

The epidemiology of genital herpes

Fabio Parazzini¹, Giada Frontino¹,
Renata Bortolus^{2,3}, Luigi Fedele¹

¹ I Clinica Ostetrico Ginecologica,
IRCCS Fondazione Policlinico Mangiagalli Regina Elena
Università di Milano, Milan, Italy

² Dottorato in Scienze dell'Educazione e della Formazione Continua,
Università di Verona

³ Ulss 4 "Alto Vicentino", Vicenza

Corresponding Author:

Dr. Fabio Parazzini

I Clinica Ostetrico Ginecologica,
IRCCS Fondazione Policlinico Mangiagalli Regina Elena,
Università di Milano, Milan, Italy,

Tel. +39/02/39014663 – Fax +39/02/33200231

e.mail: parazzini@marionegri.it

Summary

OBJECTIVE: Using PubMed and manual search, we have reviewed the main papers published in English since 1990 on the epidemiology of genital HVS infection

RESULTS: The seroprevalence of HSV-1 antibodies is extremely high (about 65-80%) in the general population, the higher rates are observed in the United States and in Africa. The seroprevalence for HSV-2 is about one-third, but still represents a common condition. A clinical manifestation of genital Herpes is observed in only 30-50% of seropositive subjects. With regards to the temporal trend, an increase has been observed in the prevalence for HSV-2 antibodies. In addition, the presence of HSV-1 antibodies has been associated with a minor risk of seroconversion for HSV-2. The frequency of seropositivity increases with age and is higher in women, in subjects with a history of sexually transmitted diseases or HIV infection.

CONCLUSIONS: HSV infection is a common condition, and its frequency increases with age.

KEY WORDS: *herpes virus simplex, epidemiology, risk factors, pregnancy.*

Introduction

Genital herpes has traditionally been considered as an infection due to HSV-2. However, both HSV-1 and -2 are currently recognised as etiological agents of genital Herpes. This paper will address the epidemiology of genital infection of Herpes simplex, independently from its subtype.

Available data in literature in regards to frequency of the seroprevalence and clinical infection and the principal risk factors for the infection were analyzed.

Finally, epidemiological data will be discussed briefly on the frequency and risk determinants of the recurrent disease, and on the frequency of HSV infection in pregnancy.

METHODS

Using PubMed and manual search, we examined the main papers published in English since 1990 on the epidemiology of genital HVS infection (using "herpes virus simplex" in combination with "epidemiology" and "risk factors" as search conditions). The available articles had to meet pre-defined inclusion criteria: they had to be cross sectional, case-control or cohort studies.

RESULTS

Frequency of HSV infection

A primary infection is represented by serocon-

version of a HSV-seronegative subject to seropositive status, i.e. the development of specific HSV antibodies. The prevalence of contact with the virus in the population can be therefore assessed by estimating the frequency of subjects with specific HSV antibodies.

The presence of HSV-1 or -2 antibodies implies that the subject has come in contact with the virus, but it does not necessarily mean that him/her have a positive clinical history of genital Herpes. In fact, seroprevalence indicates the frequency in the population of subjects with antibodies, whereas prevalence of clinical infection suggests a clinical history.

Table 1 shows the results of selected studies conducted in different populations regarding seroprevalence of HSV-1 and HSV-2 antibodies.

Overall, the prevalence of HSV-1 antibodies in the population is about 65-80%, whereas the prevalence of HSV-2 antibodies is 20-30%. In general, the higher rates are seen in Africa and United States.

In regards to the temporal trend of seroprevalence for HSV infection, some studies showed the prevalence for HSV-1 antibodies has been stationary in the last 15-20 years. On the other hand there is an increase in the prevalence of HSV-2 antibodies [1-3].

Incidence of seroconversion

Few studies have assessed the incidence of HSV infection, namely the frequency of new cases of positivity for antibodies in one year. In general it is estimated that the incidence varies from 5 to 20 cases of seroconversion for every 100 seronegative subjects per year in countries with a high prevalence, such as Northern Europe and USA.[4] The main study regarding seroconversion was conducted in USA by the Chiron HSV Vaccine Study Group in 2393 sexually-active subjects who were seronegative for HSV-2 at study initiation, and 1508 of which were seropositive for HSV-1.[5] In this study the incidence rate of HSV-2 seroconversion was 5,1/100 subjects per year. The corresponding value for HSV-1 infection was 1,6/100 subjects per year.

In Italy Suligoi and coworkers [6] have recently conducted a study on the seroincidence and seroprevalence in adolescents. This longitudinal study recruited 345 adolescents. In the study, at 11 years of age the seroprevalence of HSV-1 infection was 51.6% and that of HSV-2 was 2.6%. At 17 years of age such values were 61.4% and 4.9%, respectively. The incidence of seroconversion was 1,6 per 100 subjects per year for HSV-1 and 0.4 per 100 subjects for HSV-2.

Table 1. Frequency of subjects with specific antibodies for HSV viruses in the general population.

<i>Authors</i>	<i>Country</i>	<i>Number of subjects assessed</i>	<i>HSV-1 positive subjects (%)</i>	<i>HSV-2 positive subjects (%)</i>
Total population				
Emonyi et al, 2000 [19]	Uganda	201		58
Malkin et al, 2002[4]	France	4412	67	17
Buxbaum et al, 2003[7]	Germany	2678	13	8
Leone et al, 2004[28]	USA	5452		26
Uuskula et al, 2004[29]	Estonia	1036 (blood donors)		17
Maivy et al, 2005[30]	France	3192	66	16
Males				
Emonyi et al, 2000[19]	Uganda	74		32
Bunzli et al, 2004[31]	Switzerland	1234	77	18
Females				
Emonyi et al, 2000[19]	Uganda	127		69
Msuya et al, 2003[32]	Tanzania	382		39
Bunzli et al, 2004[31]	Switzerland	1308	83	21

Frequency of clinical history of genital Herpes

Seroconversion is not always associated with clinical manifestation of the disease and therefore the prevalence (and incidence) of a history for clinical genital Herpes is lower than that of the seroprevalence for HSV-1 and -2 antibodies.

In general, clinical manifestations appear in 25-50% of genital infections of HSV-1 and -2.[5] A prospective study conducted in USA by the Chiron HSV Vaccine Study Group reported relevant data on the incidence of clinically-manifest disease in case of HSV-1 and -2 infection.[5] In this study, the incidence of clinical genital Herpes was about 1/100 subjects per year and the frequency of symptomatic disease was 57% of new infections.

HSV-1 and HSV-2 as a cause of genital Herpes

HSV-2 is generally rejected as cause of gestional herpes.[7] However, the results displayed in the Table 2, which are available in literature.[8] show how HSV-1 represents a percentually important cause of genital infection in countries of Northern Europe and USA, whereas it is less relevant in Asia. For instance, a study conducted in Sweden in 1995 and 1999 on 108 subjects with a primary clinically-manifest herpetic genital infection demonstrated a frequency of HSV-1 of 44%. [9] On the other hand, a study conducted in Thailand showed a frequency of HSV-1 of 19% in cases of genital Herpes [10]. Some data suggest an increase in the last years of the frequency of

HSV-1 as a cause of genital Herpes, especially in Northern Europe, USA and Australia.[8, 11, 12] For example, a study conducted in Wisconsin, USA on college students showed HSV-1 to be the cause for genital Herpes in 31% of cases in 1978, whereas it was found in 78% of cases in 2001.[13] Such developments indicate that today type 1 and 2 of HSV may both represent a frequent cause of genital Herpes.

Recurrent disease and frequency of viral shedding

The frequency and severity of recurrent disease is extremely variable in each subject. Some develop numerous symptomatic episodes during the course of a year, while others only do occasionally. More in general, the frequency of relapses tend to decrease as time passes since infection.[14]

Sporadic data are available on the frequency of shedding in asymptomatic subjects.[15] In a study conducted on 79 men, the subclinical shedding rate was 2.2%. The shedding rate was higher in subjects with HSV-2 infection than in those with HSV-1 infection (Odds ratio 4.4, 95% CI 1.2-15.3).[16] A subsequent study conducted by the same research group on 110 women with a history of genital Herpes demonstrated that subclinical shedding is extremely common, as it is present in about 2 in 100 days, as well as in one-third of days during reactivation of the virus. In addition, women with a higher frequency of relapse had a higher frequency of subclinical shedding.[17] Similar overall estimates were reported in a study conducted in 30 HSV-2 positive subjects.[18]

Table 2. Percentage of isolation of HSV-1 in clinical genital Herpes.

Authors	Country	N ^o subjects	HSV-1
Puthavathana et al, 1998[10]	Thailand	75 (women)	19
Lowhagen et al, 2000[9]	Sweden	108	44
Lowhagen et al, 2002[33]	Sweden	3085	29
Roberts et al, 2003[13]	USA	499	31 (1978)
Buxbaum et al, 2003[7]	Germany	2678	20% (men) 25% (women)
Theng e Chan, 2004[34]	Singapore	241	12
Tran et al, 2004[12]	Australia	25372	16 (1980) 35 (2003)

Risk factors

Age

The prevalence of seropositivity for HSV-1 and -2 infection increases with age. Such evidence has been constantly reported in many populations.[19] Similar observations also ensue from studies conducted both in high as well as in low-risk populations for the infection.[20] In general, the rates of seroprevalence stabilize around 35 years of age in women and 45 years in men.[4]

Sex

Various studies have consistently demonstrated women to be more commonly infected by HSV than men.[20, 21] Such difference is most evident for HSV-2 infection. Seroprevalence for HSV-1 antibodies in women is about 30-40% higher than in men, and is double when considering HSV-2. Furthermore, in regards to the clinical history of genital Herpes, the risk of symptomatic disease in

women is about double that in men. It is widely recognised that women are at higher risk due to the wider surface of genital mucosa. Similar considerations have been reported to explain also the higher risk of sexual infection from HIV in women than in men, during sexual vaginal intercourse. It may likewise be that hormonal factors may take part. Hormonal changes occurring in women throughout the menstrual cycle could decrease local immune defence systems, facilitating the onset of infection. The use of oral contraceptives has also been suggested to increase the risk of seroconversion. However, such data are limited and not always clear-cut.

History of sexually-transmitted diseases

Many studies have demonstrated that a history of prior sexually-transmitted infections is associated to a higher risk of seropositivity for HSV-1 and -2.[21-23] A similar consideration is gathered by

Table 3. Frequency of subjects with specific antibodies for HSV in the female population referring to centres for sexually-transmitted diseases (STD).

<i>Authors</i>	<i>Country</i>	<i>Number of subjects assessed</i>	<i>HSV-1 positive subjects (%)</i>	<i>HSV-2 positive subjects (%)</i>
Females and males				
Varela et al, 2001[35]	Spain	374		25
Females				
Oni et al, 1994[36]	Nigeria	153	5	3
Austin et al, 1999[24]	USA	1103	72	64
Males				
Bassett et al, 1994[37]	Australia	300		65
Russel et al, 2001[38]	Australia	132		20
Sizemore et al, 2005[39]	USA	328		46

Table 4. Frequency of subjects with specific antibodies for HSVs in the population of HIV-positive subjects.

<i>Authors</i>	<i>Country</i>	<i>Number of subjects</i>	<i>HSV-1 positive subjects (%)</i>	<i>HSV-2 positive subjects (%)</i>
Da Rosa-Santos, 1996[40]	Brasil	85		73
Wutzler et al, 2000[20]	Germany		91	48
Russel et al, 2001[38]	Australia	168		61
Andreoletti et al, 2005[41]	France	436		51
Andreoletti et al, 2005[41]	France	100		66

Table 5. Frequency of specific antibodies for HSVs in the population of pregnant women.

<i>Authors</i>	<i>Country</i>	<i>Number of subjects assessed</i>	<i>HSV-1 positive subjects (%)</i>	<i>HSV-2 positive subjects (%)</i>
Tideman et al, 2001[42]	Australia	3306 (examination during pregnancy and prenatal)	79 (analysis conducted on 408 women)	11
Gaytant et al, 2002[43]	Holland	1507	61 in Nijmegen 73 in Amsterdam 75 in Rotterdam	11 in Nijmegen 35 in Amsterdam 27 in Rotterdam
Uuskula et al, 2004[29]	Estonia	794		23

the finding of a higher frequency of seropositivity in subjects referring to centres for sexually-transmitted diseases (Table 3).

Herpes and Human Immunodeficiency Virus (HIV)

The frequency of seroprevalence of HSV-1 and -2 are higher in HIV-positive subjects (see Table 4 for results of selected studies).

HSV and HIV are both sexually-acquired. It is well-known that subjects with HSV are at higher risk of HIV infection, especially in women.[20] HIV-positive subjects have a higher risk of severe infection and of recurrent disease. In addition, due to the decreased immune defence system, lesions in HIV-positive subjects are generally more diffuse and may involve the rectal or uterine mucosa in women.

Presence of HSV-1 and -2 antibodies and risk of infection with the other subtype of HSV

The presence of HSV-1 antibodies has been related to a lower risk of seroconversion for HSV-2.[24] However, data in this regard are not congruous. Undoubtedly, in subjects who are positive for HSV-1 antibodies, a seroconversion for HSV-2 develops less frequently into a clinical genital Herpes infection. When indeed it does manifest, the disease progresses in a mild form.[25]

HSV in pregnancy

Table 5 shows the seroprevalence for HSV-1 and -2 in selected studies in pregnant women. The observed prevalence is altogether similar to that reported in the general population. The prevalence of HSV-2 antibodies is indeed about 25%, with marked differences according to the populations

assessed.

An estimate of the incidence of seroconversion in pregnancy originates from a wide prospective study conducted in USA. This study included 7046 pregnant women who were negative for HSV-1 and/or -2 at conception. Among those negative for HSV-1 and -2 at the beginning of pregnancy, the seroconversion rate for HSV-1 and -2 was 3.7/100 pregnancies, while in those positive for HSV-1 and negative for HSV-2 the rate of seroconversion for HSV-2 was 1.7/100 pregnancies.[26] Clinical manifestations were observed in 34% women who had a seroconversion during pregnancy. Nonetheless acquisition of infection near labour – which is relevant for its neonatal risk – has been observed in only 9 of 94 women.

Conclusions

When reviewing the epidemiological data regarding infection by genital Herpes, it should be emphasized that the seroprevalence of HSV-1 antibodies is extremely high (about 70-80%) in the general population. The seroprevalence for HSV-2 is about one-third, but still represents a common condition. The importance of HSV infection relies on the fact that currently a relevant portion of genital Herpes infection is due to HSV-1 and such occurrence is increasing progressively.

A clinical manifestation of genital Herpes is observed in only 30-50% of seropositive subjects, although the high risk of shedding which is present even in the subclinical infection should compel the public health organisation to take into consideration all seropositive subjects.

In regards to the temporal trend, an increase has

been observed in the prevalence for HSV-2 antibodies. In addition, the presence of HSV-1 antibodies has been associated with a minor risk of seroconversion for HSV-2.

The frequency of seropositivity increases with age and is higher in women, in subjects with a history of STD or HIV infection.

Finally, neonatal infection of HSV is a relevant condition and a seroconversion in pregnancy can be observed in women negative for both HSV-1 and -2 at onset of pregnancy in about 3-4/100 pregnancies, but the rate of an infection in proximity to labour seems much lower, this the use of universal prenatal herpes screening in still controversial. [27]

References

1. Smetana Z, Dulitzky M, Movshovitz M, Isacsohn M, Seidman D, Leventon-Kriss S (1994) Selected epidemiological features of herpes genitalis in Israel based on laboratory data. *Isr J Med Sci* 30:375-9.
2. Fleming DT, McQuillan GM, Johnson RE, et al. (1997) Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 337:1105-11.
3. Lafferty WE (2002) The changing epidemiology of HSV-1 and HSV-2 and implications for serological testing. *Herpes* 9:51-5.
4. Malkin JE, Morand P, Malvy D, et al. (2002) Seroprevalence of HSV-1 and HSV-2 infection in the general French population. *Sex Transm Infect* 78:201-3.
5. Langenberg AG, Corey L, Ashley RL, Leong WP, Straus SE (1999) A prospective study of new infections with herpes simplex virus type 1 and type 2. *Chiron HSV Vaccine Study Group. N Engl J Med* 341:1432-8.
6. Suligoi B, Torri A, Grilli G, Tanzi E, Palu G (2004) Seroprevalence and seroincidence of herpes simplex virus type 1 and herpes simplex virus type 2 infections in a cohort of adolescents in Italy. *Sex Transm Dis* 31:608-10.
7. Buxbaum S, Geers M, Gross G, Schofer H, Rabenau HF, Doerr HW (2003) Epidemiology of herpes simplex virus types 1 and 2 in Germany: what has changed? *Med Microbiol Immunol* 192:177-81.
8. Ribes JA, Steele AD, Seabolt JP, Baker DJ (2001) Six-year study of the incidence of herpes in genital and nongenital cultures in a central Kentucky medical center patient population. *J Clin Microbiol* 39:3321-5.
9. Lowhagen GB, Tunback P, Andersson K, Bergstrom T, Johannisson G (2000) First episodes of genital herpes in a Swedish STD population: a study of epidemiology and transmission by the use of herpes simplex virus (HSV) typing and specific serology. *Sex Transm Infect* 76:179-82.
10. Puthavathana P, Kanyok R, Horthongkham N, Roonpitsuthipong A (1998) Prevalence of herpes simplex virus infection in patients suspected of genital herpes; and virus typing by type specific fluorescent monoclonal antibodies. *J Med Assoc Thai* 81:260-4.
11. Malkin JE (2004) Epidemiology of genital herpes simplex virus infection in developed countries. *Herpes* 11 Suppl 1:2A-23A.
12. Tran T, Druce JD, Catton MC, Kelly H, Birch CJ (2004) Changing epidemiology of genital herpes simplex virus infection in Melbourne, Australia, between 1980 and 2003. *Sex Transm Infect* 80:277-9.
13. Roberts CM, Pfister JR, Spear SJ (2003) Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. *Sex Transm Dis* 30:797-800.
14. Benedetti JK, Zeh J, Corey L (1999) Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med* 131:14-20.
15. Wald A, Zeh J, Selke S, et al. (2000) Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 342:844-50.
16. Wald A, Zeh J, Selke S, Warren T, Ashley R, Corey L (2002) Genital shedding of herpes simplex virus among men. *J Infect Dis* 186 Suppl 1:S34-9.
17. Wald A, Zeh J, Selke S, Ashley RL, Corey L (1995) Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 333:770-5.
18. Krone MR, Wald A, Tabet SR, Paradise M, Corey L, Celum CL (2000) Herpes simplex virus type 2 shedding in human immunodeficiency virus-negative men who have sex with men: frequency, patterns, and risk factors. *Clin Infect Dis* 30:261-7.
19. Emonyi IW, Gray RH, Zenilman J, et al. (2000) Seroprevalence of Herpes simplex virus type 2 (HSV-2) in Rakai district, Uganda. *East Afr Med J* 77:428-30.
20. Wutzler P, Doerr HW, Farber I, et al. (2000) Seroprevalence of herpes simplex virus type 1 and type 2 in selected German populations-relevance for the incidence of genital herpes. *J Med Virol* 61:201-7.
21. Fife KH, Bernstein DI, Tu W, et al. (2004) Predictors of herpes simplex virus type 2 antibody positivity among persons with no history of genital herpes. *Sex Transm Dis* 31:676-81.
22. Wald A, Koutsky L, Ashley RL, Corey L (1997) Genital herpes in a primary care clinic. Demographic and sexual correlates of herpes simplex type 2 infections. *Sex Transm Dis* 24:149-55.
23. Hashido M, Lee FK, Nahmias AJ, et al. (1998) An epidemiologic study of herpes simplex virus type 1 and 2 infection in Japan based on type-specific serological assays. *Epidemiol Infect* 120:179-86.
24. Austin H, Macaluso M, Nahmias A, et al. (1999) Correlates of herpes simplex virus seroprevalence among women attending a sexually transmitted disease clinic. *Sex Transm Dis* 26:329-34.
25. Slomka MJ (1996) Seroepidemiology and control of genital herpes: the value of type specific antibodies to

- herpes simplex virus. *Commun Dis Rep CDR Rev* 6:R41-5.
26. Brown ZA, Selke S, Zeh J, et al. (1997) The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 337:509-15.
 27. Urato AC, Caughey AB (2006) Universal prenatal herpes screening is a bad idea in pregnancy. *Lancet* 368:898-9.
 28. Leone P, Fleming DT, Gilseman AW, Li L, Justus S (2004) Seroprevalence of herpes simplex virus-2 in suburban primary care offices in the United States. *Sex Transm Dis* 31:311-6.
 29. Uuskula A, Nygard-Kibur M, Cowan FM, et al. (2004) The burden of infection with herpes simplex virus type 1 and type 2: seroprevalence study in Estonia. *Scand J Infect Dis* 36:727-32.
 30. Malvy D, Halioua B, Lancon F, et al. (2005) Epidemiology of genital herpes simplex virus infections in a community-based sample in France: results of the HERPIMAX study. *Sex Transm Dis* 32:499-505.
 31. Bunzli D, Wietlisbach V, Barazzoni F, Sahli R, Meylan PR (2004) Seroepidemiology of Herpes Simplex virus type 1 and 2 in Western and Southern Switzerland in adults aged 25-74 in 1992-93: a population-based study. *BMC Infect Dis* 4:10.
 32. Msuya SE, Mbizvo E, Hussain A, Sam NE, Jeansson S, Stray-Pedersen B (2003) Seroprevalence and correlates of herpes simplex virus type 2 among urban Tanzanian women. *Sex Transm Dis* 30:588-92.
 33. Lowhagen GB, Tunback P, Bergstrom T (2002) Proportion of herpes simplex virus (HSV) type 1 and type 2 among genital and extragenital HSV isolates. *Acta Derm Venereol* 82:118-20.
 34. Theng TS, Chan RK (2004) Genital herpes in a sexually-transmitted infection clinic in Singapore: a 1-year retrospective study. *Ann Acad Med Singapore* 33:200-3.
 35. Varela JA, Garcia-Corbeira P, Aguanell MV, et al. (2001) Herpes simplex virus type 2 seroepidemiology in Spain: prevalence and seroconversion rate among sexually transmitted disease clinic attendees. *Sex Transm Dis* 28:47-50.
 36. Oni AA, Adu FD, Ekweozor CC (1994) Isolation of herpes simplex virus from sexually transmitted disease patients in Ibadan, Nigeria. *Sex Transm Dis* 21:187-90.
 37. Bassett I, Donovan B, Bodsworth NJ, et al. (1994) Herpes simplex virus type 2 infection of heterosexual men attending a sexual health centre. *Med J Aust* 160:697-700.
 38. Russell DB, Tabrizi SN, Russell JM, Garland SM (2001) Seroprevalence of herpes simplex virus types 1 and 2 in HIV-infected and uninfected homosexual men in a primary care setting. *J Clin Virol* 22:305-13.
 39. Sizemore JM, Jr., Lakeman F, Whitley R, Hughes A, Hook EW, 3rd (2005) Historical correlates of genital herpes simplex virus type 2 infection in men attending an STD clinic. *Sex Transm Infect* 81:303-5.
 40. Da Rosa-Santos OL, Goncalves Da Silva A, Pereira AC, Jr. (1996) Herpes simplex virus type 2 in Brazil: seroepidemiologic survey. *Int J Dermatol* 35:794-6.
 41. Andreoletti L, Piednoir E, Legoff J, et al. (2005) High seroprevalence of herpes simplex virus type 2 infection in French human immunodeficiency virus type 1-infected outpatients. *J Clin Microbiol* 43:4215-7.
 42. Tideman RL, Taylor J, Marks C, et al. (2001) Sexual and demographic risk factors for herpes simplex type 1 and 2 in women attending an antenatal clinic. *Sex Transm Infect* 77:413-5.
 43. Gaytant MA, Steegers EA, van Laere M, et al. (2002) Seroprevalences of herpes simplex virus type 1 and type 2 among pregnant women in the Netherlands. *Sex Transm Dis* 29:710-4.