Implication of human papillomavirus (HPV) infection in the paediatric population

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WHY UNDERTAKE THIS REVIEW?

At the Scottish Human Papillomavirus Reference Laboratory we deliver human papillomavirus (HPV) testing for epidemiological, clinical and research workstreams. We also serve as a hub for enquiries relating to HPV, HPV testing and the consequences of infection. Enquiries are varied but have included those around the detection and implications of HPV infection in childhood and the rationale/justification for HPV testing in cases of suspected child sexual abuse (CSA). Given these enquiries, the sensitive nature of the issues and the associated legal implications, we took the opportunity to review the evidence on the origins and implications of HPV infection in children and to highlight any key knowledge gaps. To this end we provide a summary document that will hopefully be of use to clinicians.

HOW CAN CHILDREN ACQUIRE HPV?

HPV is a common epitheliotropic virus that can be transmitted via skin-to-skin contact. One of the more common clinical manifestations of anogenital HPV infection is genital warts, which has a peak prevalence in young adults aged 20–25 years.[1] However, anogenital warts can also arise in children, which raises questions and concerns around potential sexual abuse.

As genital HPV infection is often acquired through intimate contact, sexual abuse can of course provide a transmission route with or without penetration. However, there are other mechanisms of HPV transmission. Vertical transmission (from mother to baby) can occur transplacentally; HPV has been found in amniotic fluid and cord blood, or during passage through the birth canal. Horizontal transmission of HPV can occur via selfinoculation, that is, the child has cutaneous warts and transmits the virus to another of his/her body parts, or through heteroinoculation where the carer/close contact has warts and transmits the virus to the child.

Key messages

- While genital human papillomavirus (HPV) infection is often acquired through intimate sexual contact, other non-sexual transmission routes are possible including autoinoculation.
- Comprehensive evaluation of every case of anogenital warts in a child is necessary to determine if child sexual abuse (CSA) may have occurred.
- Molecular HPV genotyping is not currently informative for determining/confirming whether CSA has occurred.

Reports on vertical transmission of HPV between infants and their mothers conducted between 1997 and 2009 are summarised in table 1. Differences in study design, case definition of HPV positivity (eg, clinical evidence or serological/molecular evidence) make the generation of a consensus statement on the rate of vertical transmission challenging. However, the existing evidence indicates that in mothers with clinical signs of HPV infection (ie, warts) vertical transmission may be higher than in those with asymptomatic infection. This said, with respect to asymptomatic women, Castellsague *et al* found children born to cervical HPV-DNA-positive mothers were significantly more likely to be HPV-positive at the 6-week visit postpartum compared with infants born to HPV-negative mothers (p=0.02).[2] Moreover, Merckx *et al* published a meta-analysis that included 20 studies involving 3128 mother-child pairs. From the data, the researchers found significant heterogeneity among

Table 1 Rates of vertical transmission, mother–infant human papillomavirus (HPV) concordance and persistence of HPV in infant samples

Study (year)	HPV status in mothers	HPV status in infants	Concordance infant–mother	Persistence of HPV positivity (>2 samples positive)
Castellsague *et al* (2009)[2]*	66 positive 77 negative	13 (19.7%) 13 (16.9%)	5/16 (31%)	2/18 (11%)
Marais *et al* (2007)[9]†	100 positive	23/111 (20.7%)	7/23 (30.4%)	N/A
Manns *et al* (1999)[10]‡	23 positive (only looked for HPV 16 antibodies) 75 negative	1/23 (4%) (only tested at 2 years, retrospectively looked at birth) 2/75 (2.7%)	N/A	1 (4%) (negative at 5 and 11 months) 2 (2.7%)
Puranen *et al* (1997)[11]§	41 positive 18 clinical signs of HPV	39/105 (37%) 15/18 (83%)	29/42 (69%) 13/18 (72%)	N/A

*HPV DNA was detected from HPV transmission from 66 HPV-positive and 77 HPV-negative pregnant women and their infants.
†Prevalence of anti-HPV-16, HPV-11 and HPV-18 IgG antibodies was analysed in mothers and their children in an attempt to identify evidence of HPV transmission from mother to child.
‡In this report they evaluated the possible mother-to-infant transmission of HPV, using a validated serologic assay to detect antibody responses to HPV 16.
§Authors evaluated the mother–infant transmission in 106 infants born by vaginal delivery or by caesarean section and their 105 mothers using polymerase chain reaction.
HPV, human papillomavirus; N/A, not available.

different studies and a relative HPV infection risk of 33% in newborns from HPV-positive (vs negative) mothers .[3]

HOW COMMON IS HPV IN CHILDREN?

There is a paucity of data on the prevalence of HPV infection in children and the estimates that exist vary widely. From a UK perspective, O'Leary *et al*[4] conducted a study in schools and further education colleges, which involved the molecular testing of urine samples and showed the weighted prevalence of any HPV to be 1.1% for 11–14-year-old females compared with 15.4% for 15–18-year-olds. Consistent with the findings of O'Leary *et al*, Dunne *et al* noted that the younger the child the lower the prevalence (ie, in children aged under 7 years prevalence was 0.4% compared with 3.3% in children over 7 years of age).[5]

WHAT IS THE FREQUENCY OF CSA IN CHILDREN WITH ANOGENITAL WARTS?

There are relatively few studies in which the frequency of CSA in children presenting with anogenital warts have been comprehensively assessed (table 2). Three studies performed between 1996 to 2006 ranged in size from just 17 to 72 patients. de Jesus *et al* concluded that anogenital warts in children aged >5 years should raise a strong suspicion of sexual abuse.[6] In 2006, Sinclair *et al* found that children aged 4–8 years with anogenital warts had a 2.9 times increased risk of CSA compared with children aged <4 years, and those aged >8 years had a 12.1 times increased risk of CSA.[7] In the same year Marcoux *et al* reported that the mean age of onset of wart manifestation in childhood was 3 years 9 months (28% aged <2 years and 62% aged 2–6 years) and in 25% (18/72) CSA was confirmed or suspected.[8]

WHAT TO CONSIDER IF A CHILD PRESENTS WITH ANOGENITAL WARTS?

Given that HPV infection can be acquired via non-sexual mechanisms, all methods of transmission should be considered in addition to possible abuse. It seems reasonable that at least a group of children aged <2–3 years will have developed anogenital warts secondary

Table 2 Summary of studies examining the frequency of child sexual abuse in children presenting with anogenital warts

Study (year)	Children with confirmed CSA	Age of children with confirmed CSA	Children with no CSA	Age of children with no CSA
de Jesus *et al* (2001)[6](9)	8/17 (49%)	>4 years	5/17 (29%)	<3 years
Sinclair *et al* (2006)[7](10)	17/55 (31%)	0–<2 years 5/17 (29%) 2–4 years 5/17 (29%) 4–8 years 7/17 (42%) >8 years	38/55 (69%)	9/9 <2 years 17/38 (45%) 2–4 years 9/38 (24%) 4–8 years 3/38 (8%) >8 years
Marcoux *et al* (2006)[8](11)	18/72 (25%) (age data avail. for 16 children)	0–<1 years 9/16 (56%) 1–4 years 5/16 (31%) 4–8 years 2/16 (13%) >8 years	54/72 (75%) (age data avail. for 43 children)	10 (23%) <1 year 28 (65%) 1–4 years 5 (12%) 4–8 years 0>8 years

CSA, child sexual abuse.

to vertical transmission given that the duration of HPV infection can last 2–4 years after acquisition. As described above, evidence indicates that increasing age is inversely associated with the likelihood of vertical (rather than sexual) transmission. However, there is no clear or evidenced age 'cut-off' that is indicative of abuse, hence evaluation on a case-by-case basis is necessary to inform the decision as to whether a CSA investigation is required.

IS MOLECULAR HPV TESTING INFORMATIVE WHEN CONSIDERING CSA?

No. Genital warts are diagnosed clinically, and laboratory confirmation of HPV status does not add value nor would it inform treatment decisions. Additionally, molecular testing and genotyping of HPV in children is unhelpful in confirming/determining whether abuse has occurred due to (1) the transient nature of HPV infection (2) the observed lack of concordance of HPV genotype in children (even where sexual abuse has been confirmed) and the carer and (3) technical issues/challenges with testing superficial samples.

WHAT GUIDELINES COVER THE MANAGEMENT OF GENITAL WARTS IN CHILDREN?

Various guidelines related to genital wart diagnosis and CSA cases are available from different organisations, including the World Health Organization, British Association for Sexual Health and HIV and the Royal College of Paediatricians. Although some of these guidelines are relatively old, they all concur that there is limited evidenced for the use of molecular HPV testing in children to gain insight into CSA.

WHAT ADDITIONAL RESEARCH/WORK IS NEEDED?

Contemporary parent-to-child transmission studies that provide a better understanding of the detailed natural history of HPV acquisition, clearance and clinical manifestation(s) in children would help determine a 'background' level of genital HPV carriage in children and potentially identify non-sexual risk factors for transmission. Such studies would also provide more precise estimates of the development of anogenital warts secondary to vertical transmission of HPV. Additionally, prophylactic HPV vaccination has already demonstrated a significant impact on adult diagnoses of genital warts and is likely to exert an influence in children over time, both directly and indirectly through herd immunity.

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