



## Is HPV Controversial Suspicious of Male Infertility?

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Infertility is a significant health concern, affecting up to 16% of couples worldwide. Male infertility contributes to approximately 50% of these cases and arises from a variety of causes categorized as pre-testicular, testicular, and post-testicular. Sexually transmitted infections (STIs) are increasingly acknowledged by researchers and clinicians as contributing factors to male infertility (1). Among these infections, Human Papillomavirus (HPV) is the leading cause of the most prevalent STI globally, with an estimated 6.2 million new cases each year (1). Notably, recent research has documented the presence of HPV in seminal fluid, showing that sperm infection occurs even in asymptomatic, sexually active males and infertile patients. Genital HPV infection is primarily transmitted through various types of sexual contact. Additionally, horizontal transmission includes contact with fomites, fingers, the mouth, sex toys, and skin, outside of sexual activity. Self-inoculation has been identified as a possible route of transmission, as confirmed in female virgins and children with genital warts (low-risk HPV) who had no history of sexual abuse (2). Vertical transmission from mother to child has also been reported through amniotic fluid, the placenta, or contact with maternal genital mucosa during natural delivery.

Globally, the prevalence of male infertility is rising, leading many individuals to seek treatment through Assisted Reproductive Techniques (ART) each year (3). A recent meta-analysis demonstrated that HPV infection can impair fertility through mechanisms such as HPV presence in semen, formation of anti-sperm antibodies, alterations in sperm parameters (motility, morphology, vitality, and count), and increased sperm DNA fragmentation (3). From a pathophysiological perspective, HPV has been shown to infect human spermatozoa, localizing in the equatorial region of the

sperm head through an interaction between the HPV capsid L1 protein and syndecan-1. This mechanism may enable the transmission of the virus to the oocyte during fertilization (4, 5).

Furthermore, different HPV genotypes have been found to play distinct roles in adverse reproductive outcomes during intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET). For instance, the presence of HPV DNA in semen and the injection of HPV-infected sperm into the oocyte have been associated with negative impacts on fertilization rates, implantation, and embryo development. The underlying hypothesis is that HPV interferes with the fusion process between sperm and oocyte (2-4). Moreover, a subgroup analysis of eight case-control studies revealed a significant association between HPV infection and complications such as prematurity, early rupture of membranes, intrauterine growth restriction, low birth weight, and fetal death (5).

The prevention and management of HPV-related infertility involve multiple strategies. The first includes adopting general STI prevention measures and practicing good sexual hygiene, both of which have been shown to reduce HPV persistence in infected couples. Secondly, given the evidence linking HPV with male infertility, the potential of HPV vaccination to prevent infertility deserves attention. The association between male HPV infection, asthenozoospermia, and increased pregnancy loss supports the recommendation to extend HPV vaccination to adolescent males, helping to prevent HPV-related anogenital and oral cancers (6).

Further research is required to better understand the timeline for viral clearance in semen. Since nitrogen is an excellent medium for preserving viruses, HPV-positive semen samples should not be used for assisted reproduction or sperm banking (6).

The development of HPV vaccines has been a major advancement in combating HPV infections. Prophylactic HPV vaccination has been proposed as a strategy to improve male fertility, given its ability to reduce semen infections (6). Currently, vaccination against HPV is globally available and represents an effective approach to mitigate virus-related damage. Expanding immunization programs could help reduce male-to-female HPV transmission, decrease miscarriage rates, and minimize HPV-related reproductive issues (2).

In Iran, policies aimed at increasing population growth and promoting childbearing are priorities to counteract population aging and protect national resources. Concurrently, preventing sexually transmitted infections remains a key focus for the healthcare system. Integrating HPV screening and vaccination into the country's Expanded Program of Immunization (EPI) could significantly contribute to achieving health system goals and advancing childbearing initiatives.

In summary, HPV plays a critical role in infertility by causing sperm damage and reducing sperm quality, ultimately affecting reproductive success rates. Screening and vaccination against HPV should be considered essential components of infertility treatments, although further analysis of their cost-effectiveness is needed. Additionally, investigating methods for natural viral clearance and developing specialized techniques to prepare seminal fractions for ART may prove beneficial. Increasing public awareness of the clear benefits of vaccination can dispel myths and foster greater acceptance of this preventive measure.

## Footnotes

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