley, 1994). This study reports the results of screening for IgM antibodies against HSV-2 in a group of patients with bad obstetric history.

Materials and Methods

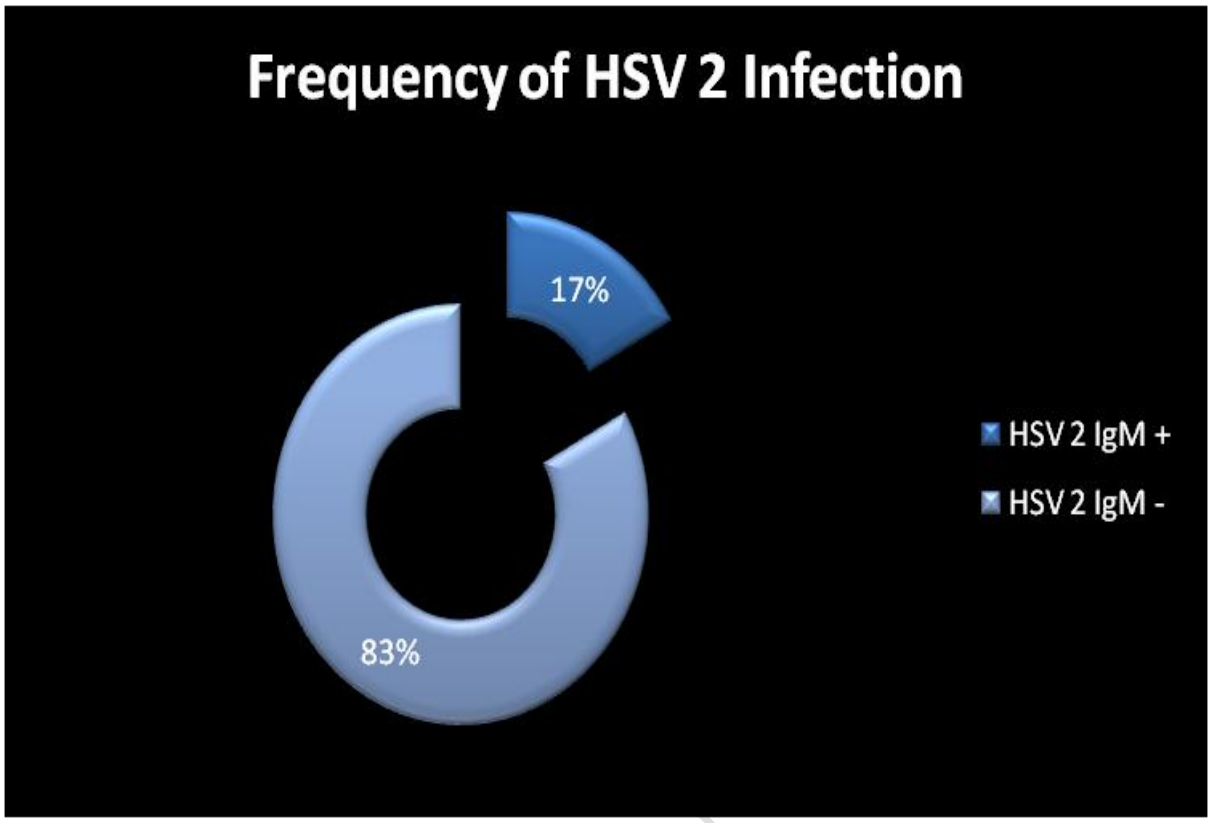
Our study was conducted retrospectively on patients recruited from Obstetric Department of JNMC. Random selection of 450 patients was done from the large group patients who presented with one of the features defined under BOH. Bad obstetric history (BOH) implies previous unfavourable fetal outcome in terms of two or more consecutive spontaneous abortions, early neonatal deaths, stillbirths, intrauterine fetal deaths, intrauterine growth retardations and congenital anomalies.

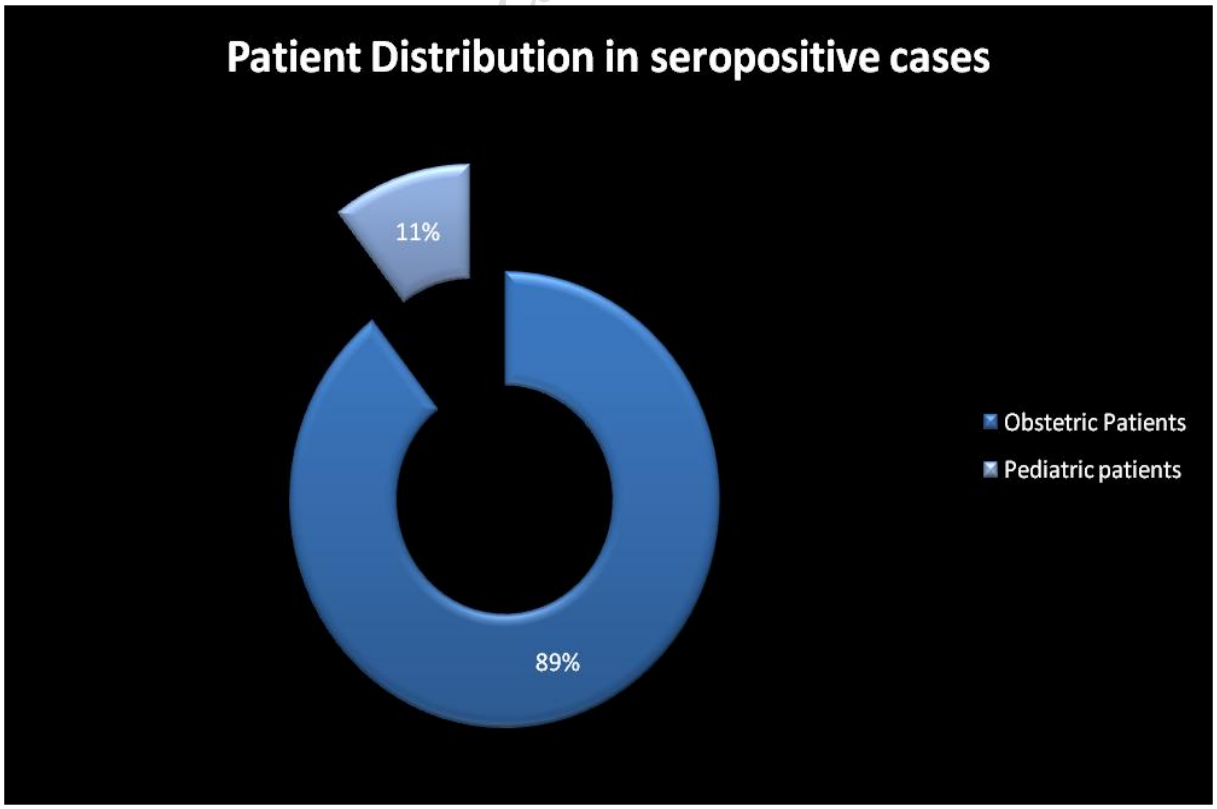
The demographic, medical, and clinical data were collected in each case based on personal interviews and medical examination. The women signed an informed consent before they were included in this study. The study was approved by the ethics committee of JNMC. Blood samples were obtained from each patient and centrifuged, and the sera were kept frozen in aliquots at −20°C until analysis. Serum samples from each patient were analyzed for qualitative specific IgM HSV-2 (ELISA- Diesse, Italy). The tests were done as per the directions given in the manual supplied along with the kits. The results were read at 450 nm in the ELISA reader. A positive IgM is an indication of recent infection.

Results

Primary infection with HSV-2 acquired by women during pregnancy accounts for half of the morbidity and mortality from HSV-2 among neonates. The other half results from reactivation of old infection. Of the 450 cases screened for anti HSV-2 IgM antibodies, 76 (16.8%) tested positive.

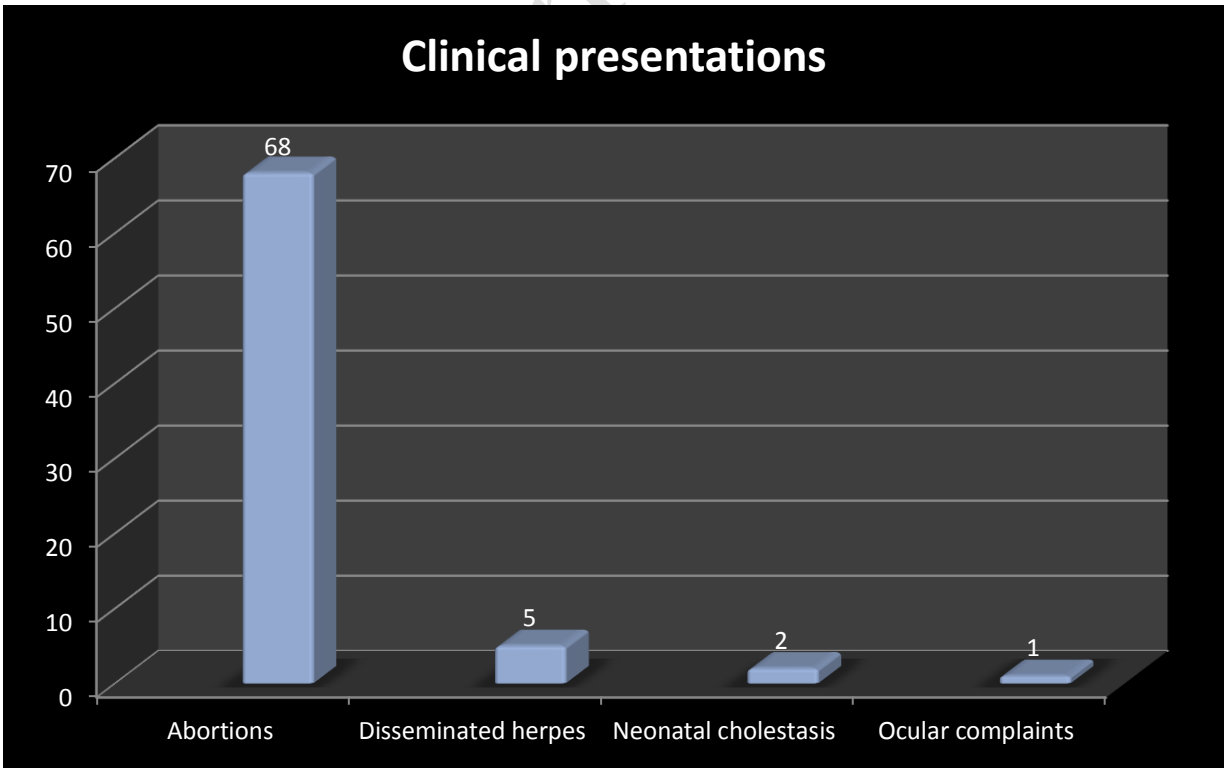
The miscarriage cases were studied under various categories like complete, incomplete, missed and threatened abortions, for the presence of infections with these pathogens. Majority 66(97%) presented with ≥2 abortions (complete) and only 2 (3%) presented single abortion (complete). Here, 33.3 % were primigravida (G1) while 39.4% were G2, 16.7%-G3, 7.6%-G4 and 3%-G5. The parity of the group was as Nullipara -13.8%, Primipara (P1)-69%, P2 -10.3% and P3 -6.9%. All patients were housewives by occupation. 30(44.1%) were from rural background while 38 (55.8%) were from urban background. Rest i.e. 8 were neonates of whom 5(6.5%) presented with disseminated herpes infection, 2 (2.6%) presented with neonatal cholestasis and only 1(1.3%) presented with eye complaints. No patient presented with fever, rashes, or any other complaints. Seropositivity rate of HSV IgM among the BOH patients of our study was 16.8%.


Frequency of HSV 2 Infection
17%
83%
HSV 2 IgM +
HSV 2 IgM -


Patient Distribution in seropositive cases
11%
89%
Obstetric Patients
Pediatric patients

Among 76 HSV positive patients, a majority (89.4%) had a history of abortion (p<0.001):

Clinical presentations	Number of cases	Percentage
Abortions	68	89.4%
Disseminated herpes	5	6.5%
Neonatal herpes	2	2.6%
Ocular complaints	1	1.3%
Total	76	100%



Among 68 seropositive female patients, 25 (36.7%) were between 20-30 years of age, 35 (51.4%) were between 30-40 years and 8 (11.7%) were between 40-50 years of age. Mean age was 33.5 years:

Age group	No. of seropositive patients	Percentage
20-30	25	36.7%
30-40	35	51.4%
40-50	8	11.7%

Discussion

HSV-2 seroprevalence studies show variation in infection by geographic location. Some of the highest prevalence of HSV-2 has been found in Africa and the Americas. Lower prevalence has been found in Western and Southern Europe than in Northern Europe and North America, and although there have been few studies, the lowest prevalence has been seen in Asia (Smith and Robinson, 2002; Reynolds, 2003; Levett, 2005). There also is a great deal of variation within regions. Our study reported a prevalence of 16.8%, whereas HSV-2 prevalence of over 40 percent have been reported in STI clinics in Pune (Reynolds et al., 2003), but in a study of low-risk blood donors in Vellore, 15 percent of females and 10 percent of males were infected (Cowan et al., 2003). HSV-2 prevalence has also been found to vary by individual-level characteristics, including gender, age, sexual activity level, marital status, socioeconomic status (SES), education, and race/ethnicity (Xu et al., 2006). However, these characteristics are insufficient to explain differences within and between countries, regions, and population subgroups, suggesting the need to identify ecologic factors which may help to explain the differences (Smith et al., 2002).

44.1% cases were from rural background while 38 (55.8%) were from urban background in our study. This was similar to other studies which also showed an urban predeliction like the prevalence of HSV-2 among pregnant women was 18.0% with a trend for lower rates in rural versus semi-urban areas (P = 0.08), whereas the prevalence of HSV-2 was 23.7% among women in Ouagadougou (N = 883), and 15.3% epidemiology of Herpes Simplex Virus Type 2 infection in rural and urban Burkina Faso (Kirakoya-Samadoulougou et al., 2010).

Though, as per previous studies (Regan et al., 1989; Alberman, 1988), maternal age and previous miscarriages had been reported as two independent risk factors for a further miscarriage, we also observe similar findings as majority (97%) presented with ≥2 abortions (complete) and only 3% presented single abortion (complete). Also, of the 68 seropositive female patients, 36.7% were between 20-30 years of age, 51.4% were between 30-40 years and only 11.7% were between 40-50 years of age.

Primary infection with HSV-2 acquired by women during pregnancy accounts for half of the morbidity and mortality from HSV-2 among neonates. The other half results from reactivation of old infection. Seropositivity rate of HSV IgM among the BOH patients of our study was 16.8%. HSV in asymptomatic women with recurrent infection during pregnancy was found to be 0.6-3% previously (Vontver et al., 1982).

The role of maternal and fetal infections in the recurrent 1st trimester loss remains controversial. This reflects the low frequency with which the necessary microbial and maternal factors combine to cause recurrent miscarriage by infection of the fetal tissue or by stimulation of an antigen–antibody response. The patient's susceptibility to chronic infection must play a determining role in some of the reported cases.

The parameters like age, gravida and parity of these patients were studied. Here, 33.3 % were primigravida (G1) while 39.4% were G2, 16.7%-G3, 7.6%-G4 and 3%-G5. The parity of the group was as Nullipara - 13.8%, Primipara (P1) - 69%, P2 - 10.3% and P3 - 6.9%. No significant correlation was observed for these factors with the incidence of miscarriages. Probable factors that play a role in the risk of abortion due to infection are:

i) Either due to primary exposure during early gestation to organisms and the capability of the organism to cause placental infection and development of an infectious carrier state.

ii) Due to immunocompromised women if the immmunoglobin titre is not normal.

iii) Due to immunosuppressants, chemotherapy, corticosteroids, or acquired immune deficiency syndrome.

Exposure to a microbe, which could establish a chronic infection and spread to the placenta in an immunocompromised patient, is probably the most obvious risk situation for habitual abortion. In routine medical practice, it is not necessary or efficient to screen universally for the unexpected, but it is necessary to be aware of the rare possibilities. Most patients with a history of recurrent miscarriage will not benefit from an extensive infection workup.

Cauchi et al. (1991) examined 165 women with a history of three or more consecutive miscarriages in the first trimester for factors that may have a bearing on subsequent pregnancy success or failure and found that factors that were found to correlate significantly with success rate were length of abortion history, total number of abortions, interval from last miscarriage to present pregnancy, and degree of subfertility. The uterine endometrium undergoes changes and the chances for a perfect implantation is less.

In the medical literature, the limited evidence linking infection and recurrent pregnancy loss in humans remains largely anecdotal and generally cannot be reproduced in prospective studies. The role of maternal and fetal infections in the recurrent first trimester loss remains controversial.

Conclusion

BOH could be because of environmental factors: infections, radiation, occupational hazards, addictions and habits. This study has confirmed the significant association of infectious causes, especially TORCH and BOH. TORCH infections are considered a known causal factor, which is treatable. The present study being retrospective and without controls has its limitations, still the observations obtained cannot be ignored. A larger prospective study with matched controls would shed more light on this issue. We recommend that all antenatal cases with BOH be routinely screened for TORCH complex, especially HSV-2, as early diagnosis and appropriate intervention of these infections will help in proper management of these cases.

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