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Maternofetal Transmission of Human Immunodeficiency Virus-1: the Role of Antibodies to the V_3 Primary Neutralizing Domain

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ABSTRACT. The increase in the number of human immunodeficiency virus-1 (HIV-1)-infected children is a direct consequence of the heterosexual spread of the disease to women and the growing number of HIV-positive i.v. drug users. It is not known how the majority of infants born to HIV-1–infected women escape HIV-1 infection, and, for those infected, the timing of HIV-1 transmission has yet to be determined. In addition, the role of maternal antibodies in the prevention of HIV-1 transmission to the fetus is unclear. We have previously demonstrated a correlation between vertical transmission and the absence of high-affinity/avidity antibodies to a peptide, KRIHIGPGRAFYT, which corresponds to a region of the primary neutralizing domain of the gp120 V_3 loop of HIV_{MN} (MN-PND). The present study examines the correlation between the presence of these high affinity antibodies in women completing a pregnancy or undergoing an elective abortion and the detection of HIV-1 infection in their aborted fetuses. In several instances, transmission occurred despite high-affinity antibodies to the MN-PND. We have, therefore, evaluated the reactivity of sera to different MN-PND variants. In one infant born to a mother with high-affinity/avidity antibodies to KRIHIGPGRAFYT (classic MN-PND), the infected baby developed antibodies to an MN-PND variant peptide against which his mother did not mount a humoral immune response during pregnancy. This finding indicates that fetal infection with MN-PND escape mutants arising during pregnancy may occur during a period when the mother is serologically negative. (*Pediatr Res* 33 (Suppl): S76–S79, 1993)

Abbreviations

HIV-1, human immunodeficiency virus-1
PCR, polymerase chain reaction
MN-PND, region of primary neutralizing domain of the gp120 V_3 loop of HIV_{MN}

HIV-1 infection in children is closely linked to infection of women. World Health Organization authorities estimate that, worldwide, 3 million women are presently HIV-1 infected. In the United States as a whole, the rate of HIV-1 infection in women is approximately 0.15%, whereas in some areas of the Bronx, New York, it exceeds 6%.

Various studies in the United States and in Europe show a maternofetal transmission rate of between 9 and 70% (1–6). The reasons for the variation over this wide range of rates of transmission are unknown. Recent studies have suggested that perinatal transmission may play a more prominent role than has been appreciated previously (7–10). Conversely, using the PCR, we (11, 12) and others (13–16) have determined the presence of the HIV-1 genome in a variety of fetal tissues obtained from elective pregnancy terminations of HIV-1–seropositive women. Our studies have shown a maternofetal transmission rate of approximately 30% by the end of the 2nd trimester (11). In our initial study of fetal tissues obtained from 2nd trimester abortuses of HIV-1–infected women, HIV-1 genomic sequences were detected in 30% (11, 12). This percentage was identical to the transmission rate recorded in babies born to HIV-1–infected women in the Bronx (1). In the present study, we have attempted to determine the fetal HIV-1 status in amniotic fluids obtained during pregnancy. In addition, we have investigated the correlation of transmission with the presence of high-affinity antibodies to the MN-PND.

STUDY DESIGN

Patients. Blood and amniotic fluid were obtained at delivery from 18 women with known fetal outcome. The status of infection of infants was determined by clinical, serologic (ELISA, Western blot), and virologic methods (viral culture and PCR) as has previously been reported by us (13). Babies born to HIV-1–infected women were followed for more than 15 mo. This study is part of an ongoing research protocol that has been approved by the Albert Einstein College of Medicine Committee on Clinical Investigation and the Health and Hospitals Corporation of the City of New York. Informed consent was obtained from the participants.

Methods. The HIV-1 ELISA and Western blot were performed with commercially available ELISA kits (DuPont, Boston, MA) and Western blot strips (DuPont/Biotech). Immune complexes in amniotic fluid were precipitated with polyethylene glycol and disrupted at 37°C for 60 min. HIV-1 p24 antigen was then determined using a commercial Antigen Capture ELISA kit (DuPont). IgG, IgM, and IgA anti-HIV-1 present in the disrupted complexes were determined using commercial Western blot strips (DuPont/Biotech) developed with alkaline-phosphatase–conjugated antibodies directed against human IgA, IgM, and IgG.

The antigen-limiting ELISA was performed as previously reported (17). In a modification of the previous method, some ELISA plates were coated with four different peptides: *1*) KRI-

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HIGPGRAFYT, *2*) IYIGPGRAFYT, *3*) KSITKGPGRVIYA, and *4*) SRVTLGPGRVWYT.

RESULTS

Amniotic fluids. Free HIV-1 p24 antigen was detected in only one of the 18 amniotic fluid specimens studied. Immune complexes were precipitated from 11 amniotic fluid samples; when complexes were dissociated, HIV-1 p24 was found in six of those precipitates (56%). HIV-1 p24 was detected in association with IgA-containing immune complexes in three precipitates; in each instance, the HIV-1 genome was detected in the fetus by PCR. In contrast, fetal HIV-1 infection did not correlate with the presence of IgG or IgM immune complexes associated with HIV-1 p24.

Fetal studies. Of 18 maternal-fetal pairs examined, eight mothers had high-affinity antibodies to the KRIHIGPGRAFYT epitope and 10 fetuses were found to be HIV-1 infected. Only three of 10 mothers with an infected fetus had high-affinity serum antibodies (Table 1), whereas five of eight nontransmitting mothers had high-affinity antibodies (Table 2).

Infant studies. All sera of HIV-1–infected women giving birth were reactive in the regular MN-PND ELISA. In contrast, when an antigen-limiting ELISA (which detects high-affinity/avidity antibodies) was used, 14 of 16 nontransmitting mothers and four of 17 transmitting mothers had high-affinity antibodies.

PND-variant studies. Serum obtained from one mother who had high-affinity antibodies to the MN-PND and whose infant was HIV-1 infected was further tested for reactivity to MN-PND variants including IYIGPGRAFYT. Although the mother had no high-affinity antibodies to this variant peptide, the baby developed high-affinity antibodies against this variant in the 1st year of life.

DISCUSSION

Several studies have recently suggested that HIV-1 transmission from mother to fetus may occur late in pregnancy (7–10). This conclusion was based on the evidence that HIV-1 could not be cultured and PCR analyses were also negative in cord blood of newborns later proved to be HIV-1 infected. This phenomenon can, however, also be explained as a latent fetal infection that is activated postnatally. The latter hypothesis finds support in two recent studies showing the presence of HIV-1 genomic sequences in fetal tissues in the absence of culturable virus (7, 11, 12), and a similar phenomenon was observed in transgenic mice carrying Moloney Murine Leukemia Virus DNA (18, 19). Many of these animals displayed no expression of Moloney Murine Leukemia Virus DNA at birth, which suggests no viral particle production *in utero*.

Table 1. *Anti–MN-PND high-affinity antibodies in maternal sera at time of abortion of HIV-1–positive fetuses (cut-off OD ± 5 SD = 0.243)*

GA* (wk)	ELISA OD†	Affinity
12	0.468	High
12	0.140	Low
15	0.032	Low
15	0.348	High
16	0.091	Low
18	0.785	High
19	0.222	Low
21	0.218	Low
21	0.210	Low
23	0.240	Low

* Gestational age.

† At antigen concentration of 50 ng/well.

Table 2. *Anti–MN-PND high-affinity antibodies in maternal sera at time of abortion of HIV-1–negative fetuses (cut-off OD ± 5 SD = 0.243)*

GA* (wk)	ELISA OD†	Affinity
11	0.380	High
12	0.274	High
15	1.060	High
15	0.032	Low
17	0.039	Low
18	0.019	Low
20	0.603	High
24	0.878	High

* Gestational age.

† At antigen concentration of 50 ng/well.

The present studies were designed to further substantiate fetal HIV-1 infection *in utero* and to correlate infection with the maternal humoral immune response to the V_3 MN-PND.

Maternal IgA generally does not cross the placenta and is not found in the amniotic fluid unless it is actively synthesized by the fetus. In the present study, we found that p24 was associated with IgA immune complexes in three of six amniotic fluid samples that were positive for immune complexes and for which the fetal outcome was known. In all such cases, fetal HIV-1 infection was documented by PCR.

Studies correlating the role of antibodies to gp120 or to the V_3 loop with reduction of transmission rates yielded conflicting results (20–25). We have shown in preliminary studies that high-affinity/avidity antibodies to the MN-PND were associated with lack of transmission of HIV-1 to the fetus (17). Other investigators using different methodologies have been unable to confirm these results (23–25). And yet, HIV-1 infection in chimpanzees could be blocked by an MAb to the gp120 V_3 domain (26). We have therefore expanded our investigation to a blinded study of a larger cohort of maternofetal pairs. Eighteen fetal tissues and the respective maternal sera were evaluated for high-affinity antibodies to MN-PND (Tables 1 and 2). Although a trend toward reduced transmission in the presence of high-affinity/avidity antibodies to the MN-PND was noted, this correlation was not statistically significant.

Sera from HIV-1–infected women at delivery showed a similar trend. Although 14 of 16 nontransmitting mothers had high-affinity antibodies to the MN-PND, only four of 17 transmitting mothers had these antibodies. HIV-1 infection despite these high-affinity antibodies may be due to several mechanisms: *1*) Transmission may have occurred at a time when the protective antibodies were not yet produced by the mother, *e.g.* an immunosilent window period; *2*) high affinity does not necessarily always correlate with virus neutralization (data not shown); and *3*) a specific mutant different from the classic MN-PND tested in our system crossed the placenta. The latter possibility was suggested by a study of serum PND reactivities of an HIV-1–infected baby born to a mother with high-affinity antibodies to the MN-PND. During the 1st year of life, this baby developed antibodies against a PND peptide that differed by one amino acid from the MN-PND. It is therefore possible that this baby was infected *in utero* by an escape mutant against which the mother had not yet mounted an appropriate immune response.

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FLOOR DISCUSSION

Dr. Yolken: Please summarize your feelings about the percentage of cases you see in New York that are actually due to *in utero* infection—before the last 2 wk of gestation. Are there differences in percentages in the different populations, such as New York *versus* San Francisco? How much of the difference is due to intrauterine infection and how much is due to the birth process, as Dr. Levy suggested?

Dr. Rubinstein: Our fetal studies are restricted to abortuses from a population of young women of a mean age of 17, many of whom are drug abusers and/or promiscuous. Among this group of women, many cofactors may influence HIV-1 transmission. When we studied fetal tissues from abortuses in this population, we observed a transmission rate of 30%—exactly the same transmission rate recorded in babies born to HIV-1–infected women in the same urban area. It is difficult to accurately determine in our studies what proportion of infants were infected *in utero* or perinatally. Recent studies using viral cultures and PCR show that about half of the infected babies are negative with these tests in the first 2 to 3 wk of life. However, when a wide range of immune functions are assessed near birth, abnormalities are found in at least two thirds of these babies, suggesting that they were infected *in utero*.

Dr. Levy: A point you make is that free virus is the source of transmission. If you could block free virus, you could affect the maternofetal transmission whenever it occurs. This is quite different from sexual transmission or blood transfusion, in which the virus-infected cells are most important. A low CD4 count seems to correlate with high free virus, and the high-affinity antibodies you discussed may block transmission of free virus. This seems to say that the plasma viremia is probably the most important factor to measure during pregnancy. You cannot measure it by p24; you must culture the virus. I predict that those women with multiple births in whose fetuses virus was detectable will have high plasma viremia. These women may also be getting fresh new viruses over time through more sexual contacts. Then the virus in the fetal tissue may be totally different, by Wolinski PCR, as compared with cultured virus. A new virus strain from the blood may go over to the fetus each time. Our group has looked at a few of the transmissions of mother to child in Dr. Wara's program and has found that the viruses in two examples are quite distinct. This finding suggests that the mother's immune system may control one virus well but not another strain. You would not detect the response in the mother until transmission, when the virus is able to find a naive host. It would be good if your group or a coordinating group would measure plasma viremia by cell culture techniques and look at the viruses.

Dr. Rubinstein: We do measure viremia by cell culture techniques and by a modified p24 assay. This assay measures p24 complexed with an antibody as well as free p24. Quantitative viral culture assays are also available. So far, no clear-cut correlation with plasma viremia could be found with regard to maternofetal transmission. However, one has to keep in mind that viremia is quantitated at one point during pregnancy and may change at another time point. In most of the women, we have only one or two points of study predelivery. It appears that there is, for example, a viremic spike at delivery in some of the women studied.

I agree with your remark concerning escape mutants. If antibody responses to those different PND peptides are monitored in the mother and in her baby at age 3 to 12 mo, in many cases discordant responses are noted. In sequential studies, pattern changes are noted during pregnancy. These findings suggest that the mother responds immunologically to different HIV-1 strains. Theoretically, new escape mutants against which high-affinity antibodies have not yet been formed by the mother are more likely to cross the placenta. To prevent such transmission, a treatment trial is being developed in which hyperimmune gamma globulin reactive with a broad range of viral strains is infused during pregnancy. Alternatively, one could immunize women with a PND vaccine using a cocktail of different V3 peptides. That is, in fact, what is planned for our AIDS transmission blocking vaccine. We will use several different PND peptides to try to get a broad antibody response that goes across the range of the different virus variants. We found that vaccinees make neutralizing antibodies to these peptides. They also have some T-cell responses, as measured by IL-2 secretion and by *in vitro* lymphoproliferative responses to the PND peptide with which they were immunized but not to all related PND peptides. Certainly, any vaccine or antibody that is narrowly targeted to one strain of the V3 loop will not be highly effective.

Dr. Stiehm: You did not mention one other form of transmission–breast milk feedings. About 30 to 50% of mothers who seroconvert or produce infected afterbirth will transmit HIV via

this route. What percent is due to breast milk transmission, in Africa for example, where nearly 100% of mothers breast-feed and almost all are seropositive throughout pregnancy?

Dr. Rubinstein: Your question is difficult to answer in the context of presently known epidemiologic data. If we assume that transmission occurs prenatally, then the addition of breast-feeding is not going to make much of a difference. In fact, in some of the African studies, the transmission rate remains around 30%, the same as in our area. On the other hand, at the Sienna Consensus meeting in January 1992, there were reports suggesting that the postnatal transmission rate by breast-feeding in selected populations of women has been 30 or 40%. In our patient population, few women, most of whom are drug users, breast-feed or have any interest in breast-feeding.

Dr. Berger: You mentioned the antibody levels in the premature babies run about 10% of the IgG level in the mother. You implied that the transfer of HIV-specific antibodies was higher. Why?

Dr. Rubinstein: It is possible that fetal immune responses contribute to the antibody titer, or that there is selective transport of anti-HIV antibodies. The majority of the antibodies were of the IgG1 subclass, and we know that IgG1 antibodies cross the placenta more avidly than the other subclasses.

Dr. Fischer: I echo Dr. Wara's and Dr. Levy's comments about the low transmission rate. In our population, we have been prospectively enrolling women who have been picked up through routine screening. They are all asymptomatic Walter Reed Stage 1 or Walter Reed Stage 2. Our group has less than a 10% transmission rate, which probably relates to the health of the mother and not to obstetrical practices, since the babies are born in a number of hospitals in the military system. Thus, in the ongoing studies of transmission with antibody, either through passive immunization or just following natural antibodies, we must look carefully at the status of the mother and characterize that status carefully as part of the overall scenario of maternofetal transmission. Do you have any information on those mothers who did and did not transmit, by stage of disease?

Dr. Rubinstein: We have information on all the mothers in the study; a wide range of hematologic, immunologic, and virologic parameters have been evaluated. The transmission rate appears to be lower in women with more stable clinical condition and with higher CD4 cell counts. Our analysis did not show, however, a drop from 30 to 10% transmission when we compared CD4 cell counts above and below 400. In the recent European study, CD4 counts above and below 700 showed a more significant correlation with transmission. In the first study of 15 women, published by us in the *Proceedings of the National Academy of Sciences (USA)*, practically all were asymptomatic and most had normal immunologic parameters. In that group, the transmission correlated best with the high-affinity antibodies to the PND. It is possible that these women, who were in the early stages of the disease, were infected by a small number of variants and that their high-affinity antibodies covered the spectrum of that small number of variants and thus did not allow transmission to occur. Several investigators have shown that as the disease progresses the number of virus variants increases and so does the chance for immunosilent periods to new variants and for HIV transmission to the fetus.

Dr. Gupta: Commonly, *in utero* infection is associated with IgM response. Do we know how much IgM specific antibody to HIV is made in these patients?

Dr. Rubinstein: We studied this issue with Dr. Steve Litwin about 8 years ago and did not find a correlation between IgM responses and infection or lack of infection.

Dr. Gupta: Wouldn't it be surprising that the women would not make IgM antibodies if they have an infection *in utero?*

Dr. Rubinstein: We have found IgM antibodies during pregnancy and in the newborn. At delivery, they may be in the phase of IgG and IgA production. We can turn the argument around. Ontogenetically, IgA responses come after IgM and IgG. We should therefore also expect IgA responses. In fact, IgA responses are not only present in the first months of life in HIV-infected infants but can also be detected *in utero* in the amniotic fluid.

Dr. Gupta: It seems all right to get an IgA response, but not finding IgM, a specific antibody in sufficient titer, always surprises me. We diagnose a number of congenital infections by looking at this specific antibody to the microbes.

Dr. Rubinstein: I agree. I did not mean to say that we do not find IgM antibodies. IgM antibodies are found but do not correlate with transmission or lack of transmission of HIV-1. According to Dr. Shearer's presentation at this meeting, we may also consider stimulation of the immune system by innate viral particles or virus subcomponents leading to an IgM response. Therefore, the response does not necessarily have to correlate with infection or lack of infection.

Dr. Ochs: There seems to be a consensus that the viremia plays an important role in transmission from mother to fetus. As far as I understand it, AZT (azidothymidine) decreases the number of viruses that are excreted and circulate in the plasma. Furthermore, we have heard that AZT improves the immune status of the treated patient. Could someone comment on the AZT trial that was started some time ago by Dr. Brown in Seattle? How many patients have been enrolled in this study? How many were pregnant women?

Dr. Mofenson: Perhaps you mean the ACTG (AIDS Clinical Trial Group) protocol 076, a multicenter trial designed to enroll almost 700 women. About 50 women are enrolled so far. AZT is given to the mother, starting from 18 to 34 wk of gestation, and to the newborn for 6 wk postdelivery. There are no data yet available from that trial.

Dr. Ochs: I think that Dr. Brown has five or six pregnant women enrolled and none of the children got infected.

Dr. Rubinstein: There are about 50 women who were treated with AZT during pregnancy and who did not belong to the 076 trial. The number is too small to draw conclusions. If I remember correctly, the transmission rate in this cohort was around 12 or 13%.

Dr. Wara: About 13% is correct. The question none of us can answer yet is whether the women enrolled in that trial were easily captured—had an earlier-stage disease; it was not a controlled trial. Does the low transmission rate reflect the state of disease in the woman who is infected? We will not know that answer until the results of 076 are evaluated.

Dr. Heiner: We have studied only 25 maternofetal pairs from which we had cord blood and maternal serum. We have done about 25 different kinds of assays using different HIV peptides, the V_3 loop peptides, some recombinant proteins, and so on. We tried to correlate and see which antibodies might be protective, but we have not found any that seem protective. In a number of instances, we have seen antibodies in the mother that might be enhancing infection, so there might be a correlation, but not enough to be significant. We should study this further. In three mothers, we found high levels of antibodies to IGF protein. Their babies were infected, and those antibodies were higher than any in control populations. There also seem to be some antibodies to a few other peptides.

Dr. Rubinstein: I agree, but as Dr. Levy has also shown, it appears that the high-affinity antibodies are not the enhancing ones. The low-affinity antibodies are probably capable of enhancing infection. We did not look at the same broad spectrum of targets as Dr. Heiner did. Our studies focused on the high-affinity antibodies to the MN-PND.