Transplacental Transmission of Human Papillomavirus

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ABSTRACT

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.

INTRODUCTION

Human papilloma virus (HPV) is well recognized as the sole causal agent of cervical cancer. Next to this, HPV is also playing an important role in the etiology of other conditions. This includes head-and-neck tumors, skin diseases (warts, condyloma) and potentially even other conditions. Within the family of HPV viruses two subclassifications can be distinguished based on their oncogenic potential, i.e. high-risk HPV (HR-HPV) and low-risk HPV types (LR-HPV) (1). Different categorization protocols are used to distinguish HR-HPV and LR-HPV. Here, the categorization according to Schiffman et al. (2009) will be used. HPV is one of the most common, sexually transmitted viruses in adults (2). Most young women become infected with HPV; their lifetime incidence is estimated to be as high as 80%. Most infections are asymptomatic and have the tendency to clear spontaneously. Yearly, around 500,000 women are diagnosed with cervical cancer, and total burden of HPV-related cancers worldwide in women adds up to over 10% of all cancer cases (3).

HPV infection in adults is the main field of interest in HPV research. However, HPV infection is not limited to adults can also affects children. Data on this topic is slowly becoming available. By the presence of HPV in a wide range of pathologies, Syrjānen et al. (2010) indicates that HPV infection in miniors in not essentially asymptomatic. Genital warts, oral papillomas and recurrent respiratory papillomatosis (RRP) are described as mucosal HPV infections, while skin warts and lichen sclerosis are covered by cutaneous HPV infections in children (4). Most cutaneous HPV types can persist over a long time without causing any symptomatic disease.

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However, once skin warts are present, this might predict less immunity and this implies a certain caution towards genital HPV lesions (3). It has been described that common warts at the age of 11-16 years are significantly associated with higher risk for development of cervical cancer. Most recognized benign HPV lesions in minors are skin warts and laryngeal papillomas. RRP is a more rare and critical HPV related disease as it can be life-threatening due to total respiratory obstruction (5). Anogenital warts often raise suspicion of sexual abuse but other routes of infection have to be equally taken into account.

Condylomata acuminata in children may be, but are not necessarily, an indicator of sexual abuse. Each individual case therefore requires careful examination, with consideration of other possible means of transmission (6). This paradigm has been changed over the past decade as children with no history of sexual abuse can equally be affected by HPV related diseases. The route of effective infection still remains unclear but autoinoculation, vertical and horizontal transmission have been suggested (7). Vertical transmission can be divided into three categories according to the time of HPV infection: peri-conceptual, prenatal and perinatal transmission. HPV DNA has been detected in spermatozoids, endometrium and ovaries indicating the possibility of peri-conceptual transmission (8). Intrauterine or prenatal transmission is considered as a possible route of infection because of the reported presence of HPV DNA in amniotic fluid, placenta and cord blood samples (9). Perinatal transmission takes place after close contact of the fetus with infected cervical and vaginal cells of the mother during delivery. It is a matter of debate if mother-to-child transmission (MTCT) of HPV has to be considered an important infection route (10).

Data on HPV infection in children, including newborns, is slowly becoming available. The extent to which HPV and HPV related diseases in minors can be found, remains however ambiguous (11). Only crude prevalence estimations are currently at hand. Prevalence rates of HPV infections ranging from 0% up to 70% have been described in the recent literature. Next to the fact that not all HPV infections result in disease, the studied population and technical limitations contribute to this extreme range. The same wide range of prevalence's can be observed in pregnant women, ranging from 5.4 to 68.8% (12). Several studies report an increased prevalence of genital HPV infections during pregnancy. This may be related to two factors, hormonal changes that may encourage HPV replication and transient immunosuppression. An important consequence is the decrease of trophoblast cells and the trophoblastendometrial cell adhesion (13).

POSSIBLE MECHANISMS OF HPV VERTICAL TRANSMISSION

Although HPV DNA has been detected in different sites of the male reproductive tract, sperm cells, semen, endometrium, and ovaries, 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 secund oocytes, and the transcriptional activity of HPV-16 in sperm was confirmed in vivo (14). 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. HPV DNA has been detected in amniotic fluid, placenta, and the umbilical cord (15). 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 (16). 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 and the umbilical cord, is correlated with cervical intraepithelial lesions in pregnant women (17). Once believed to be low, the HPV vertical transmission rate has shown inconsistent results, probably due to the heterogeneous nature of the clinical trials. Despite this, in a sys-
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%) and an increased incidence of juvenile respiratory papillomatosis after prolonged delivery (>10 hours) (29). At the same time, Tenti et al 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 (30). The view hypothesis 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 (31). However, there is no clear consensus about the degree of protection that cesarean delivery can offer against maternal–fetal transmission of HPV (32). This lack of agreement is based on 3 hypotheses: the risk of disease transmission would be low; a cesarean delivery does not ensure complete protection, because papillomatosis transmission has even been observed in elective cesarean delivery; and the risks resulting from a cesarean section are greater than the potential benefits (33). 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 (34).

PERSPECTIVES AND CONCLUSIONS

This review discusses the current concepts regarding the 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 this context, 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 predis-
position 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 partner (father) during the prenatal exams? Should semen banks be subject to a screening for HPV?

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