Silent Herpes Simplex virus infection in women with preterm premature rupture of membranes

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Summary:

Background: genital herpes simplex virus infection in pregnancy poses a major risk to the fetus and it has been associated with bad obstetric out come causing preterm labor, intrauterine growth retardation and spontaneous abortion. This study was conducted to determine if premature rupture of membranes before 37 weeks of gestational age are observed with subclinical shedding of herpes simplex virus (HSV).

Patients and methods: Cervical swabs were taken from 75 women with a history of preterm premature rupture of membranes before 37 weeks of gestation, and 20 women with normal obstetrical history for the presence of HSV antigen using Enzyme linked Immuno Sorbent Assay (ELISA) method.

Results: HSV antigen was detected in 37 swabs(49.3%) which revealed a significant association with preterm premature rupture membranes(PPROM) compared to control group($P<0.05$).The majority of HSV infected women were asymptomatic 34(91.9%), and 23(56.1%) of the cases was associated with history of recurrent PPROM, compared to those women with history of single PPROM.

Conclusion: The risk of maternal transmission of HSV to the fetus or newborn is a major health concern and the high rates of undiagnosed or asymptomatic HSV infections complicate the issue of prevention. With advent of serologic test that can reliably detect the virus in asymptomatic patient. Maternal HSV screening now is mandatory.

Key words: HSV, preterm PROM, maternal herpes.

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Introduction:

The HSVs are part of a large family of DNA viruses, of which eight are known to be infectious in humans. Both HSV types 1 (HSV-1) and 2 (HSV-2) are transmitted across epithelial mucosal cells as well as through skin interruptions, and migrate to nerve tissues, where they persist in a latent stage. HSV-1 predominates in orofacial lesions and typically is found in the trigeminal ganglia, while HSV-2 is most commonly found in the lumbosacral ganglia (1).

Genital HSV infections are often subclinical and, even if symptomatic, have nonspecific signs and symptoms. An estimated 2% of women will acquire HSV-1 or HSV-2 during pregnancy. Viral shedding can be detected from viral culture of the cervix, labia or both (2).

Maternal –fetal transmission of HSV mostly occurs due to presence of the virus in the genital tract during delivery; unfortunately, most cases of neonatal herpes occur in women who do not have a known history of genital herpes.(3,4) Although transmission may also occur prenatally which carry a risk of neonatal transmission, maternal HSV has been associated with adverse out comes including preterm labor, growth retardation and abortion(5,6) Initial HSV-2 infection has been associated with preterm birth (7). It is, however, less easily transmitted to the newborn than HSV-1(1). Premature rupture of membranes (PROM) is the rupture of the fetal membranes before the onset of labor. In most cases, this occurs near term, but when membrane rupture occurs before 37 weeks' gestation, it is known as preterm PROM. Preterm PROM complicates approximately 3 percent of pregnancies and leads to one third of preterm births (8) .It increases the risk of prematurity and leads to a number of other perinatal and neonatal complications, including a 1 to 2 percent risk of fetal death.(6,9)

The aim of this study was to search for the presence of HSV infection among selected women with history of preterm premature rupture of membranes.

Patients and methods

Patients: This study was carried out during the period from October 2008 to September 2009. Patients were recruited from out patient clinic for obstetrics and gynecology in Al-Khadimyia teaching hospital.Seventy five multiparous women with history of rupture of membranes before 37 weeks of gestation age were included in this study. Their mean age ± SD was 28.23 ± 4 years (range 23-41 year). Twenty normal women with history of normal vaginal delivery age matched as a control group.

All patients gave informed consents for swabbing of cervix and external genitalia.

History of chronic or pregnancy induced medical diseases, vaginal bleeding or discharge, polyhydramnios, multiple pregnancy, history of previous surgical procedures that may result in

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preterm PROM include cerclage and amniocentesis were excluded.

Methods: Swabbing of external genitalia and cervical canal was performed using cotton tipped sterile swab with a wooden shaft. The specimen was kept dry at -20 °C for the detection of HSV antigen. This was carried out using Enzyme linked Immuno Sorbent Assay (ELISA), Wellcozyme, WZ02.

Results:

Herpes simplex virus antigen was detected in 37 out of 75 women (49.3%) with history of preterm premature rupture membranes (their pregnancy gestational age ranged between 30- 37 wks) compared to 4(20%) of the control group (X^2=5.538 and P=0.019)table-1.

Most of cases with HSV infection are asymptomatic 34(91.9%) and only3cases (8.1%) had a history of genital lesion compared to none of the control group who had HSV positive antigen .Table-2

The presence of HSV antigen was significantly associated with history of recurrent PROM in 23(56.1%), compared to those women with history of single PROM (X^2=5.090 and P<0.05) table -3.

Statistical Analysis:

Comparisons between groups were made by the X^2 or Fisher's exact test. A p-value less than 0.05 were considered significant.

Table-1: HSV-antigen among study groups

Study groups	HSV –antigen		Total No. (%)
	Positive No. (%)	Negative No. (%)	
PROM	37(49.3)	38(50.7)	75(78.95)
Control	4(20)	16(80)	20(21.05)
Total	41	54	95(100)

Table-2: Associated symptoms with HSV infection in study groups

Study groups HSV +ve	Genital lesion No. (%)	Asymptomatic No. (%)	Total No. (%)
PROM	3(8.1)	34(91.9)	37(100)
Control	0(0)	4(100)	4(100)

Table-3: Correlation between single and recurrent PROM with HSV infection.

X^2=5.090 DF=1 P=0.024

PROM	HSV –antigen		Total No.
	Positive No. (%)	Negative No. (%)	
Single	14(41.2)	20(58.8)	34(100)
Recurrent	23(56.1)	18(43.9)	41(100)
Total no. (%)	37(49.3)	38(50.7)	75(100)

Discussion:

The prevalence of genital herpes is increasing in our country, and most individuals are unaware of their infection (9, 10). Most cases of genital HSV infection in women occur without signs or symptoms of disease and are associated with cervical viral shedding. Almost none of this viral shedding is accompanied by clinically detectable genital lesions (11, 12)

Although some studies revealed that asymptomatic viral shedding in recurrent disease at term has not been associated with neonatal herpes (1), the maximum risk for development of a neonatal herpes infection in the face of PPROM and active recurrent genital herpes was 10.4%. This was equal to the mortality rate and was 75% lower than the major morbidity rate caused by prematurity. If delivery had occurred on the day the herpes lesions developed, on average, the neonates would have been nearly 2 weeks more premature, thereby potentially increasing the morbidity and mortality related to prematurity. These data concur with the American College of Obstetricians and Gynecologists(ACOG) consensus and expert opinion and would suggest that expectant management of PPROM at less than or equal to 31 weeks' gestation with active recurrent genital herpes is warranted (14).

A study by Major (13) of HSV in PPROM before 31 weeks' gestation found that the risks of neonatal mortality were similar between preterm delivery and neonatal infection (14).When there is preterm premature rupture of the membranes (PPROM), the risks of prematurity outweigh the risks of HSV transmission, except in the situation of intra-amniotic infection. Pregnant women should be counseled regarding the risks of HSV acquisition during pregnancy. It's extremely important to consider serologic testing for pregnant women and suppression therapy during pregnancy in order to decrease maternal infection and surgical risk due to cesarean delivery, as well as neonatal morbidity and mortality (15).

Suppressive therapy during the last month of pregnancy reduces the likelihood of viral shedding at term (16). Studies have reported reductions in neonatal infection when acyclovir or valacyclovir are given beginning at 36 weeks' gestation.(17,18) Acyclovir prophylaxis is beneficial even when the woman has no clinical outbreaks during pregnancy.(19) Persistence of viral shedding has been reported in the absence of clinical outbreaks, when lesions are present or prodromal symptoms occur at the onset of labor, both the CDC and ACOG continue to recommend cesarean birth to minimize the risk of viral exposure to the infant, even if suppressive therapy has been used(20). Cesarean birth before ruptured membranes virtually eliminates the risk of intrapartum transmission to the infant (21). Both detection of women at risk of infection and prevention of viral shedding near time of birth can contribute to improved outcomes (22). An effective screening program would need to include all pregnant women because most cases of neonatal

herpes occur in infant born to women with out history of HSV.

References:

1-*Brown ZA, Gardella C, Wald A, Morrow RA, Corey L. genital herpes complicating pregnancy. Obstet. Gynecol 2005; 106:845-56.*

2- *Herpes simplex. In: Pickering LK, ed. Red Book, 2009: the report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics, 2009:363-73.*

3- *Xu F, Sternberg MR, Kottiri BJ, McQuillan GM, Lee FK, Nahmias AJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006; 296: 964- 973.*

4- *Xu F, Markowitz LE, Gottlieb SL, Berman SM. Seroprevalence of herpes Simplex virus types 1 and 2 in pregnant women in the United States. Am J Obstet Gynecol. 2007; 196:43.e1-43.e6*

5- *Brown ZA, Selke SA, Zeh H, Kopelman J, Maslow A, Ashley RL, et al. Acquisition of herpes simplex virus during pregnancy. N Engl J Med.1997; 337:507-515.*

6- *Friese K. The role of infection in preterm labour. BJOG 2003; 110(20): 52-54.*

7- Brown ZA, Benedetti J, Selke S, Ashley R, Watts DH, Corey L. Asymptomatic maternal shedding of herpes simplex virus at the onset of labor: Relationship to preterm labor. Obstet Gynecol. 1996; 87:483-488.

8- *Mercer BM. Preterm premature ruptures of the membranes. ObstetGynecol 2003; 101:178-93.*

9- *Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;* ***342****: 1500–1507.*

10- *Abdulla SF, Abdul majeed BA, Mukhlis FA and Al-Omer LS. herpes Simplex Virus infection in women with history of abortion: A cause to be searched for.J Fac Med (Baghdad) 2003; 45 No.3-4:120-127.*

11- *Brown ZA, Voniver LA, Benedetti J, Critchlow CW, Hickok DE, Sells CJ, et al. Genital herpes in pregnancy: Risk factors associated with recurrences and asymptomatic shedding. Am J Obstet Gynecol. 1985; 153:24-30.*

12- *Hensleigh PA, Andrews WW, Brown Z, Greenspoon J, Yasukawa L, Prober CG. Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. Obstet Gynecol 1997; 89:891-5.*

13- *Major CA, Towers CV, Lewis DF, Garite J. Expectant management of preterm premature rupture of membranes complicated by active recurrent genital herpes. Am J Obstet Gynecol. 2003;188:1551-1554.*

14- *American College of Obstetricians and Gynecologists. Practice Bulletin No. 82 (Management of herpes in pregnancy). Obstet Gynecol. 2007;109:1489-1498.*

15- Thung SF, Grobman WA. The cost effectiveness of routine antenatal screening for maternal herpes simplex virus-1and -2 antibodies. Am J Obstet Gynecol 2005; 192:483-8.

16- *Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: A systematic review. Obstet Gynecol. 2003;102:1396-1403.*

17-*Watts DH, Brown ZA, Money D, Selke S, Huang ML, Sacks SL, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. Am J Obstet Gynecol. 2003;188:836-843.*

18-*Andrews WW, Kimberlin DF, Whitley R, Cliver S, Ramsey PS, Deeter R*

. Valacyclovir therapy to reduce recurrent genital herpes in pregnant women. Am J Obstet Gynecol. 2006;194:774-781

19-*Little SE, Caughey AB. Acyclovir prophylaxis for pregnant women with a known history of herpes simplex virus: A cost effectiveness analysis. Am J Obstet Gynecol. 2005; 193:1274-1279.*

20- *Centers for Disease Control and Prevention.Genital herpes: CDC fact sheet,2007. (Accessed September 4, 2009, at http://www.cdc.gov/std/herpes/STDFactherpes.htm.)*

21-*Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003; 289:203-9.*

22- *Cleary KL, Paré E, Stamilio D, MaconesGA. Type-specific screening for asymptomatic herpes infection in pregnancy: a decision analysis. BJOG 2005; 112:731-6.*