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Waning Immunity to Varicella in Infants of Human Immunodeficiency Virus - Seropositive and Seronegative Mothers

SHAHANA A. CHOUDHURY, MD¹, GWINNETT LADSON, MD², EDWARD R. HILLS, MD³, and FRANK HATCHER, PHD⁴

SHAHANA A. CHOUDHURY: schoudhury@mmc.edu; GWINNETT LADSON: gladson@mmc.edu; EDWARD R. HILLS: ehills@mmc.edu; FRANK HATCHER: hatcherf@aquinascollege.edu

¹ Department of Pediatrics, Meharry Medical College, 1005 D.B Todd Blvd, Nashville, TN 37208; Tele: 615-327-6856/6332; Fax: 615-327-5835/5989

² Department of Obstetrics/Gynecology, Meharry Medical College, 1005 D.B Todd Blvd, Nashville, TN 37208 Tele: 615-327- 6284, Fax: 615-327- 6296

³ Department of Obstetrics/Gynecology, Meharry Medical College, 1005 D.B Todd Blvd, Nashville, TN 37208 Tel: 615-327- 6284; Fax: 615-327- 6296

⁴ Aquinas College, Nashville, TN 37205, Tel: 615-297-7545; Fax: 615-279-3892

Abstract

Immunity to varicella in HIV- exposed and unexposed infants born to unvaccinated mothers, acquiring protective antibodies at birth declined to non-protective (<1:8) levels by 5 months of age. Thus infants become susceptible to varicella before 12 months, recommended time for varicella immunizations in the US. Vaccination of susceptible HIV- seronegative women in the post-partum period may be important to consider.

Keywords

varicella zoster virus; passively acquired antibodies; HIV status

BACKGROUND

The incidence of varicella in the United States has significantly decreased as a result of universal varicella vaccination administered at 12 months of age since 1995 ¹ and a second dose at 4–5 years of age introduced in year 2006. ² Although varicella outbreaks continue to be reported in vaccinated populations in the United States even after receiving 2 doses, ³ disease severities are milder than in primary varicella in susceptible individuals. As overall disease incidence declines, the risk for exposure to VZV decreases, leading to susceptible children in adolescence and adulthood.

Varicella can cause significant morbidity and mortality, particularly in young and immunocompromised populations. ^{4, 5} Therefore, it is not surprising that young infants and HIV- seropositive individuals suffer more complications with this infection. ^{6–9} A recent study has suggested that even HIV- exposed but uninfected infants can suffer higher morbidities when infected with this virus, reflecting a clinical immunodeficiency. ¹⁰

Varicella during pregnancy is not common, presumably due to immunity in most women of childbearing age.¹¹ Infants in their first few weeks of life are thought to be protected by passive IgG antibodies from their mothers. Varicella infection during the first and third trimesters of pregnancy can be complicated by congenital varicella syndrome and pneumonitis or meningitis.^{11–13}

Duration of passive immunities to VZV during infancy has not been well studied. A recent study from France has documented significant decline of these antibodies during infancy,¹⁴ but the French study did not include HIV-exposed infants. Therefore, we studied immunity levels to VZV between unvaccinated HIV- seropositive and seronegative mothers, cord blood of their infants and duration of passive immunities in the first 6 months of infants' lives to determine if disparities existed between the two groups.

METHODS

Study Population

The protocol was reviewed and approved by the Institutional Review Board at Meharry Medical College (MMC) and informed written consents were obtained from each pregnant woman. The study was conducted between June, 2000 and August, 2001.

Pregnant Women

Fifteen HIV- seropositive pregnant women attending obstetric clinics at MMC and Metro-Nashville General Hospital were enrolled into the study during their first, second, or third trimester of pregnancy. Age of the subjects, HIV testing results, antiretroviral therapy, T cell counts and viral loads were obtained from the medical records of the patients. Twenty-nine HIV- seronegative pregnant women attending the same clinic (matched for age) served as the control group. None of the pregnant women received intravenous immunoglobulin or varicella vaccination in their life time. Pregnant women were followed prospectively up to their deliveries.

Infants

Cord bloods from infants were obtained at the time of delivery. Gestational ages of the newborn infants were noted from their medical records. Infants were followed up to a mean of 5 months of age when repeat blood samples were obtained.

All cord bloods were mother- infant pairs. All infants were born at term. Twelve of 15 (80%) HIV- exposed and 13 of 29 (45%) HIV- unexposed (control) infants were available for follow- up at 3– 6 months of age. None of the infants had contracted varicella during the study period.

Sample Size Calculation

The sample size required to achieve statistically significant results was based on a previous study.¹⁵ A sample size of 14 in each group would have 80% power to detect a difference in means of 1.6 in antibody levels to varicella and a standard deviation of 1.165 using a two group t-test with a 0.01 two-sided significance level.

Determination of Antibody Titers

Antibody titers against VZV were performed by indirect fluorescent antibody (IFA) at Specialty Laboratories, Santa Monica, California. Baseline and follow- up antibody levels were evaluated in both HIV- exposed and unexposed cord bloods and peripheral bloods of

infants at mean of 5 months of age. Correlates of immunity were defined as antibody titer > 1:8 IFA.

Immunologic and Virologic Studies

T cell analyses were performed by flow cytometry at MMC for HIV- seronegative group and at Vanderbilt University Medical Center (VUMC) core laboratories, Nashville, TN for HIV- seropositive and exposed subjects. HIV viral loads in HIV- seropositive pregnant women, and HIV deoxyribonucleic acid (DNA) testing in their infants were performed by polymerase chain reaction (PCR) at VUMC.

Statistical Analysis

Prevalence of immunity to VZV between HIV and control groups and between cord and peripheral bloods of infants (matched pairs) at follow-up was compared by two- tailed Fisher's exact test. CD4 cell counts between the HIV and control mothers were compared by a two-tailed t-test. Immunologic (CD4 cell counts/mm³) and virologic (viral load copies/ml) parameters were correlated with VZV antibody levels within the HIV group by Spearman correlation and linear regression tests. A p value ≤ 0.05 was considered significant. Software Intercooled stata version 8.0 was used for statistical analyses.

RESULTS

Pregnant Women and Infants

The mean (range) ages of pregnant women at the time of serologic assays were comparable. None of the HIV- seropositive women were in the category of adult immunodeficiency syndrome (AIDS) based on a clinical history of opportunistic infections or CD4 counts less than 200 cells per mm³. Eight of 15 (53%) HIV-seropositive pregnant women were on antiretroviral therapy at entry, and all (100%) were on combination therapy (zidovudine, dideoxyinosine, stavudine, lamivudine) at the time of delivery. All HIV- exposed infants tested negative for HIV by DNA PCR at birth, 1 month and 6 months of age

Immunity to Varicella in Mothers

Fifteen of 15 (100%) HIV- seropositive and 26 of 29 (90%) seronegative pregnant women were immune to VZV.

Immunity to Varicella in Infants

Protective immunity to varicella was comparable in 14 of 15 (93%) HIV- exposed and 26 of 29 (90%) unexposed cord blood samples. Using infant paired data only, the protective immunity cord bloods 11/12 (92%) HIV-exposed and 13/13 (100%) unexposed infants, declined to non-protective levels in 11/12 (92%) HIV-exposed and 10/13 (77%) unexposed infants (see Figure, Supplemental Digital Content 1).

Immunological Parameters in Mothers

Mean CD4 counts were significantly (p = 0.01) lower in all HIV- seropositive (609/mm³) compared to the 20/29 (69%) HIV- seronegative (997/mm³) mothers.

DISCUSSION

This manuscript describes a study of immunity to varicella in HIV-seropositive and seronegative pregnant women and passive immunity in their infants. All 15 HIV- seropositive women on antiretroviral therapy had serologic evidence of immunity, with transplacental transfer in 14/15 (93%); Twenty-six of 29 (90%) HIV-seronegative mothers

were immune to VZV, and antibody was transferred across the placenta in all 26. At a mean of 5 months of age, the passively acquired maternal antibody had disappeared in 11/12 (92%) HIV-exposed (none infected with HIV) and in 10/13 (77%) HIV- unexposed infants. This decline in antibody was expected, given the $\frac{1}{2}$ life of IgG of one month. At the same time, the fact that babies born to HIV-seropositive mothers had passive protection against varicella equal to the babies for HIV-seronegative mothers is important. Both groups of mothers had antibody from natural infections rather than vaccine. Therefore, the findings in this report will not be applicable to pregnant women who have acquired their VZV immunity solely through varicella immunization, without ever having had community (wild-type) chicken pox. Since varicella vaccination is not universal except in North America (and a few other countries), the report remains relevant to children born throughout most of the world.

This study fills a gap in our knowledge about the duration of VZV antibody titers in infants following delivery to mothers known to have had both HIV infection and chickenpox. A recent study from France ¹⁴ has determined that their babies had high VZV titers at birth and low titers by 4–5 months of age. Therefore, the current study confirms the French study and expands the data to include HIV-seropositive subjects. Thus, the study provides important clinical information to neonatologists and pediatricians.

Our findings suggest that both HIV- exposed and unexposed infants become susceptible to varicella infection well before the currently recommended time for routine VZV immunizations at 12 months in the USA. In addition, susceptible pregnant women will also be at risk for contracting varicella infection from these babies. We could not determine the impact of maternal clinical, immunologic or virologic deterioration on VZV immunity levels within the HIV- seropositive mothers from this study. We recommend routine VZV screening during pregnancy of all women and vaccination of susceptible HIV- seronegative women prior to the hospital discharge. Health care providers involved in the care of HIV-seropositive mothers need to be aware and consider prophylaxis with oral acyclovir or one dose of IVIG for their patients within 96 hours of their infants' exposure to varicella outbreaks at day care centers. In addition, maintaining adequate numbers of CD4 counts and lower viral loads with highly active antiretroviral therapy during pregnancy in HIV-seropositive women should be reinforced. Further prospective studies need to be conducted with a larger population to evaluate effect of CD4 counts and viral loads on immunity levels in HIV- seropositive mothers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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