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LOW INCIDENCE OF HUMAN PAPILLOMAVIRUS TYPE 16 ANTIBODY SEROCONVERSION IN YOUNG CHILDREN

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Human papillomaviruses have been identified as the primary etiologic agents associated with cervical cancer, the second most common malignancy among women worldwide.¹ A single human papillomavirus (HPV) type, HPV 16, is the virus detected in more than one-half of cancers. Epidemiologic data have demonstrated that anogenital HPV, including HPV 16, are sexually transmitted. Because of the strong association between HPV and cervical cancer, a concerted effort has been made to develop prophylactic vaccines.² Before effective vaccine interventions can be promoted, a better understanding of potential nonsexual routes of virus transmission will be necessary, so that these vaccines are targeted to populations at greatest risk and timed to be given before infection occurs. In this report we evaluated possible mother to infant transmission of HPV, using a previously validated serologic assay to detect antibody responses to HPV 16.³

Methods. The investigation included 100 mother-infant pairs enrolled in a larger prospective study in Kingston, Jamaica, that was originally developed to study factors associated with vertical transmission of human T cell lymphotropic virus type I.⁴ Study subjects were enrolled from antenatal clinics at two public hospitals between 1989 and 1990. All mother-infant pairs selected for the current analysis were seronegative for human T cell lymphotropic virus type I and for human immunodeficiency virus type 1. The maternal serum samples obtained were drawn on average within 6 weeks of the time of delivery. Infants enrolled in the study were followed until at least 24 months of age. For this evaluation the infant samples collected nearest 2 years of age were initially tested. If reactivity to HPV antigens was found, prior and subsequent samples were assayed to establish seroconversion or persistent infection. All infants were breast-fed, with median duration of breast-feeding of 8.6 months (range, 0.3 to 42 months). Signed informed consent was obtained from all study participants and/or their parents or guardians. This study was approved by the Institutional Review Boards of the National Cancer Institute and the University of the West Indies.

Serum samples were tested for IgG to HPV 16 virus-like particles (VLPs) in an enzyme-linked immunoassay (ELISA).³ All samples were tested in duplicate on the same plate. The optical density

(OD) results of the duplicates were averaged and scored as negative, positive or indeterminate, based on standard control specimens tested on each ELISA plate. Positive results were determined by applying cut points set in previous investigations (positive OD>1.017, negative OD<0.904) to the mean-adjusted OD value for each duplicate sample.

Test results and subject demographic data were analyzed using a statistical analysis software package (SAS, Cary, NC). Frequencies and relative risks were computed, and differences between proportions were tested by chi square or Fisher's exact test. Differences between means were calculated with Student's *t* test.

Results. HPV 16 antibodies were detected in 23 (24%) of 98 mothers. Two maternal samples were indeterminate. Mothers in the study had a mean age of 26 years (range, 15 to 44). The 23 seropositive mothers had a mean age of 27 years (range, 19 to 39) compared with a mean age of 22 years (range, 15 to 44) among 75 seronegative mothers, a nonsignificant difference (*P* = 0.25).

Infant samples were tested at a mean age of 22 months (range, 15 to 26). Only 1 of 23 (4.3%) infants born to seropositive mothers and 2 of 75 (2.7%) infants born to seronegative mothers had antibodies to HPV 16 VLPs, a nonsignificant difference [relative risk, 1.44 (95% confidence interval, 0.28, 7.43)]. The serologic profiles of the three seropositive infants are detailed in [Table 1](#). In the one concordant mother-infant pair (Case 1), the mother was antibody-positive at the time of the infant's birth. Antibodies were detected in the infant at 23 months of age. As expected the infant also was seropositive at time of birth. However, the infant was seronegative at 5 and 11 months.

Case	Infant's Age (months)	Infant's HPV 16 Antibody Status	Mother's HPV 16 Antibody Status	Infant's Age (months)	Infant's HPV 16 Antibody Status
1	0	Positive	Positive	5	Negative
	11	Negative	Positive	11	Negative
	23	Positive	Positive	23	Positive
2	0	Negative	Negative	21	Positive
	23	Positive	Negative	60	Positive
3	0	Negative	Negative	11	Negative
	12	Negative	Negative	55	Positive

TABLE 1. Antibody profiles of HPV-seropositive infants and their mothers

Among the discordant mother-infant pairs (Cases 2 and 3), HPV seropositivity was detectable in the infants at 21 and 23 months of age and again at 60 and 55 months, respectively. As with the one concordant mother-infant pair, however, the children were seronegative at 5 to 6 months and 11 to 12 months of age. Maternal samples were HPV 16-seronegative on multiple determinations. Maternal cervical specimens were not collected for HPV DNA testing. No disease was clinically apparent in the three seropositive infants.

Discussion. Our data revealed that 3% of children developed antibodies to HPV 16 VLP between 1 and 2 years of age, suggesting a low rate of postnatal infection. In contrast 24% of the mothers were HPV 16-seropositive, consistent with sexual transmission as the principal mode of transmission. The detection of antibodies at 5 years of age in the two children with available specimens indicates that HPV 16 VLP antibodies can persist for years. The observation that all three seropositive children were HPV 16 antibody-negative at 5 to 6 months and again at 11 to 12 months of age shows that seroconversion occurred in each child between 1 and 2 years of age. However, infants born to HPV antibody-positive women were not at significantly higher risk than those born to antibody-negative women, suggesting that the rate of vertical transmission is low.

Several prior reports have suggested that anogenital types of HPV can be detected by PCR in oral

mucosa, genital or perineal specimens of infants although at relatively low frequencies.^{5, 6} One prospective study found that perinatal transmission from HPV DNA-positive mothers at 34 weeks of gestation was at a maximum 2.8%.⁵ This report also found that the children's HPV status was not always concordant with the mother's status at time of delivery.

In the current study two infants who had antibodies at 2 years and persistent antibodies at 5 years of age were born to seronegative mothers. Several explanations are plausible for this paradox. First, the mothers' antibody results could be false negatives. Studies have found negative ELISA antibody results in about one-half of the women in whom HPV 16 DNA was detected by PCR in cervical cytology.⁷ Viscidi et al.⁷ suggest that these women fail to mount a detectable antibody response because of low viral load. If so the mothers in our study could in fact harbor infectious HPV.^{8, 9} Another possibility is that infection occurred postnatally through a nonvertical source. One report has suggested that fomites may potentially provide a nonsexual opportunity for spread of HPV infection.¹⁰ Further confirmation of this observation with additional investigation is needed. Finally the seroreactivity observed in these infants may have been caused by cross-reactivity with other HPV types. Even if this is the case, the antibody responses were persistent for at least 3 years in these infants. Other studies in which a similar ELISA assay was used have successfully correlated antibody with HPV DNA status in low risk virginal populations.¹¹

Earlier investigations of vertical transmission were limited to the detection of HPV DNA in oral mucosa or anogenital specimens. Our serologic data provide some evidence that vertical transmission occurs but it is rare, and they suggest that other nonsexual routes of transmission to young children may also occur. If these results are confirmed, understanding the consequences of HPV 16 infection early in life will be important.

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