



Human Papillomavirus Infection Is an Unresolved Challenge in Assisted Reproductive Techniques

Human papillomavirus (HPV) is the most common type of sexually transmitted infection in men and women at reproductive age with devastating socio-economic impacts across nations. The total cost for prevention and treatment of HPV-related diseases was more than 8 billion dollars in 2010 (1). This DNA virus can infect both cutaneous and mucosal squamous epithelium; its high-risk variant strains frequently lead to formation of benign lesions (warts or papillomas) and intraepithelial neoplasms such as cervical cancer and, to a lesser extent, other malignancies including vulva, vagina, anus, oropharynx, and penile cancer (2). Most HPV infections are subclinical, and few of them have mild to moderate symptoms. A lot of studies on pathogenesis of HPV have been conducted among women, while our data on its infection and pathogenesis among men is limited. The overall prevalence of high-risk and non-pathogenic strains of HPV in different communities was estimated to be about 12% in 2012 which varies in different age groups, depending on their sexual activity. The incubation interval of HPV ranges between 1-8 months. Compared to the complications of HPV infection in women, men experience transient types without clinical consequences, which is a neglected area of research in HPV treatment programs. However, research on men has recently received increasing attention due to association of HPV with genital warts, penile, anorectal, and oropharyngeal cancers (1). HPV-6 and HPV-11 are the most common low-risk types of the infection often leading to anogenital warts, while HPV-16 and -18 are the most common oncogenic or high-risk types and the cause of more than 70% of cervical cancers (2). The infected men might transmit HPV to their sexual partners. Therefore, the study of HPV pathogenesis in men and its possible role in male and female infertility and early development or miscarriage of fetus has particular importance. Recent studies suggest the possible roles of HPV in male infertility, yet it is not clear whether HPV infections can silently damage the reproductive system or not. Therefore, the detection of HPV is important in the diagnosis of infertility in order to opt for different assisted reproductive techniques (ART) among HPV-positive patients (3). Literature review over the past two decades shows that the prevalence of HPV infection in infertile men with leukocytospermia is higher than the fertile ones. It has been shown that HPV infection in men is the cause of unexplained infertility; based on previous research, the rate of HPV infection of semen is approximately 2-31% in overall community, while its prevalence in couples with unexplained infertility is nearly 10-35.7%. Similarly, there is a lot of evidence on a possible link between HPV sperm infection and male infertility, indicating that HPV infection is associated with decreased sperm motility, increased sperm DNA fragmentation, and idiopathic asthenozoospermia; in fact, active transcription of well-defined HPV-specific genes in men can result in infertility via damaging sperm motility. In addition, higher levels of anti-sperm antibodies are detected in men infected with HPV (4). Infection with HPV-16 has been reported to affect oocyte fertilization, fetal development, and increased blastomeres apoptosis which consequently influences embryo implantation in the endometrium. In animal studies, HPV-16 and -18 via E6/E7 transcripts block embryonic development at two-cell stage. In addition, HPV infection in women is usually associated with tubal factor infertility through stimulation of the immune response or production of high levels of proinflammatory cytokines (1, 2, 5).

HPV is deemed similar to other STIs viruses in binding to two separate regions along the equatorial segment of spermatozoa. The presence of glycosaminoglycans or other molecules on sperm surface appears to mediate the interaction and binding of HPV to sperm. In addition, the equatorial segment is the region that sperm attaches to the plasma membrane of oocyte through fertilization process. Binding of HPV to sperm does not affect its ability to fertilize the oocyte; however, HPV-infected sperm can transmit viral genome to oocyte, which may be expressed in the developing blastocysts. Nevertheless, it is still unclear whether HPV infection can affect the subsequent zygote, embryo, and fetus development (1, 2).

Association of HPV infection with preterm birth, miscarriage, or premature rupture of membranes is another scenario for its effect on reproduction. *In vitro* transfection of embryonic trophoblast by plasmids containing HPV genome increases the rate of apoptosis 3-6 times in comparison to control embryos. Therefore, trophoblast cell death is the cause of placental insufficiency, failure of invasion to endometrium, and ultimately premature rupture of membrane and early miscarriage (1-3).

In about 10 to 30% of women, HPV virus will be cleared by the affected individuals' immune system within 3 months, and in 90 % of cases, it will go away within two years. HPV infection remains in 10% of infected

women whose cellular immune response is unable to remove the viral load. Therefore, these women are always at risk for HPV-related diseases and possibly cervical cancer. Accordingly, vaccination of high-risk individuals especially young women is necessary since they are vulnerable to cervical cancer as a result of high HPV viral load (1).

Currently, the research for effective protocols addressing washing and selecting the sperm for ART is a hot topic. In fact, these guidelines should provide instructions on how to remove HPV from the surface of sperm. The routine method of semen processing applied in ART has been found to be ineffective in eliminating HPV bound to sperm (6). It seems that vaccination of men can be an effective strategy to prevent HPV-related sperm disorders and infertility until researchers discover and introduce new methods for removal of HPV from semen and sperm surface.

Though HPV vaccine can prevent genital warts, cervical dysplasia, and cervical cancer following HPV infection, vaccination of men and women against HPV can also reduce its harmful consequences on human fertility. *In vitro* studies have shown that vaccination can prevent HPV-related sperm damages, trophoblast apoptosis, and spontaneous abortion. Moreover, it can alleviate the serious concern of sperm banks about HPV infection of donated sperm (1, 3).

Therefore, the effects of HPV on early embryo development are not conclusive and the research in the field is still in its infancy. However, the available experimental findings confirmed the possible negative effects of HPV on increased blastocyst apoptosis and decreased trophoblast cell attachment to the endometrium. Accordingly, new scientific approaches should be used to better understand the exact role of HPV infection in male and female infertility and early pregnancy development. Regarding current evidence on the relationship between HPV gametes infection and abnormalities at early stages of human reproduction, vaccination of young men, women, and couples is a reliable option to protect their fertility and improve ART outcomes in idiopathic infertility that might be linked to HPV infection.

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