Follow-up of Pregnant Women at High Risk of Transmitting Herpes Simplex Virus[1]

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Prospects for neonatal herpes transmission were studied in a group of pregnant Chilean women at high herpetic risk—including 59 with a history of genital herpes, 11 with a first genital herpes episode during the observed pregnancy, and 16 whose sexual partners had a history of genital herpes. Each woman completed a survey questionnaire, provided serologic samples for detection of herpes simplex virus (HSV), and provided periodic samples taken with cotton swabs for HSV isolation. The 86 women who completed the study had an average age of 28 years; most (58.8%) were primiparas.

Only 21 of the 86 subjects yielded HSV isolates (predominantly HSV-2) from weekly cotton swab samples taken from the 34th week of pregnancy onward. HSV-2 predominance was found both in the symptomatic cases and in the three asymptomatic ones. Of six subjects found to be shedding HSV at the time of delivery, only one exhibited asymptomatic shedding.

These findings are consistent with the following conclusions derived from studies in developed countries: (1) Isolation of HSV in pregnancy does not define a greater risk of shedding HSV during childbirth. (2) In nearly all (five of six) cases, HSV shedding during childbirth involved symptomatic episodes of herpes that clearly defined the steps to be taken by the physician. (3) Despite this, the finding of one asymptomatic case demonstrates that the physician should request a test for HSV isolation at the time of delivery by a woman at high herpetic risk.

The significant rise in the prevalence of genital infection by the herpes simplex virus (HSV) in recent years has increased the number of pregnant women carrying this infection and the incidence of neonatal herpes (*1, 2*). Genital herpes can be classified as primary herpetic infection (arising from first exposure of the individual to the etiologic agent), first herpetic episode (first clinical manifestation of the infection in a patient whose primary infection was asymptomatic), and herpetic recurrences (periodically recurring clinical episodes that can be either symptomatic or asymptomatic).

Pregnant women at especially high risk of transmitting this infection to their newborn children are those experiencing a primary herpetic infection during pregnancy, as in such cases there is greater probability that the virus will be transmitted to the fetus, mainly during labor or after causing viremia in the mother (*1, 2*). However, the most frequent form of infection of a child born to a mother who is a carrier of recurring genital herpes is through the infected birth canal, regardless of whether the mother's infection is symptomatic or asymptomatic (*4*). Infection of the newborn results, in most cases, in the development of neonatal herpes,

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a serious disease whose mortality exceeds 70% if untreated (*5, 6*). The reason why it is now important to identify both pregnant women able to infect their children and all infected neonates is because effective treatment is available whose timely administration significantly reduces mortality associated with this disease (*7, 8*).

The aim of the research reported here was to study the behavior of HSV infection in Chilean women during the final stage of pregnancy and childbirth, with an eye to learning more about prevention and timely diagnosis of neonatal herpes.

MATERIALS AND METHODS

Between August 1988 and August 1990, all gyneco-obstetric centers in Santiago were afforded an opportunity to refer pregnant women at high risk of having a genital herpes infection to the Virologic Clinic of the University of Chile's School of Medicine. This clinic restricts the care it provides to specific population groups in accordance with the needs of current research projects.

Pregnant women considered at high risk were those who had a history of HSV infection or whose sexual partners had such a history. A total of 123 such pregnant women took part in the study.

An epidemiologic survey questionnaire was administered to each woman to determine her socioeconomic and cultural background as well as her gyneco-obstetric and herpetic history. Also, each woman participated in a serologic study directed at identifying seroconversion cases and diagnosing primary herpetic infections. In addition, beginning in the 34th week of pregnancy, weekly tests were administered to isolate HSV. Work was also done to isolate the virus from samples obtained during childbirth from those pregnant women with a history of herpes infection and those entering the study group following detection of a first active herpes episode after the 34th week of pregnancy.

Virologic Study

Virus Isolation

The presence of HSV was investigated at the clinic's virology laboratory by inoculating samples taken directly from the subject's lesions, or from the vulvointroital area when no lesion was observed. The samples, obtained with a sterile cotton swab, were placed in a Dulbeco virus culture medium with 2% fetal sera (and also containing penicillin, gentamicin, and Fungizone) and were processed immediately. They were then inoculated in duplicate into tubes with a confluent monolayer of VERO cells and were incubated at 37° C.

These samples were examined every day for 7 days with an optical microscope. Those showing no cytopathic effect were classified as negative. Those showing a nonspecific effect or a characteristic cytopathic effect were subcultured and frozen for subsequent typing.

Virus Typing

The isolated viral strains were identified and typed with anti-HSV-1 and anti-HSV-2 type-specific monoclonal antibodies. For this purpose we used the direct immunofluorescence technique (Pathfinder® detection system from the Kallestad Laboratory, Austin, Texas, USA). Positive cells exhibited a green-apple-colored perinuclear or cytoplasmic fluorescence.

Serologic Study

In the case of subjects experiencing a first genital herpes episode, blood samples obtained during the infection's acute and convalescent phases were tested by

complement fixation for the presence of anti-HSV antibodies in order to characterize the seroconversion process and diagnose cases of primary infection. These tests employed viral antigen prepared in our laboratory with strains isolated from patients with herpetic lesions and typed with monoclonal antibodies.

RESULTS

Of the 123 pregnant women originally accepted for inclusion in the study, 86 completed the scheduled follow-up. The mean age of these 86 subjects was 28; 77.8% had received secondary education, 24.4% technical (vocational) education, and 53.4% university education. Over half (58.8%) of the subjects were primiparas, while 41.2% were multiparas. Mean age at initiation of sexual activity was 20 years, within a reported range of 14 to 23.

The 86 subjects were classified as being at high herpetic risk for the following reasons: 59 (68.6%) had a history of genital herpes; 16 (18.6%) had a sexual partner with a history of herpes; and 11 (12.7%) had a first episode of genital herpes during pregnancy, of whom 5 (5.8% of the 86) had primary genital herpes infections confirmed by serology through seroconversion. In addition, 8 (9.3%) of the study subjects had a history of condyloma and 1 subject (1.2%) had a history of chlamydial infection.

Table 1 shows the kinds of herpes lesions reported by the study subjects and their sexual partners. In 26 cases (30.2%) a history of genital herpes was reported by both the pregnant woman and her partner.

Regarding virus isolation from samples obtained from the 34th week of pregnancy onward, no HSV was isolated from 65 of the subjects. The remaining 21 subjects (24%) exhibited some type of herpetic episode, of which 16 were recurring episodes and 5 were episodes associated with primary infections. HSV-1 and HSV-2 were isolated from 2 (9.5%) and 18 (85.7%) of these subjects, respectively; in 1 case it was not possible to type the virus. This noteworthy predominance of HSV-2 was found both in the symptomatic cases and in 3 cases where asymptomatic viral shedding was detected.

HSV shedding at the time of delivery was detected in six cases, only one of which involved an episode of asymptomatic shedding of the virus. Characteristics of these cases are shown in Table 2.

DISCUSSION AND CONCLUSIONS

The study data indicate that many of the women who completed the follow-up had a relatively high sociocultural level (defined in terms of family income and education). This could have been due to any of several reasons, including the following: increased concern on the part of the subject's obstetrician regarding the need to study the history of the infection;

Table 1. Characteristics of herpes infections reported by pregnant women and their sexual partners; Santiago, Chile, 1988–1990.

		History					
		Genital herpes		Labial herpes		Gluteal herpes	
Reported by	No.	No.	(%)	No.	(%)	No.	(%)
Pregnant woman	86	59	(68.6)	38	(44.2)	6	(7.0)
Sexual partner	86	48	(55.8)	25	(29.1)	2	(2.3)
Total	172	107	(62.2)	63	(36.6)	8	(4.7)

Table 2. Characteristics of cases where HSV was isolated from cotton swab samples taken from study subjects at the time of delivery.

Case No.	Type of HSV isolated	Clinical manifestations	Type of episode	Isolation of the virus during pregnancy	Type of delivery	Neonate	Treatment of the neonate
1	HSV-1	Yes	Recurring	+	Cesarean	Normal	–
2	HSV-2	Yes	Recurring	–	Vaginal	Normal	–
3	HSV-2	No	Recurring	–	Vaginal	Normal	+
4	HSV-2	Yes	Recurring	+	Cesarean	Normal	–
5	HSV-2	Yes	Primary infection	–	Vaginal	Died	–
6	Not identified	Yes	Primary infection	–	Cesarean	Normal	+

greater knowledge on the part of the subject about this particular viral infection; and, accordingly, a more accurate history and greater willingness to institute appropriate controls.

The high-risk classification of most study subjects (59, or 68.6%) was based on a personal history of genital herpes infection (see Table 1); only 16 subjects (18.6%) were classified as high-risk because of the histories of their sexual partners. This is consistent with the distribution of pregnant high-risk subjects included in a similar U.S. study (*9*), of whom 85% had a history of genital herpes.

It should be pointed out, however, that in our study the remaining 11 women (12.8%) were classified as high-risk because they had a first episode of genital herpes during pregnancy. This contrasts with the study population of the foregoing study, only 5% of whose members developed a first episode during pregnancy (*9*). In our study, 5 of the 11 cases with the first clinical episode during pregnancy had their primary genital infections confirmed—both by isolation of the virus from lesion samples and by clear demonstration of seroconversion in test results obtained with acute and convalescent sera.

During the follow-up conducted after the 34th week of pregnancy on 81 of our high-risk subjects (excluding the 5 with primary infection), HSV (types 1 and 2) was isolated from 16. Of these, 13 had a symptomatic herpetic episode and 3 shed the virus asymptomatically. Altogether, HSV-2 was identified in over 80% of the isolates obtained during pregnancy, which once again underscores the significant role played by HSV-2, especially in subjects with recurring symptomatic or asymptomatic episodes.

These results are consistent with those of studies conducted among other population groups and confirm the selective advantage of HSV-2 in establishing a latent infection that may later reemerge in the genital area.

Of greatest relevance to the study of a pregnant woman at high herpetic risk is the presence of the virus in the genital area during childbirth, which is when it is most frequently transmitted from mother to child. As indicated in Table 2, we were able to confirm the presence of a clinical episode of genital herpes (HSV-1 or HSV-2) during childbirth in 5 cases (5.8% of the 86 women studied). This percentage is clearly lower than that found by similar studies, in which the incidence of symptomatic genital herpes episodes during childbirth among high-risk women was in the range of 11–13% (*9*, *10*).

Of the 81 women who were asymptomatic at the time of delivery, the virus was isolated from only one (Case No. 3 in Table 2). This low isolation rate from asymptomatic subjects is similar to that

estimated by other authors (*11–13*). In other words, our results underscore the infrequency of asymptomatic HSV shedding during childbirth among women at high herpetic risk. Hence, the likelihood that these high-risk women who are asymptomatic at the time of childbirth will infect their newborns through viral shedding at delivery is very small.

In summing up, it seems important to mention certain conclusions derived from our results that are consistent with the results of studies conducted in developed countries. These are as follows:

1. Isolation of HSV during pregnancy does not make it possible to define a greater or lesser risk of shedding the virus during childbirth, for which reason it is not advisable to apply the protocol of follow-up examinations beginning in the 34th week of pregnancy (*4*).
2. In nearly all (5 out of 6) cases, shedding of the virus during childbirth involved symptomatic episodes of herpes that clearly indicated the measures to be taken by the obstetrician.
3. The above notwithstanding, the detection of an asymptomatic case points up the need to recommend that the physician request isolation of the virus at the time of delivery by women at high risk. If the test results are positive, the obstetrician and the neonatologist will be able to define the risk to the neonate and decide upon appropriate treatment, whether on the basis of close observation or through the use of antiviral medications of proven efficacy such as acyclovir (*14*).

All in all, while there is no clear concept dictating the treatment of pregnant women at high herpetic risk, the general recommendation is to proceed with a vaginal delivery for asymptomatic women and a cesarean section for symptomatic patients or those with prodromal manifestations. The decision of the physician should be based on the results of a careful examination of the genital tract and on exhaustive questioning of the patient aimed at identifying possible prodromal manifestations. It is recommended that samples be taken at the time of delivery for isolation of HSV from those asymptomatic women at high herpetic risk who deliver vaginally, in order to identify neonates at risk and determine the best course of treatment.

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New United Nations Program on AIDS

In a resolution adopted on 21 January, the Executive Board of the World Health Organization, meeting in Geneva, recommended the establishment of a cosponsored United Nations Program on HIV/AIDS. The aim of the Program is to achieve global coordination of policies, approaches, and funding in the urgent struggle to slow the spread of the disease. The Program will be administered by WHO.

The Program will bring together six organizations within the United Nations system: the United Nations Children's Fund (UNICEF), the United Nations Development Program (UNDP), the United Nations Educational, Scientific, and Cultural Organization (UNESCO), the United Nations Population Fund (UNFPA), the World Bank, and WHO.

The main objectives of the new UN program are (1) to provide global leadership in response to the pandemic; (2) to advocate greater political commitment; (3) to provide technical, strategic, and policy direction; (4) to ensure collaboration among UN system organizations, governments, and nongovernmental organizations; and (5) to strengthen the capacity of governments to coordinate and carry out HIV/AIDS activities.

A cosponsored UN program will ensure a united, coordinated effort and reduce duplication. It will encourage joint and coordinated fund raising at the global and country levels and better integration of ideas and approaches among the UN agencies. Governments struggling to cope with the growing numbers of HIV infections and AIDS cases will receive more comprehensive support from UN organizations and help in coordinating the efforts of other donor agencies. The Program will also help encourage global-scale application of prevention and control activities, such as education programs and treatment of sexually transmitted diseases.

Source: World Health Organization. Press Release WHO/6. Geneva: 21 January 1994.