Human Papillomavirus Vertical Transmission: Review of Current Data

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Despite the increasing evidence of human papillomavirus (HPV) vertical transmission, this route is regarded as less clinically important because of the detections of transient HPV DNA. However, recent studies have provided clear evidence of papillomavirus productive infection in lymphocytes, placenta, and bovine fetal tissue. Furthermore, a model of papillomavirus latency has been recently proposed that could explain the failure or transience in HPV detection observed in some infected infants. This new evidence of hematogeneous and vertical spread of HPV suggests that these modes of transmission should be investigated in greater detail to obtain a better understanding of the infection and a fuller awareness of the preventive measures that can be taken against HPV-related diseases.

Keywords. human papillomavirus; vertical transmission; human cancers; human papillomatosis.

Human papillomavirus (HPV) is the most common sexually transmitted infection among humans, and represents a well-established cause of cervical cancer in females and a significant factor in the development of anogenital, head, and neck cancers [1].

A number of investigations have found that HPV infection may also be transmitted by nonsexual routes [2], as HPV DNA has been detected in blood and in reproductive and placental cells, as well as in infants, in children, and in individuals who have never had sexual intercourse [2–4]. HPV horizontal transmission through saliva or other contact has been invoked to explain cases of oral infection in infants whose mothers are HPV negative [5], and investigations of vertical transmission have led to conflicting results and transient HPV detections in children [6, 7]. Thereby, we are still unable to fully understand the clinical relevance of these findings, for either pregnancy or pediatric care.

In theory, vertical transmission can occur through the following mechanisms of transmission: periconceptual transmission (during fertilization of an oocyte or immediately after fertilization), prenatal (during pregnancy), and perinatal (during or immediately after birth). In this review, we will discuss the significance and implications of the presence of papillomavirus in nonepithelial sites, and examine the possible consequences of fetal exposure to HPV and the extent to which these new findings can provide a better understanding of the natural history of papillomavirus infection.

POSSIBLE MECHANISMS OF HPV VERTICAL TRANSMISSION

Although HPV DNA has been detected in different sites of the male reproductive tract [8–10], sperm cells [4, 11, 12], semen [13, 14], endometrium, and ovaries [15], which suggests that HPV could be transmitted during the fertilization of an oocyte or immediately afterward, the significance of these findings is still unknown. In vitro analyses have indicated the viability of HPV infection in spermatozoids and the transcription of HPV genes in fecund oocytes [8–10, 16–20], and the transcriptional activity of HPV-16 in sperm
was confirmed in vivo [21]. However, further investigations are necessary to confirm this route of transmission.

For this reason, the discussion about the possible mechanisms of HPV vertical transmission will center on the prenatal and perinatal routes, which are better understood.

**PRENATAL TRANSMISSION**

The observation of infants showing signs of HPV-induced lesions at birth, such as laryngeal and anogenital lesions, has led to the belief that intrauterine HPV transmission can occur [22, 23]. HPV DNA has been detected in amniotic fluid [3], placenta, and the umbilical cord [7]. Both chorionic and placental tissue can be infected through the hematogenous route and hence, HPV can be spread to amniotic cells that are then ingested by the fetus [2, 3]. Transplacental infection, another possible means of HPV intrauterine transmission, can occur through the ascending route from the maternal genital tract, as it has been shown that the presence of HPV-DNA, both in amniotic fluid [3] and the umbilical cord [2], is correlated with cervical intraepithelial lesions in pregnant women.

Once believed to be low, the HPV vertical transmission rate has shown inconsistent results, probably due to the heterogeneous nature of the clinical trials [24]. Despite this, in a systematic quantitative review, Medeiros et al [24] reported a pooled relative risk of mother-to-child HPV transmission (4.8) when the mother is shown to be HPV positive. Additionally, the risk of the newborn having the same HPV type as that found in the maternal genital tract is 4 times greater when the umbilical cord blood is positive for the same HPV [25]. Evidence from the cervical samples indicates that mothers who transmit HPV to their infants have a higher viral load than those who do not [26].

Sarkola et al [25] reported that peripheral blood samples from all mothers who had HPV in the placenta and umbilical cord tested negative for HPV. According to these authors, the detection of viral DNA in their samples appears to be due to a maternal history of productive infection and not the detection of viral genetic material during pregnancy. However, there remains the possibility that HPV infected the placenta during early pregnancy and had already cleared the cervix at the time of delivery [2].

During pregnancy, the uterine canal undergoes anatomic and immunologic changes that may increase the susceptibility of pregnant women to infections [27]. In addition to other human viruses such as HIV, cytomegalovirus, and Epstein-Barr virus, HPV may be able to infect the placenta or cells of fetal origin [28]. The transplacentational transmission of HIV and maternal cells, including lymphocytes, is a phenomenon that has already been described and can be stimulated by pathologic conditions [28, 29]. Reports of the presence of HPV in polymorphonuclear cells suggest that the transfer of maternal cells could allow the virus to pass through maternal-fetal barrier. Additionally, as observed for hepatitis B virus and herpesvirus, under certain immunosuppressive conditions, there can be an increase in the passage of lymphocytes carrying latent HPV through the maternal-fetal barrier [28].

HPV trophoblast infection has been described in different studies [25, 30, 31]. Furthermore, You et al [32] demonstrated in vitro that trophoblast cells are broadly permissive for HPV and that this virus is able to complete its life cycle in trophoblast cell cultures.

**PERINATAL TRANSMISSION**

In this section, perinatal transmission will be considered as the result of the fetus coming into contact with infected cells of the vagina and cervix during birth. Some authors have demonstrated that there is both an increased rate of HPV detection among newborns by vaginal delivery (51.4%), compared to those delivered by cesarean section (27.3%) [33] and an increased incidence of juvenile respiratory papillomatosis after prolonged delivery (>10 hours) [34]. At the same time, Tenti et al [35] observed a low potential for viral transmission to the oropharyngeal mucosa of newborns from mothers without changes in oncotic colpocytology or a history of genital warts.

The view that a cesarean delivery provides protection against the transmission of neonatal herpes in pregnant women with obvious injuries has led to the suggestion that this procedure can be adopted for perinatal pregnant women with genital warts [27]. However, there is no clear consensus about the degree of protection that cesarean delivery can offer against maternal–fetal transmission of HPV [2]. This lack of agreement is based on 3 hypotheses: (1) the risk of disease transmission would be low; (2) a cesarean delivery does not ensure complete protection, because papillomatosis transmission has even been observed in elective cesarean delivery; and (3) the risks resulting from a cesarean section are greater than the potential benefits [5, 34]. In rare circumstances, the cesarean is recommended for women with genital warts that cause obstruction in the birth canal, or in cases where vaginal delivery will result in excessive bleeding due to laceration of the warty lesions [27].

**HPV VIRAL LATENCY**

Given the lack of a clear understanding of the natural history of HPV, this raises a key question: Does the failure to detect viral DNA transmitted from a previously infected individual represent viral clearance or a state of viral latency [36]? In
natural history studies, women may undergo multiple transient states that can lead to detection of HPV DNA in cervical samples [37]. Thus, because it is impossible to detect viral DNA in an individual, we cannot differentiate between the following states: DNA-negative individuals who are not infected and immune; DNA-negative individuals not infected and susceptible; and DNA-negative and infected individuals [36].

Viral latency has been invoked to justify this situation. This viral status, which is characterized by a significant decrease in viral protein expression and the establishment of papillomavirus DNA in the episomal form, restricts the infection to basal cells of the epithelium [38], where they remain controlled by a responsive immunologic memory [39]. However, factors that suppress the immune system allow an occurrence of viral reactivation [38], as described in studies that have detected fulminant warts in immunosuppressed individuals [39].

Animal models of papillomavirus infection have provided valuable experimental evidence for viral latency [38]. The observations obtained from cottontail rabbit papillomavirus and canine oral papillomavirus models have shown that latent viral particles are virologically active under certain conditions. This is analogous to the detection of HPV DNA in normal laryngeal epithelium of patients with recurrent respiratory papillomatosis (RRP) in remission [40]. A model of HPV latency has been proposed to carry this out [36].

The limited understanding of this scenario has clear implications for a literal interpretation of the status of HPV infection, particularly for infants. Some studies suggest that detection of HPV DNA in newborns is only persistent in the early days [35] or months [6, 26]; other authors have reported cases in which HPV persists until the first [41] and third years of life [5]. The assumption that detection of HPV in newborns, from a vertical transmission, is clinically insignificant because it may not be persistent ignores the viral latency and the real implications of this mode of transmission (Figure 1).

**EVIDENCE OF PAPILLOMAVIRUS VERTICAL TRANSMISSION THROUGH ANIMAL MODELS OF INFECTION BASED ON BOVINE PAPILLOMAVIRUS**

To date, no studies have clearly demonstrated HPV vertical transmission in humans. However, studies with BPV (bovine papillomavirus) have shown the most consistent data to support the viability of hematogenous and vertical transmission [42, 43].

BPV is responsible for the development of skin lesions and cancers in bovids [42, 44, 45]. BPV vertical transmission was initially suggested after viral detection in the blood of cows and their offspring [45]. These reports were followed by detection of BPV DNA in the reproductive tracts of bovids, fluids and gametes, and embryonic annexes [44–49]. After the detection of BPV protein in lymphocytes [42], this cell was postulated as a vehicle for carrying BPV to the reproductive tract [49].

Recent discoveries made by Roperto et al [43] may represent a watershed in the investigation of papillomavirus vertical transmission, as their study showed productive infection of BPV-2 in cells of the uterine epithelium and chorionic placenta. Additionally, E5 oncoprotein was characterized to form a complex with the platelet-derived growth factor β receptor (PDGFßR), both in the trophoblast cells and in bovine fetal organs [43]. This complex might be associated with an abnormal organogenesis in the embryo and an impairment of pregnancy [43]. Together, these significant findings corroborate the hypothesis of the vertical transmission of this virus.

**IMPLICATIONS OF HPV VERTICAL TRANSMISSION**

Since the 1990s, various groups have investigated HPV vertical transmission and detected viral DNA and antibodies in both pregnant mothers and in newborns [2]. However, different techniques and methodologies for sample collection (buccal swab, cervical brush, blood) or detection of viral DNA (hybridization by Southern blotting, polymerase chain reaction) have variable sensitivities and have yielded conflicting results [2, 36]. Owing to the incomprehension of the molecular mechanisms governing viral latency and the development of natural immunity against HPV, and the failure to assess viral activity, the presence of HPV-DNA in blood and reproductive and embryonic cells was treated as a transitional marker, which represented less frequent and/or nonpersistent events.

Animal models suggest that papillomavirus can be spread to different tissues by lymphocyte infection, in particular to the reproductive tract and gametes [49]. Additionally, recent experiments with cattle confirm in vivo the viability of productive papillomavirus infection in cells of the placenta. Even though HPV-DNA was also found in lymphocytes, the outcomes of this finding need further investigation.

Nobbenhuis et al [50] showed that the first 2 trimesters of pregnancy are characterized by an increasing susceptibility to HPV. It can represent a latent HPV activated during early pregnancy. In vivo and in vitro assays have shown that the levels of steroid hormones, which characteristically rise during pregnancy, may act as HPV cofactors in epithelial proliferation [27]. This means that this “window of accessibility” may increase the exposure of the fetus to vertical transmission.

The possible implications of HPV vertical transmission are wide-ranging, given the oncogenic characteristics of HPV [1]. One of the well-characterized clinical complications is RRP, which is the development of lesions in the larynx, vocal cords,
and oral and nasal mucous membranes, and in rare cases, reaches the trachea and bronchi [2, 51]. RRP has a bimodal age distribution that includes the juvenile form and an adult form [51]. Although some studies have established a relationship between juvenile RRP and the presence of maternal genital warts in 30%–50% of patients [2], the majority of children who develop this disease are born from women with no history of genital warts during pregnancy [34].

Although the results are less clear than those of RRP, the presence of HPV in semen has been linked to male infertility; asthenozoospermia has been linked to viral detection, and infertile men have a prevalent HPV infection in the spermatozoid [4, 19, 20]. The exact prevalence of HPV-DNA in sperm remains a controversial issue. HPV semen infection was found in 10% of the samples from asymptomatic men who had unprotected intercourse [13]; this figure rose to 53.8% among patients affected by genital warts and 40.9% of patients who had an HPV-positive female partner [14]. Despite our lack of a clear understanding of the role of HPV in the semen, the literature raises the possibility that spermatozoids might act as a vector in the transmission of HPV DNA. This may occur both in the cumulus cells, where it can lead to implantation failure [52], and in the embryo, where it may explain why some HPV-negative pregnant women give birth to HPV-positive infants [2]. Perino et al [53] reported an increased risk of abortion when HPV-DNA testing was positive in the female partner (40% infected vs 13.7% noninfected), which was even higher when the sperm samples of the male partner were infected (66.7% infected vs 15% not infected).

In pregnant women, the risk of HPV transplacental dissemination and the subsequent development of disorders such as hydatidiform mole and choriocarcinoma have been supported by in vitro assays. HPV has been shown to deregulate trophoblast–endometrial cell adhesion and invasion [30, 54] and this finding supports the emergence of disorders and impairments in pregnancy resulting from the action of HPV in the placenta, such as genetic abnormalities of the fetus, spontaneous abortions, and premature births [30, 31]. According to Hermonat et al [31], 60% (15/25) of the samples obtained from spontaneous abortion products and 20% (3/15) of those obtained from elective abortion products were positive for the presence of HPV E6 and E7 genes. Furthermore, HPV-16 DNA in syncytiotrophoblastic cells was detected in 29% of the samples collected from the spontaneous abortion group. Finally, the exposure of a 2-cell mouse embryo to HPV-DNA demonstrated a decrease in blastocyst formation and a reduced hatching process [55].

Interestingly, Roperto et al [43] found that E5/PDGFβR complex, which is important for the development of urinary bladder carcinogenesis, was also characterized in bovine fetal organs. Although HPV E5 protein is not characterized by the main viral oncoprotein, its action on the epidermal growth factor receptor (EGFR) and its correlation with cell cycle disorders in the epithelium [56] have already been described. If the findings obtained with BPV are extrapolated for infection in humans, it can be postulated that E5/EGFR complex is related to disorders of the embryonic attachments described in the literature. In addition to a possible relationship with

Figure 1. Natural history model of human papillomavirus (HPV) infection and DNA transition states showing the possible influences of vertical transmission and viral latency. The DNA detection from infants who have acquired HPV from their mothers could be transient due to viral latency. Under some circumstances as immunosuppression, the latent virus can be reactivated and induce the formation of lesions, which could progress to cancer or not. Alternatively, the immunosuppression could contribute to viral reactivation and/or acquisition during pregnancy, which could possibly result in vertical transmission.
pregnancy loss, HPV infection was also linked to spontaneous premature births. The HPV-DNA was detected more frequently in the extravillous trophoblast region of placentas from spontaneous preterm delivery cases (15/30) than from controls (6/30) [30]. These findings support the hypothesis that HPV infection could cause abnormal placental functions which, in turn, may partly be the origin of prematurity.

Finally, the exposure of the fetal immune system to viral antigens might reduce the postpartum immune response to viral proteins, a phenomenon that might be applicable to children who develop Burkitt lymphoma and may have antibodies against Epstein-Barr virus in the first 6 months of life [22]. Considering what has been proposed for the HPV latency model, it can also be assumed that contact between the embryo or fetus with viral antigens does not have an immediate effect such as abortion or malformation. Rather, the virus remains in a latency period until some cellular disturbance stimulates the viral activation and replication. Taken together, these hypotheses could partly explain cases in which HPV-positive women give birth to HPV-negative infants, as well as the familial tendency to develop HPV-related cancers [3].

**PERSPECTIVES AND CONCLUSIONS**

This review discusses the current concepts with regard to HPV vertical transmission. However, it should be stressed that there is still no way to describe in detail how this phenomenon occurs. This subset of work suggests a complex network of events leading to mother-to-child HPV transmission, which could be a combination of factors linked to HPV infection during pregnancy and to the pregnant mother herself (eg, age, mode of delivery). In addition, the impact of HPV transmission on embryonic outcomes seems to depend on the precise moment of infection. In light of this, others significant questions arise: How should we proceed when HPV DNA is identified in the mother during the pregnancy? Even on the basis of conservative clinical reasoning from which the puerperal period can reverse a greater predisposition to HPV by pregnant women, this situation seems to increase the exposure of the fetus to vertical transmission. Moreover, questions about HPV in men are also important. Should research about HPV infections be extended to the fathers during the prenatal exams? Should semen banks be subject to a screening for HPV?

The number of reports of nonepithelial tropism of HPV is still increasing, and the impact of this scenario must be investigated. Further work should focus clearly on the question of characterizing these nonsexual routes of transmission and should employ methodologies that are sensitive enough to distinguish between HPV latency and productive/active infection [2, 6]. With vaccination programs against HPV still being set up in various countries, it is crucial to have a proper understanding of the natural history of HPV.

**Notes**

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