HIV Seroconversion During Pregnancy and Risk for Mother-to-Infant Transmission

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Summary: Pregnant women infected with HIV-1 were enrolled in a prospective mother-to-infant transmission study from 1992 through 1994 in Bangkok. In participating hospitals, voluntary HIV testing was routinely offered at the beginning of antenatal care and again in the middle of the third trimester of pregnancy. Women who seroconverted to HIV during pregnancy were compared with women who had tested positive on their first antenatal test. Maternal HIV RNA levels were determined during pregnancy, at delivery, and postpartum using RNA polymerase chain reaction (PCR), and infection status in infants was determined by DNA PCR. No infants were breastfed, but prophylactic antiretroviral therapy was not yet used in Thailand to prevent transmission from mother to infant. Among enrolled women, 16 who seroconverted during pregnancy and 279 who were HIV-1–seropositive at their first antenatal test gave birth. Median plasma RNA levels at delivery were similar for the two groups (17,505 and 20,845 copies/ml, respectively; \( p = .8 \)). Two (13.3%) of 15 infants born to women who seroconverted and 66 (24.8%) of 266 infants born to previously HIV-seropositive women were infected with HIV (\( p = .5 \)). There was no increased risk for mother-to-infant HIV transmission and no significant difference in viral load at delivery between HIV-infected women who seroconverted to HIV during pregnancy and those who were HIV-seropositive when first tested. Key Words: HIV—Perinatal transmission—Pregnancy—Seroconversion—Thailand—Viral load.

Researchers have hypothesized that the risk for mother-to-infant HIV transmission may be higher for HIV-infected women who seroconvert to HIV during pregnancy than for those who are seropositive before pregnancy (1). This hypothesis is based on the observations that the concentration of HIV in blood is high during the few weeks between infection and seroconversion (2,3), that a high concentration of HIV in blood during delivery is a strong risk factor for transmission (4–6), and that seroconversion during breast-feeding is associated with a high risk for transmission from mother to infant (7). In addition, it has been suggested that infants born to recently infected women receive less neutralizing antibody protection from their mothers (1). We tested this...
hypothesis in a prospective cohort study by comparing women who seroconverted to HIV during pregnancy and women who were HIV-seropositive when antenatal care began.

METHODS

This study was conducted as part of a prospective mother-to-infant HIV transmission study at Siriraj, Rajavithi, and Children’s Hospitals in Bangkok from 1992 through 1994. During this period, HIV seroprevalence increased from 1.4% to 2% among the approximately 35,000 women who entered antenatal care each year at Siriraj and Rajavithi Hospitals. In these hospitals, information about HIV testing is given to all women who start antenatal care. Voluntary HIV antibody testing along with routine screening for syphilis and hepatitis B antibody is offered at the first antenatal visit and again in the middle of the third trimester of pregnancy. HIV-1 antibody testing is done in hospital laboratories by using enzyme immunoassay; supplemental testing is done by Western blot or particle agglutination. HIV-infected women are provided infant formula and advised not to breast-feed. The study was conducted before the results of the AIDS Clinical Trials Group 076 study ended (8); antiretroviral prophylaxis was not yet used to prevent transmission from mother to infant.

Women who tested seropositive for HIV-1 were informed and offered enrollment in a prospective study of HIV-infected pregnant women and their children; enrollment and study procedures have been described (4,9). Two types of HIV-infected women were enrolled in the study. Women who tested HIV-seropositive on their first antenatal test during the first or second trimester are referred to as “previously seropositive women”; those who tested negative on their first antenatal test but positive during a subsequent antenatal visit or at delivery are referred to as “women who seroconverted.”

Women who consented to enrollment were interviewed, and venous blood specimens were collected during each remaining trimester, at delivery, and at 6 and 12 months postpartum. Viral load was measured according to published methods (4,10) in all delivery specimens and in each specimen from women who seroconverted. Women who seroconverted were followed up for 5 years after giving birth.

Infants had study visits at birth and every 2 to 3 months until they reached 18 months of age. Blood specimens were collected at birth and at 2 and 6 months of age for HIV DNA polymerase chain reaction (PCR) testing to determine infection outcome (4). Infants were considered to be infected with HIV if they had two positive DNA PCR test results or one positive PCR result and an AIDS-defining condition (11). Infants were considered to be uninfected if two samples were PCR-negative (at least one obtained at >6 months of age) or if they tested HIV-negative by enzyme immunoassay. Infants who did not meet either criteria were considered to have unknown infection status.

The distributions of variables were compared between groups by using the χ² or Fisher exact test for dichotomous variables or the Wilcoxon rank sum test for continuous variables. The study was approved by the Ethical Review of Research Committee, Ministry of Public Health, Nonthaburi, Thailand, and an Institutional Review Board of the Centers for Disease Control and Prevention, Atlanta, Georgia, U.S.A.

RESULTS

Overall, 342 HIV-infected pregnant women were enrolled: 326 who were previously seropositive and 16 who seroconverted. Forty-seven (15%) previously seropositive women were lost to follow-up before delivery, including 16 women who had a miscarriage, abortion, or stillbirth. Thus, 279 women who were previously seropositive and 16 who seroconverted gave birth during the study period. For previously seropositive women, the positive HIV test was at a median of 19 weeks’ estimated gestation (25th–75th percentiles, 14–24 weeks). For women who seroconverted, the last negative HIV test was at a median of 12 weeks’ estimated gestation (25th–75th percentiles, 10.5–17 weeks), the interval between the last negative and first positive tests ranged from 98 to 211 days (median, 146 days), and the interval between the first positive test and delivery ranged from 8 to 68 days (median, 32 days) before delivery. When we defined the seroconversion date as the midpoint between the last negative and first positive tests, the interval between seroconversion and delivery ranged from 62 to 150 days (median, 108 days).

Demographic, immunologic, and delivery characteristics and plasma RNA concentrations at delivery were similar in the two groups (Table 1). For the women who seroconverted, no clear pattern of plasma viral load was seen in late pregnancy, at delivery, or during 12 months of postpartum follow-up (Fig. 1). For these women, the median viral load (copies/ml) was 20,209 in the third trimester (n = 13), 17,505 at delivery (n = 15), 18,124 at 6 months postpartum (n = 14), and 20,390 at 12 months postpartum (n = 14). The viral concentration increased by >0.5 log between the third trimester and delivery in only 1 of the 13 women with results from both times. The median CD4⁺ cell counts were 490 and 555 cells/µl at 6 months postpartum (p = .3) and 450 and 540 cells/µl at 12 months postpartum (p = .3) for the women who were previously seropositive and those who seroconverted, respectively.

Infection status was determined for the infants of 266 (95%) women who were previously seropositive and 15 (94%) women who seroconverted. Of these infants, 66 (24.8%; 95% confidence interval [CI]: 19.7%–30.5%) in the former group and 2 (13.3%; 95% CI: 1.7%–40.5%) in the latter group were infected (p = .5). Of the 2 infected infants born to women who seroconverted, the PCR test result from a specimen collected in the first 72 hours of life was positive for 1 and negative for the other. Five years after giving birth, 9 (56%) women who seroconverted remained in follow-up, 7 (44%) had been lost to follow-up, and none were known to have died.

DISCUSSION

Our study does not suggest an increased risk for mother-to-infant HIV transmission among women who
seroconvert during pregnancy. Other researchers have reported smaller numbers of women who seroconverted during pregnancy but without clear evidence of increased risk for transmission to their children; some reports suggested an increase in risk (12–15), whereas others did not (16,17).

High levels of HIV in the blood have been observed for several weeks after infection with HIV, and seroconversion seems to coincide with the decline in viremia (2,3). Thus, for women in whom HIV antibodies develop during pregnancy, it is likely that the viral RNA concentration has declined to steady-state levels by delivery. Our observation of similar HIV RNA concentrations at delivery in women who seroconverted during pregnancy and those who were already seropositive when antenatal care began supports this hypothesis. Further, because most mother-to-infant HIV transmission seems to occur near the time of delivery (18,19) and high viral load at delivery is a strong risk factor for transmission (4), it should not be surprising that the risk for transmission was not higher for women who seroconverted 2 to 5 months before delivery than for those who were already seropositive in the second trimester of pregnancy. This finding does not conflict with the observation of a high risk for postnatal transmission among women who seroconvert while breast-feeding (7), because these infants would be exposed to breast milk during the peak of viremia. The potential role of lower neutralizing antibody in increasing the risk for transmission from mother to infant among recently infected women remains unclear (20).

Our study has several limitations. Although this is the largest reported series of seroconversions during pregnancy, the sample is still too small for definitive statistical comparisons with the enrolled women who were previously seropositive. Our design did not allow us to enroll women who seroconverted near delivery and might have a higher transmission risk than women who seroconvert earlier. At the same time, we cannot determine how many of the previously seropositive women had seroconverted shortly before their first antenatal test; if this proportion were large, it could help to explain the

![FIG. 1. Plasma HIV RNA concentration (log_{10} copies/ml) in 16 women who seroconverted, by infection status of infant.](image-url)

### TABLE 1. Comparison of women who tested HIV-seropositive at first antenatal test and women who seroconverted during pregnancy

<table>
<thead>
<tr>
<th>Positive at first test (n = 279)</th>
<th>Seroconverted during pregnancy (n = 16)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>22 years</td>
<td>23 years</td>
</tr>
<tr>
<td>Median number of prior liver births</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Commercial prostitution (%)</td>
<td>29/279 (10.4)</td>
<td>1/16 (6.3)</td>
</tr>
<tr>
<td>Injection drug use (%)</td>
<td>4/279 (1.4)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>Subtype E infection (%)</td>
<td>267/278 (96)</td>
<td>15/16 (93.8)</td>
</tr>
<tr>
<td>Median CD4+ count at delivery</td>
<td>450 cells/µl</td>
<td>460 cells/µl</td>
</tr>
<tr>
<td>Median CD8+ count at delivery</td>
<td>910 cells/µl</td>
<td>1065 cells/µl</td>
</tr>
<tr>
<td>Median viral load at delivery</td>
<td>20,845 copies/ml</td>
<td>17,505 copies/ml</td>
</tr>
<tr>
<td>Median duration ruptured membranes</td>
<td>2 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>Cesarean section (%)</td>
<td>33/279 (11.8)</td>
<td>1/16 (6.3)</td>
</tr>
<tr>
<td>Gestational age &lt;37 weeks (%)</td>
<td>12/277 (4.3)</td>
<td>1/15 (6.6)</td>
</tr>
<tr>
<td>Birthweight &lt;2500 g (%)</td>
<td>29/279 (10.4)</td>
<td>2/16 (12.5)</td>
</tr>
<tr>
<td>Infant infected (%)</td>
<td>66/266 (24.8)</td>
<td>2/15 (13.3)</td>
</tr>
</tbody>
</table>
similarity of the two groups in our study. We did not measure neutralizing antibody or cytotoxic T-lymphocyte responses, so this study cannot shed light on their possible role in transmission from women who seroconverted. Finally, it is possible that some of the negative antibody tests for the women who seroconverted gave false-negative results.

Although seroconversion during pregnancy may not substantially increase the risk for mother-to-infant transmission, it nonetheless poses a practical problem for preventing such transmission. Because interventions to prevent transmission (e.g., zidovudine prophylaxis, infant formula) must begin during pregnancy or shortly after delivery, women who seroconvert after routine antenatal HIV testing would not normally be identified or receive these interventions. For this and other reasons, antenatal care may be a good setting in which to reinforce behaviors to prevent HIV infection during and after pregnancy. In addition, in settings where the incidence of HIV infection among young women is high, repeat HIV testing late in pregnancy or at delivery, especially using rapid tests, may lead to a diagnosis of HIV infection in many women in time for these women and their children to benefit from interventions to prevent mother-to-infant transmission. Although technically feasible in Thailand, the use of this approach should be guided by considerations of cost-effectiveness.

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