Pregnancies in Human Immunodeficiency Virus–Infected Sex Partners of Hemophilic Men

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• **We investigated 24 completed pregnancies of 20 healthy, human immunodeficiency virus (HIV)–seropositive sex partners of 20 seropositive hemophilic men. One woman had recurrent herpes simplex type 2 infection; no woman was known to use illicit drugs or to have other purported cofactors for vertical HIV transmission. For 8 offspring, the mothers learned of their partners' serostatus and received counseling against pregnancy prior to the fifth month of gestation; for 9 offspring (37.5%), the mothers learned of their own seropositivity and received counseling prior to the fifth month. Acquired immunodeficiency syndrome developed in 7 (35%) of 20 fathers, 4 of whom died; HIV-related symptoms developed in 4; severe liver disease developed in 2; and 7 (35%) were in good health. In four mothers (20%) HIV-related symptoms developed. Five offspring were breast-fed for 2 days to more than 3 years, two while the mother was known to be seropositive; four of these were seronegative and healthy, and one was seropositive at 30 months of age and had persistent cervical lymphadenopathy at 48 months of age. Infants were born at term; median birth weight was 2.86 kg. Solely on the basis of serologic studies and symptoms for those with more than 15 months of follow-up, the minimum perinatal transmission rate for this group of women without putative transmission cofactors (drug usage, promiscuity, malnutrition, HIV symptoms) was at least 25%, a rate comparable to that reported for women in other risk groups.**

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In March 1987, the Centers for Disease Control, Atlanta, Ga, in cooperation with the National Hemophilia Foundation (NHF), conducted a survey of all US hemophilia treatment centers (HTCs) and physicians known to treat patients with hemophilia[1] to determine (1) whether sex partners of hemophilic men known to be infected with human immunodeficiency virus (HIV) were being tested for HIV antibody, (2) the HIV seroprevalence rate among partners being tested, and (3) the extent of compliance with the NHF and Public Health Service guidance and recommendations for preventing sexual and perinatal transmission of HIV.[2-10] Two hundred thirty-seven (96%) of the 246 health care providers contacted responded, reporting on 2276 spouses/sex partners of a comparable number of known HIV-seropositive hemophilic patients. Despite recommendations against un-protected intercourse by and with seropositive or nonserotested hemophilic men, 280 couples reported pregnancies since January 1985, representing a fertility rate of 54.7 per 1000 women per year. This rate was comparable to the US fertility rate for this time period, suggesting that counseling was not as effective as had been hoped.[11,12] (The US fertility rate for 1985 was 66.2 per 1000 women aged 15 through 44 years old; for 1986, it was 65.4 per 1000; and for 1987 [provisional estimate], it was 66.1 per 1000.) Eight percent of these pregnancies were to women known to be HIV seropositive; 39% were to women not tested for HIV antibody. In part because of these findings, counseling and education of this population were intensified and federal monies were earmarked for transmission prevention within this population.[13]

In the fall of 1988 and in January 1989, we obtained follow-up information on the HIV seropositive mother/father pairs and their offspring from the 1987 survey. We believed that this group could provide insight into three important perinatal HIV questions: (1) Why did reportedly intelligent and educated at-risk couples procreate despite counseling and recommendations to the contrary? This information might be helpful in determining more appropriate techniques and content of counseling and education for various at-risk populations. (2) What were the family structures into which these children were born and how did parental HIV infection affect those structures? (3) Evidence exists that "cofactors" play a role in horizontal HIV transmission (eg, sexually transmitted diseases, immunodeficiency, drug usage, HIV symptoms),[14,15] and some data suggest that maternal HIV symptoms are associated with infant symptoms of HIV.[16,17] Most studies of perinatal HIV transmission have as a primary postulate that cofactors for horizontal transmission also play a role in vertical transmission (the National Institute on Drug Abuse Technical Review Meeting on Perinatal HIV Infection, October 17 and 18, 1988); however, to our knowledge, no data currently exist to support or refute this postulate. We therefore wished to also ask how the HIV infection status of children born to this survey's reportedly monogamous, well-nourished, non–drug-abusing, asymptomatic HIV-infected women compared with that reported for infants born to HIV-infected women in other risk groups.

PATIENTS AND METHODS

All HTCs reporting pregnancies of seropositive women in the 1987 survey were contacted by telephone in October 1988 and again in January 1989. Information was obtained on 23 of all 24 reported pregnancies, including 1 therapeutic abortion and 22 live

births, and also on three subsequent births to two of these seropositive women. One initially reported live birth could not be confirmed and one HTC required that one liveborn child (reportedly with acquired immunodeficiency syndrome [AIDS]) not be included herein, for reasons of confidentiality. The therapeutic abortion was to an HIV-asymptomatic woman and will not be discussed further. Information was provided from the medical records of the HTC and other physicians. No identified information was obtained and household members were not contacted for the purpose of this study. Human immunodeficiency virus serotesting in all cases was done locally and/or as part of ongoing research or health department studies using a screening assay, with confirmation with an appropriate second technique.[4] Counseling concerning the meaning of antibody results, the risk of HIV transmission by sexual contact and from mother to fetus, and the mortality associated with HIV infection was reportedly given at least when results were shared with the tested individual, and often earlier. General HTC recommendations and individual counseling reportedly also included a recommendation against pregnancy for a sex partner of a hemophilic man; sometimes this recommendation was made in extremely strong terms. Of the women described herein, none were using illicit drugs or were known to have sexual relations other than those noted here; one hemophilic father used illicit drugs. (This low prevalence of other risk factors is consistent with questionnaire responses from the Centers for Disease Control's ongoing hemophilic household study[18][Dale Lawrence, MD, unpublished data, 1989].)

A "planned pregnancy" was defined highly conservatively herein, as one in which one or both parents indicated to HTC personnel that he/she was actively attempting to procreate. Pregnancies that followed a parent's(s') indications of "readiness" for a child or conscious avoidance of pregnancy prevention were included herein as "unplanned." "Planned" thus indicates a very conscious choice on the parent's(s') part. The 95% confidence intervals (95% CI) were calculated for moderate or extreme proportions, where appropriate.[19]

RESULTS

Parental Characteristics

The fathers' ages ranged from 22 to 40 years, and mothers' ages ranged from 17 years to the mid-30s. Six (30%) of 20 couples were unmarried; for at least 5 of these couples, the couple was no longer together at the time of follow-up and the mother had the sole responsibility for their child. Three (21%) of 14 married couples had since divorced, 2 of which had married because of pregnancy. Wives of two husbands who died of AIDS have new sexual partners. One remarried; her current spouse is reportedly using condoms for all intercourse. The other is pregnant by her current partner. Four couples (20%) were unemployed at the time of follow-up; five fathers (25%) and four mothers (20%) were employed in professional or technical areas; two fathers and one mother were employed in sales; and one father and three mothers were employed in office or security work. Seven mothers had no employment but full home care responsibilities; one mother was a high school student.

As of October 1988, 4 (20%) of 20 mothers had probable HIV-associated symptoms, 1 refused to return to the HTC after learning her antibody result, and 15 were known to be in good health. In seven fathers (35%) AIDS developed, and four of these died; four (20%) had HIV-related symptoms; two (10%) had severe liver disease; and seven (35%) were in good health. Only five couples were known to have consisted of two healthy partners.

Planning of Pregnancy, by Knowledge of Parents' Serostatus: All Offspring of HIV-Seropositive Sex Partners of Hemophilic Men*

Couple Member Knowing Result	Prior to Conception		Prior to Delivery	
	Planned	Unplanned	Planned	Unplanned
Neither	7	12	3	6
Male/not female	1	0	1	0
Female/not male	0	1	0	0
Both	1	2	5	9
Total No. of Pregnancies	**9**	**15**	**9**	**15**

*HIV indicates human immunodeficiency virus.

Parental Serotesting and Notification

For 7 (29%) of the total 24 offspring, the father had been serotested prior to conception; two men were not informed of their test results until after the child was born—in one case due to a study investigator not notifying the HTC and in another, because the HTC could not locate the father. For 10 offspring (42%), the father was tested during the pregnancy (for 4, in the first trimester, for 4 in the second, and for 2 in the third); and for seven (29%), the father was tested after the birth. The mothers knew the fathers' serostatus prior to the conception of four infants (17%), and their own, prior to the conception of five (21%). In nine pregnancies, the mother learned of the father's serostatus during the pregnancy; in four of these, the mother learned at less than 5 months' gestation. In seven pregnancies, the mother learned of her own serostatus during the pregnancy; in four of these, she learned at less than 5 months' gestation. Thus, for at least nine women, abortion would have been a medicolegal option in any state in the United States at the time she learned she was seropositive. Two mothers were serotested specifically because of pregnancy; one was tested because of possibly HIV-related symptoms in her infant. One was tested prior to her husband, when she was hospitalized for surgery; three were tested when AIDS developed in their hemophilic sex partners; four were tested by their health department or as participants in ongoing studies; and nine were tested in response to HTC recommendations (seven were tested within a month of their male partner's testing; one was tested 9 months following the man's testing; and one was tested at approximately 2 years after the man's testing).

Planned Pregnancies

Nine (37%) of these pregnancies were planned; three by at least the mother and six definitely by both parents (Table). One planned pregnancy was to a woman whose husband was tested prior to conception but who did not learn of his test results until after conception; this woman was tested during her pregnancy. Another planned pregnancy was in an unemployed woman whose unemployed boyfriend did not inform her of

his serostatus, although he knew it and had been fully counseled prior to conception; she was serotested after AIDS developed in the male partner, when the infant was 7 months old. Two planned pregnancies were to one couple told they were seropositive when the mother was in the first month of the second pregnancy; the mother also had a child from a previous marriage. Another planned pregnancy was to a Spanish-speaking couple with two other children; this couple was unaware that hemophilic patients were at risk of HIV infection. The wives of two hemophilic brothers living in different cities each had a planned pregnancy. Neither father had been counseled against procreation prior to the pregnancies; these fathers and mothers were all serotested during the pregnancies.

Reasons given for planning pregnancies, despite at least some HTC counseling in most cases, included denial that the offspring could really become infected ("It won't happen to us." "The risks are really low."); willingness to "take their chances"; unwillingness to consider the possible consequences ("I don't want to think about it"); a sense of invincibility, in that they had "conquered" hemophilia and would similarly triumph over HIV; and that "even if we are infected, we want a baby."

Unplanned Pregnancies

Two pregnancies were unplanned by a couple known to be seropositive prior to both conceptions but whose religion prohibited contraception. This couple's first child, also included in this survey, was the product of another unplanned pregnancy and was born 5 months before either parent knew his/her serostatus. This mother subsequently had a tubal ligation. Another unplanned pregnancy was to a couple of the same religion as the aforementioned couple. This couple also knew their serostatus prior to conception, already had a number of male offspring, and verbalized a desire for a girl. A fifth unplanned pregnancy of note was to an unemployed, unmarried couple having a long-term relationship. The couple did not know their serostatus prior to conception and the mother was of borderline normal intelligence. She had a subsequent pregnancy with the same sex partner that was terminated therapeutically; 2 months later she had a tubal ligation. The father was an illicit drug user and has no involvement in the care of this child. One pregnancy was to an unmarried couple expressing readiness for a child; the woman had reported consulting a family planning physician prior to conception and had been advised that being a sex partner of a hemophilic man did not place her at risk for HIV infection.

Pregnancy Outcomes

For these descriptions and analyses, we included only the 15 mother/father pairs and their 18 offspring with likely intrauterine HIV exposure, ie, those for whom the mother was either (1) seropositive on testing done prior to conception (n = 5), during the pregnancy (first trimester [n = 3], second trimester [n = 23], third trimester [n = 2]), at delivery (n = 1), or within 1 month following delivery (n = 2), or (2) tested more than 1 month after delivery, but had an offspring who was seropositive at older than 15 months of age (n = 3, mother tested at 4, 7, and 16 months after delivery). These criteria excluded the following: one infant born 37 months prior to the mother's serotesting and breast-fed for more than 3 years (child was seronegative at 37 months of age and in good health at 58 months of age); one infant born 10 months prior to the mother's serotesting and breast-fed for 2 days (this child was seronegative at 19 months of age and in good health at 37 months of age); one infant born 5 months prior to the mother's serotesting, breast-fed for 12 months, and a sibling of two offspring included in these analyses, one of whom had symptoms of HIV infection (excluded child was seronegative at 3 months of age and in good health at 42 months of age); one infant born 24 months prior to the mother's serotesting and whose father died of AIDS 7 months after this child's birth (this child was seronegative at 31 months of age and in good health at 43 months of age); one infant born 6 months prior to his mother's serotesting (the mother would not return to the HTC after being told her test results; the mother's and infant's health and infant's serostatus are not known); and one infant born 5 months prior to the mother's serotesting and whose father died of AIDS 11 months after the child's birth (this child was seronegative at 11 months of age and in good health at 36 months of age).

None of the infants included in the descriptive analyses were born prematurely; median birth weight was 2.86 kg. (The US average birth weight for 1985 and 1986 was 3.37 kg.) Two infants were delivered by cesarean section, one reportedly because the mother was infected with HIV and herpes simplex virus type 2. These mothers were found to be seropositive in their fourth and sixth months of pregnancy; the infants were seronegative at 12 and 18 months of age. Two included infants were breast-fed, one for 9 to 12 months and one for 7 months, although the latter mother knew she was seropositive. The former mother was serotested when her child was 16 months old, because the child had marked cervical lymphadenopathy; the child was seropositive at 30 months of age. The second breast-feeding mother had also breast-fed an older infant, born 5 months prior to the mother's serotesting and not included in these analyses, for 12 months. Both her breast-fed infants were seronegative, at 9 and 3 months of age, respectively, and they remain in good health. A third offspring of this same mother is included in these analyses and was not breast-fed (in response to intensive counseling of the mother by HTC personnel); this infant was seropositive and hospitalized at 4 months of age for presumptive *Pneumocystis carinii* pneumonia, responsive to appropriate antibiotic therapy, and at follow-up was failing to thrive. Offspring of two other mothers died of *P carinii* pneumonia confirmed by bronchial washings, one at 11 months of age and one at 4 months of age. By parental report and HTC provider observations, the remaining 15 (83%) of 18 children were in good health, without obvious developmental abnormalities, serious infections, failure to thrive, oral candidiasis, or diarrhea. One of these 15 children, who was seropositive at 44 months of age, had been diagnosed as having idiopathic thrombocytopenia in infancy; this has since resolved.

Serostatus and Clinical Status of All Infants

The median time since delivery of all 24 infants was 30.5 months (range, 8 to

57 months). Seven (30%) of 23 children were HIV seropositive at last testing. In addition, 1 child with presumptive *P carinii* pneumonia and failure to thrive was seropositive at 7 months of age and seronegative at the latest two testings. Four (31%) of 13 children serotested when they were older than 15 months of age were positive. Two of these four were also repeatedly HIV culture positive, and three seronegative children were also antigen negative; to the HTC personnel's knowledge, none had been tested for HIV-1 proviral DNA by polymerase chain reaction. Three infants (12.5%) were diagnosed as having *P carinii* pneumonia; two of these died of *P carinii* pneumonia and were seropositive at the time of death and one was the infant noted above, now seronegative. An additional two children seropositive when they were older than 15 months of age had questionably HIV-related symptoms (lymphadenopathy and idiopathic thrombocytopenia purpura). The mothers of these five symptomatic children were in good health at the time of follow-up. None of these children have any other known potential source of HIV infection besides maternal transmission. We estimated the minimum perinatal transmission rate for this group two ways. First, we included those followed up for at least 15 months and seronegative at latest testing, those seropositive when they were older than 15 months of age, and infants dying of *P carinii* pneumonia (AIDS) who would have been older than 15 months of age had they lived. One infant whose mother was tested because of his symptoms and one infant without serotesting were excluded. The minimum transmission rate was 25.0% (5/20) (95% CI, 9.6% to 49.4%). (Median birth weight of these five infants was 2.9 kg [range, 2.7 to 3.5 kg].) Second, in addition we excluded any child whose mother was serotested more than 1 month following the child's birth, giving a minimum transmission rate of 23.1% (3/13) (95% CI, 6.2 to 54.0).

Sibships

Three of three sibships included one pregnancy and one seropositive child, although not all seropositive children were older than 15 months of age when last tested and cannot therefore be considered necessarily infected: one pair had an older sibling seropositive at 26 months of age and a younger sibling seronegative at 17 months of age; a second set had the oldest sibling (not included in the analyses) seronegative at 3 months of age, the second sibling seronegative at 9 months of age, and the youngest sibling seropositive at 4 months of age and subsequently seronegative but symptomatic with presumptive *P carinii* pneumonia and failure to thrive; and a third pair had an older sibling seronegative at 11 months of age and a younger sibling seropositive at 7 months of age.

COMMENT

To our knowledge, this is the first study to examine reasons why couples with stable health care provider contacts would fail to implement public health guidelines for prevention of HIV transmission. In 1987, we had hoped to find the fertility rate for this population nearly zero, and certainly not comparable to that of the United States as a whole, since widely disseminated Public Health Service and NHF recommendations at the time of these pregnancies were for at least HIV-untested or seropositive hemophilic men to avoid unprotected intercourse and procreation until more was known about HIV transmission and outcome risks.[1-10] We thus wished to find out more about whether seropositive couples were aware of the male and/or female partners' serostatus at the time of the pregnancies, if the mothers were serotested because of pregnancy or a desire for pregnancy, whether therapeutic termination of pregnancy would have been a medicolegally available option at the point parents were serotested, whether the pregnancies were planned, couples' attitudes about the fetuses'/infants' risks of HIV infection, and the effects of HIV on the family structure into which these children were born.

Thirty-seven and five-tenths percent of the pregnancies (nine) were actively planned; in at least 37.5% (nine) of all pregnancies the mother learned of her seropositivity at a point in which pregnancy termination would have been a medicolegal option. These data support the following impediments to recommendation compliance: lack of information, a strong level of denial (including a sense of invincibility because they had already dealt successfully with the potential problems associated with hemophilia), religious beliefs, and poor communication at all levels, including among research coordinators, HTC personnel, hemophilic men, and these patients' female sex partners. Finances are now in place to help HTCs address these problems.[13]

It would be interesting to compare the characteristics of these childbearing HIV-infected couples with those of nonprocreating HIV-infected hemophilic men and their sex partners. Unfortunately, to our knowledge, data are not available concerning the demographic characteristics, occupations, marital status, and marital stability of the HIV-seropositive or the general US hemophilic population. The age distribution of the couples discussed in this article was certainly neither lower than that of a cohort of factor-product recipients from across the United States for which participation was limited to persons older than 13 years of age (median age, 22 years; n = 220) nor lower than that of hemophilic patients receiving care at California HTCs[20,21] (11% were 5 years old or younger; 15% were 6 to 12 years old; 7% were 13 to 16 years old; 9% were 17 to 20 years old; and 58% were 21 years old or older; n = 1438).

A recent study suggested that counseling and education can lead to increased condom usage by HIV-infected African prostitutes because of concern about infecting their clients.[22] There is every reason to expect that with counseling and education, hemophilic men will show a similar concern for their wives, girlfriends, and potential offspring. However, our data support a need for outreach to ethnic minorities and women having relatively unstable relationships with hemophilic men, all of whom might not know HTC personnel well or consider these personnel their own health care providers. Also, it may be useful in counseling hemophilic couples considering parenthood to note that the offspring of these particular couples were faced with a high rate of parental morbidity/mortality (one or both parents were clinically symptomatic in 14 [74%] of 19 households) and

conjugal instability (50% of households were not intact).

This study also provides case-specific information pertinent to a number of perinatal HIV debates: the roles of vaginal delivery and breast-feeding in HIV transmission, the relation between pregnancy and maternal symptoms, the relation between maternal symptoms and infant symptoms, and the effect of HIV on intrauterine growth and length of gestation. We will briefly review our data in relation to several of these. Human immunodeficiency virus has been isolated from breast milk; breast milk was implicated as a possible source of HIV infection for at least four infants[23-26] and epidemiologically it was linked to higher rates of infant seropositivity.[27] The Public Health Service recommends that HIV-seropositive women not breast-feed.[2] In our study, five children were breast-fed, two by mothers who were known to be seropositive while breast-feeding. Four were healthy and seronegative at follow-up, and one breast-fed infant was seropositive at 30 months of age. It has been suggested that HIV symptoms in mothers is associated with symptoms in infants; however, subsequent evaluations in one of these studies failed to support the initial finding.[16,17,28] All our study mothers were healthy at the time of pregnancy and the mothers of the five symptomatic children were in good health at follow-up. Conversely, the four mothers who were symptomatic at follow-up had healthy, seronegative children. Finally, the infants in our study were born full term, with birth weights close to the US average, suggesting that maternal HIV infection does not necessarily lead to clinically significant intrauterine growth retardation or prematurity, findings consistent with those of three large, multicenter studies involving mothers in other risk groups.[27-29]

To our knowledge, this is the first study to examine the rate of vertical HIV transmission and maternal/child symptoms in women who had few or no purported "transmission cofactors", eg, promiscuity and associated sexually transmitted diseases, intravenous drug abuse, malnutrition, and HIV symptoms. Indeed, few data exist to quantitate the risk of vertical transmission by HIV-infected women in any risk group. Most studies are based on symptomatic infants, siblings, or mothers, and thus these results cannot be generalized.[30,31] Four studies have been published in which seropositive women were followed up to completion of pregnancy. In one report, 92 completed pregnancies of drug-abusing women were evaluated; 56% of the women were reportedly HIV seropositive, but the timing of antibody testing in relation to the pregnancy was not given.[30] Seventeen children had AIDS or AIDS-related complex develop; the latter was not defined and the length of evaluation was not stated. The rate of transmission was estimated to be approximately 35%. In another prospective, multicenter study of seropositive women serotested prior to or at delivery, 100 infants were followed up for more than 15 months.[28] Eighty-five percent of the enrolled women had abused drugs; 7% had contact with an infected drug-abusing sex partner as their only certain HIV risk factor. Fifteen children remained seropositive and an additional four died of AIDS, giving a minimum transmission rate of 19%, based on serologic findings and symptoms. An additional five were virus or antigen positive, giving a final rate of 24% (95% CI, 16% to 32%). However, not all children, and not a representative sample, had cultures taken or were antigen tested. The third study, also a multicenter one, estimated a transmission rate of 32.6%, based on serologic findings and symptoms for 89 children older than 15 months of age (95% CI, 22.3% to 42.9%, by our calculations).[29] The fourth study was of 308 mother-child pairs in 51 obstetrical and pediatric centers in France; 62% of the mothers were drug addicts. Thirty-two (27%) of 128 infants had serologic "or other" evidence of HIV infection at 18 months of age.[27]

Additional smaller or less advanced studies include prospective studies of seropositive women from Haiti, Zambia, and Kenya and of additional groups of seropositive drug-abusing women or female sex partners of drug-abusing men[32] (information from the National Institute on Drug Abuse Technical Review Meeting on Perinatal HIV Infection, October 17 and 18, 1988). In all of these reports, transmission rates ranged from 10% to 41%, based on data from seroevaluation at older than 12 months or older than 15 months of age; transmission rates were often based on culture and antigen assays, as well as serotesting. Thus, these transmission rates are consistent with our own minimum rate of 25.0%, despite the differences in transmission categories/lifestyles and the absence of symptoms in our seropositive mothers. Furthermore, evidence is accumulating that infected children, unlike infected adults, may not infrequently be seronegative.[16,27,33-35] Therefore, we cannot overemphasize that our rate, based solely on clinical symptoms or positive serologic findings at older than 15 months of age, represents a minimum transmission risk. We conclude that infants of HIV-infected women are at extremely high risk of HIV infection, even if the infected mother is healthy and has no purported cofactors for vertical HIV transmission.

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CORRECTION

Incorrect Spelling of Author's Name.—In the article entitled "Wood-Burning Stoves and Lower Respiratory Tract Infection in American Indian Children," published in the January issue of *AJDC* (1990;144:105-108), the second author's last name was spelled incorrectly. It should have read Morgenlander (not Morganlander, as submitted by the authors).