Human papilloma virus infection prior to coitarche

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OBJECTIVE: The aim of our study was to determine the prevalence and the natural course of anogenital human papilloma virus (HPV) infections in girls prior to coitarche attending an outpatient gynecological unit.

STUDY DESIGN: Specimens were taken from the anogenital region of 114 unselected 4-15 year old girls who were referred consecutively for various gynecological problems.

RESULTS: Four girls were excluded because of sexual abuse. Low-risk HPV-deoxyribonucleic acid (DNA) was detected in 4 girls (3.6%) and high-risk HPV DNA in 15 children (13.6%). Two girls testing positive for HPV DNA had clinical apparent warts. After 1 year, 2 children had persistent high-risk HPV DNA, and in 1 case we found a switch from high-risk to low-risk HPV DNA.

CONCLUSION: Subclinical genital low- and high-risk HPV infections are common in girls without any history of sexual abuse or sexual activity. We found persistence of genital HPV infection in children, which could be a reservoir for HPV-associated diseases later in life.

Key words: children, girls, human papilloma virus, persistence

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C urrently, > 200 genotypes of human papilloma viruses (HPV) have been identified and around 30 types of HPV cause specifically anogenital infections.1,2 HPV affecting the anogenital region are divided into high-risk and low-risk virus types, depending on their ability to cause malignant disease in the infected epithelium. High-risk types like 16 and 18 are responsible for about 80% of the cases of cervical cancer and are also involved in the pathogenesis of other cancer types like penile cancers,3,4 or oropharyngeallogenic cancers.5-7 Whereas HPV types 6 and 11 are responsible for more than 90% of cases of genital warts, they are rarely associated with malignancies.

Studies have shown that subclinical infections are the most common manifestation of HPV infection. Different authors reported between 15% and 36% of subclinical infections in sexually active adults.8,9 Nevertheless, the vast majority of HPV infections regress spontaneously within 2 years in immunocompetent hosts.10 Whereas sexual activity is by far the most important way of transmission in adults, there is little known about the mode of transmission and the natural history of HPV infection in children. Although sexual abuse is considered to play an important role of HPV acquisition in children, there is strong evidence for vertical transmission during pregnancy and delivery and horizontal transmission like autoinoculation or heteroinoculation through direct contact or fomites.11-13

The purpose of our study was to determine the prevalence of subclinical anogenital HPV infections in girls prior to sexual activity and the persistence and natural history of subclinical HPV infections. The natural history and epidemiology of HPV infections in children are of particular interest because little is known about the consequences of HPV infections early in life in regard to later development of malignant diseases. Furthermore, the knowledge of the epidemiology of HPV infection is necessary for designing effective vaccination programs.

In view of possible nonsexual transmission ways of HPV infection in early childhood and infancy, current recommendations of HPV vaccination in children just prior to coitarche need to be reappraised. Thus, it could be more beneficial to vaccinate children directly after delivery or during infancy as discussed by Cason and Mant.14

Materials and Methods

Participants

The study sample consisted of 114 unselected consecutive 4-15 year old girls who were referred to our outpatient clinic for children and adolescent gynecology of the University Hospital of Vienna (Austria) for various gynecological problems between June 2000 and June 2001. The main diagnoses for referral were vulvovaginitis (55%), tempoanomalies (8%), ovarian cysts (6%), and suspected sexual abuse (6%). Twenty-five percent of the patients came without referral diagnosis for various reasons. The follow-up period for positive tested participants was extended up to 4 years. Those children (n = 4) with a history of sexual abuse or suspected sexual abuse were excluded from the study.
In cases of positive testing for HPV, participants were followed up after 1 year at the earliest and up to 4 years after the first visit by telephone recall. In the event of repeated positive testing for HPV, participants were recalled a third time.

Questionnaires regarding the mode of delivery of participants, clinically apparent warts (anogenital and nongenital), and suspicious Papanicolaou smears and subsequent HPV typing in caretakers and family members were handed out to caretakers of positive testing participants during the follow-up examination. We conducted a telephone interview with the caretaker when the participants did not show up for further examinations.

Statistical analysis
Univariate analyses were used to describe the study participants and the frequency of HPV infection in this study population and contingency table analysis to compare frequencies. SPSS 14.0 (SPSS Inc, Chicago, IL) was used for statistical calculations and $P < .05$ was regarded statistically significant.

RESULTS
Between June 2000 and June 2001, 114 unselected consecutive 4-15 year old girls prior to coitarche were evaluated in our clinic (Figure 2); 4 girls had to be excluded from the study because of suspected or verified sexual abuse. Two of these excluded girls tested negative for HPV and the other 2 girls tested positive for low-risk HPV. The mean age of the remaining participants ($n = 110$) was 9.3 ± 3.4 years.

HPV DNA was found in 20 of 110 participants (18.2%); 4 of the children (3.6%) tested positive for low-risk HPV, and 15 children (13.6%) showed positive results for high-risk HPV (Table). One of those girls had clinically apparent genital warts, and the specimen of this girl (0.9%) contained low- and high-risk HPV DNA. Another girl with visible genital warts tested positive only for high-risk HPV DNA. There was no statistical significant difference in the mean age of positive ($n = 20$) and negative ($n = 90$) testing subjects ($9.2 ± 3.5$ years vs $9.7 ± 3.1$ years, $P = .883$). A meaningful statistical correlation of positive HPV swab testing to the referral diagnosis could not be achieved because of the small numbers in some diagnosis subgroups and the great number of patients without referral diagnosis (many parents were presenting their children without referral by a specialist).

For the subsequent follow-up, we excluded the 2 girls with genital warts because we wanted to evaluate the persistence of HPV DNA in children without visible lesions. Furthermore, we excluded 2 participants from follow-up examinations because they started sexual activity between first and second visit. Despite numerous efforts to reschedule appointments for examinations, we lost 8 participants during the follow-up period.

We also encountered problems concerning the questionnaires because only 5 caretakers of the participants answered them. One of the caretakers willingly answered the questionnaire during the telephone interview but did not show up for the scheduled follow-up examination. One completed questionnaire was returned by a participant who had to be excluded because of the onset of sexual activity in the meantime. Five of the 8 participants following the invitation for further HPV evaluations refused to answer the questionnaire. According to the 5 returned questionnaires, all of these participants were born vaginally and neither the caretakers nor 1 of the family members had genital or extragenital warts. But there was no verification for this information by a health care provider, although we requested such an examination of the caretakers.

In the follow-up, we found no HPV DNA in the sample of 1 girl who tested positive for low-risk HPV during the first visit. We also detected no HPV DNA in the samples of 4 girls who tested previously positive for high-risk HPV. Persistence of low-risk HPV DNA was detected in 2 cases during the follow-up. In 1 subject high-risk HPV DNA was found.
during the first visit and low-risk HPV DNA during the follow-up examination.

Of the 3 girls remaining positive for HPV DNA testing, 1 did not show up for a third appointment and 1 started sexual activity between the first follow-up examination and the second recall. Nevertheless, we tested the latter girl and found no HPV DNA anymore. The third participant tested negative for HPV DNA 4 years after the first follow-up.

**COMMENT**

Our results show that subclinical genital low- and high-risk HPV infection is common in girls without any history of sexual abuse or consensual sexual activity. Among our examined children, we found HPV DNA in 20 of 110 (18%) anogenital samples. Our findings of the prevalence of anogenital HPV DNA in children are consistent with reported HPV detection rates by polymerase chain reaction (PCR) in the literature ranging between 3% and 55%. Comparison of published studies about HPV prevalence in children is difficult because different techniques of sample collection and HPV detection are reported.

With the Hybrid Capture test, we used a detection method that does not amplify DNA and has a low analytic sensitivity in contrast to HPV detection by PCR. Therefore, we believe that we probably underestimated the rate of HPV infection in our subjects. On the other hand, testing of HPV DNA by the Hybrid Capture system is more likely to reveal HPV infections rather than detecting contaminations.

We did not use a second method for confirming HPV DNA because there was only 1 test commercially available for us in the routine clinical setting.

In reviewing the literature, we found different data concerning the HPV infection rate in probable and confirmed sexually abused children. Siegfried et al reported positive testing for HPV 16-DNA by PCR in 2 of 40 patients (5%) referred to their clinic for probable or confirmed sexual abuse, whereas Stevens-Simon et al found low- and high-risk HPV DNA by PCR in 5 of 31 girls (16%) with confirmed or suspected sexual abuse. Furthermore, these authors reported that none of the 9 girls in whom sexual abuse could be ruled out tested positive for HPV DNA. Gutman et al also found no HPV DNA in their control group and detected HPV DNA by Southern blotting in 5 of 15 severely sexually abused girls (33%).

These findings of HPV DNA detection rates in sexually abused children do not match with our results in girls without any evidence of sexual abuse because a lower rate of HPV DNA detection should be expected in nonabused children when sexual transmission is also considered to be the most important route of HPV infection in children. However, the relatively high rate of HPV DNA in our subjects could reflect an underestimation of sexual abuse. Sinclair et al found that nearly one third of 7.3% HPV DNA–positive testing girls (124/1689 cases) were likely to be sexually abused.

In contrast to the studies of Sinclair et al, Stevens-Simon et al, and Gutman et al, our enrolled children were not referred to our clinic for suspected sexual abuse, and therefore, the perspective of our service differed significantly from those of the above mentioned authors. This difference in perspectives seems to be important as already mentioned by Sinclair et al themselves. We think that detected HPV DNA or even clinically apparent anogenital warts do not necessarily indicate sexual contact or abuse.

Obviously our study population consisted of referred patients, which could be source of bias if we want to extrapolate the results of our study to the general population. But this limitation is also true for all other published data on this topic to date, as far as we know.

A further limitation of our study is the fact that only approximately half of the HPV-positive patients were available for control examinations so that hypotheses regarding the natural course of symptom-free HPV infection are on a weak basis.

Hence, we take other modes of transmission into account in girls without any evidence of sexual abuse. Putative nonsexual routes of transmission like vertical transmission during delivery, horizontal transmission at bathing, and diapering and other indirect and direct modes of HPV acquisition are described in detail by nu-

![Figure 2: Study flow chart](image-url)
However, those 2 girls tested negative for types of HPV DNA as in the first visit. Because of a disappointing follow-up rate, we were facing difficulties in the study with a high percentage of spontaneous change from HPV-positive to asymptomatic women. J Soc Gynecol Investig 3-8.


REFERENCES


The current recommendation for prophylactic vaccination against HPV is targeted on young girls and boys who are about to start their sexual activity. We, however, found a high rate of HPV infections in young girls prior to sexual activity and hence unknown but apparently nonsexual ways of acquisition of these infections. Therefore, the recommendation to immunize children just before starting consensual sexual activity can be questioned because children with acquisition of HPV infection during childhood without sexual activity could have less benefit from the vaccination, if HPV infection leads to seroconversion or to chronic cervical shedding of HPV DNA. Prevalence data of HPV infection in the general population of young children are needed to decide whether prophylactic vaccination at birth or in early childhood could be more beneficial as discussed by Cason and Mant. 14

Our study demonstrates for the first time that subclinical HPV infection is also common in girls prior to coitarche without any history of sexual abuse or consensual sexual activity. Therefore, we recommend being very careful when suspecting sexual abuse only on the basis of positive HPV testing. On the other hand, HPV testing in population-based representative sample of young girls could be crucial to decide whether vaccination against HPV at a younger age is more beneficial than the current practice. Furthermore, it is also unclear whether there is a different mode of transmission responsible for clinically visible HPV lesions and subclinical infection.


