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Implications of HPV infection in the paediatric population

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Key message points:

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

Contributorship statement:

Daniel Guerendiain: Drafted manuscript.

Ingolfur Johannessen: Assisted in critical appraisal of manuscript.

Kirsten Healy: Assisted in literature review and in critical appraisal of manuscript.

Kate Cuschieri: Assisted in drafting and critical appraisal of manuscript.

Why undertake this review?

At the Scottish HPV Reference laboratory we deliver HPV testing for epidemiological, clinical and research work-streams. 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 legal implications associated, 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?

Human papillomavirus (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, ano-genital 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 autoinoculation i.e. the child has cutaneous warts and transmits virus to another of his/her body parts or through heteroinoculation where the carer/close contact has warts and transmits virus to child.

Reports on vertical transmission of HPV between the infants and their mothers conducted between 1997 to 2009 are summarised in Table 1, [2, 6, 7, and 8]. Differences in study design, case definition of HPV positivity (e.g. 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 (i.e. warts) vertical transmission may be higher than in those with asymptomatic infection. This said, with respect to asymptomatic women, Castellsague found children born to cervical HPV-DNA positive mothers were significantly more likely to be HPV positive at the 6 week visit post partum compared to infants born to HPV negative mothers ($p=0.02$), [2]. Moreover, Merckx published a meta-analysis of, which included 20 studies or 3128 mother-child pairs. From the data, they found significant heterogeneity among different studies, and a relative risk increase of 33% [3].

Table 1. Rates of vertical transmission, mother – infant HPV concordance and persistence of HPV in infant samples.

Study, Year	HPV status in mothers	HPV status in infant	Concordance Infant - Mother	Persistence of HPV positivity (>2 samples positive) only 18 samples tested >2
[2] Castellsague (2009) ^a	66 positive 77 negative	13 (19.7%) 13 (16.9%)	5/16 (31%) samples (315)	2/18 (11%)
[6] Marais (2007) ^b	100 positive	23/111 infants (20.7%)	7/23 (30.4%)	N/A
[7] Manns (1999) ^c	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%)
[8] Puranen (1997) ^d	41 positive 18 clinical signs of HPV	39/105 (37%) 15/18 (83%)	29/42 (69%) 13/18 (72%)	N/A

a) HPV DNA was detected from HPV transmission from 66 HPV-positive and 77 HPV-negative pregnant women and their infants. b) 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. c) 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. d) Authors evaluated the mother-infant transmission in 106 infants born by vaginal delivery or by caesarean section and their 105 mothers using PCR.

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 [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 to 15.4% for 15-18 year olds. Consistent with the findings of O Leary, Dunne noted that the younger the child the lower the prevalence i.e. in children under 7 years of age the prevalence was 0.4% compared to 3.3% in children over 7 years of age [5].

What is the frequency of CSA in children with ano-genital warts?

There are relatively few studies in which the frequency of child sexual abuse in children presenting with ano-genital warts have been comprehensively assessed (Table 2). Three studies performed between 1996 to 2006 ranged in size from 17- to just 72 patients. De Jesus concluded that ano

genital warts in children > 5 years of age should raise a strong suspicion of sexual abuse, [9]. In 2006, Sinclair found that children compared to children less than 4 years of age, children aged 4-8 years with ano-genital warts had a 2.9x increased risk of child sexual abuse compared to children < 4 years of age, and those > 8 years of age had a 12.1x increased risk of child sexual abuse, [10]. In the same year Marcoux reported that the mean age of onset of wart manifestation in childhood was 3 years 9 months (28% <2 yrs and 62% 2-6yrs) and in 25% (18/72) child sexual abuse was confirmed or suspected, [11].

Table 2. Summary of above studies looking at the frequency of child sexual abuse in children presenting with ano-genital warts.

Study, Year	Number of children with confirmed child sexual abuse	Age of children with confirmed child sexual abuse	Number of children with no child sexual abuse	Age of children with no child sexual abuse
[9] De Jesus (2001)	8/17 (49%)	>4 years	5/17 (29%)	<3 years
[10] Sinclair (2006)	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%) 2-4years 9/38(24%) 4-8years 3/38(8%) >8years
[11] Marcoux (2006)	18/72 (25%) Only age data for 16/18	0 - < 1 years 9/16 (56%) 1-4years 5/16(31%) 4-8years 2/16(13%) >8years	54/72 (75%) Only age data for 43/54	10(23%) <1year 28(65%) 1-4years 5(12%) 4-8years 0 > 8 years

What to consider if the child presents 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 <2-3 years will have developed anogenital warts secondary 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” which 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 exist that relate to the management of genital warts in children?

Various guidelines related to genital wart diagnosis and child sexual abuse cases are available from different organisations, including WHO, BASHH and the Royal College of Paediatricians. Although some of these guidelines are relative elderly, they converge on the point 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 ano-genital 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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