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Original Research Article

Impact of human papillomavirus (HPV) prophylactic vaccination on infertile male patients with HPV semen infection: A systematic review

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Abstract

Purpose: *To characterize the impact of prophylactic vaccination against human papillomavirus (HPV) on infertile male patients with HPV semen infection.*
Methods: *This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. First, an electronic search of PubMed, Scopus and Web of Science databases from 2018 to 2023 using specific keywords was conducted. Thereafter, three authors independently screened the articles and removed duplicates. Following the acquisition of the papers, a quality analysis was conducted using the Strengthening the Reporting of Observational Studies in Epidemiology Criteria.*
Results: *A total of 41 pregnancies were reported out of which 15.3 % were in control group and 38.9 % were in the vaccinated group ($p < 0.05$). The clearance of HPV DNA correlated significantly with a serum HPV antibody titer of ≥ 1:125 at initial examination. Compared with individuals who tested negative for HPV, those who became seropositive at 12 ($p = 0.039$), 18 ($p = 0.034$) and 24 months ($p = 0.034$) had fewer multiple infections and a lower incidence of HPV infection in semen.*
Conclusion: *Examination of the association between male fertility and HPV reveals a clear correlation between HPV infection and male infertility, specifically asthenospermia and oligoasthenospermia. Further studies are needed to fully understand the benefits of this approach in managing male infertility.*

Keywords: *Human papillomavirus, HPV vaccine, Prophylactic vaccination, Infertility, Semen*

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INTRODUCTION

Human papillomavirus (HPV) is the most prevalent sexually transmitted virus worldwide [1]. HPV infection causes over 95 % of cervical cancer cases and is responsible for 630,000 cancer cases annually in men and women, posing a serious threat to global public health [2]. While young age and sexual activity are the primary risk factors for human papillomavirus infection, other factors such as inflammation of the affected area, smoking, oral contraceptive

use, other sexually transmitted diseases and immunocompromising conditions such as human immunodeficiency virus infection are also implicated as risk factors [3–5]. It belongs to the *Papillomaviridae* family, which comprises double-stranded DNA viruses [6–10]. Of the > 200 documented HPV genotypes, approximately 85 were identified in humans [11]. The species target specific epithelial tissues, such as the skin and anogenital mucosa, with some linked to genital lesions, including benign anogenital warts (AGWs) and cervical cancer [12].

Genital HPV is the most common sexually transmitted infection (STI) worldwide, with an estimated 75 % of sexually active individuals experiencing at least one HPV infection in their lifetime [13]. This virus can colonize several areas of the human body, including the uterus, cervix, external genitalia of both sexes, anorectal and even the oral and cutaneous regions. Additionally, infection with the virus is typically associated with sexual activity [12].

While women have been the primary focus of HPV-related studies, interest in male HPV infection is growing. Males also experience HPV infections and manifest symptoms, as well as act as carriers and transmit HPV [14]. In males, HPV causes cutaneous warts in the anal, oropharyngeal and penile regions. In addition, AGWs occur in males with respiratory papillomatosis [15]. HPV types 6 and 11 are associated with AGWs, while types 16 and 18 are linked to male penile and anal cancers [16–21]. The virus has also been found in male accessory glands such as seminal vesicles, prostate gland and the bulbourethral glands, potentially affecting seminal fluid production and fertility [22].

The increasing prevalence of infertility in couples engaging in unprotected sex necessitates an evaluation of the relationship between HPV and infertility, particularly in males [23]. Currently, three types of HPV vaccinations are administered worldwide: quadrivalent (qHPV), 9-valent (9vHPV) and bivalent [24,25]. These vaccines primarily target HPV types 16 and 18, which cause most HPV-associated cancers. The qHPV and 9vHPV vaccines also prevent HPV types 6 and 11, responsible for 90 % of genital warts [26]. The 9vHPV vaccine, approved in 2015, provides additional protection against five more oncogenic HPV strains, which account for 10 % of HPV-related cancer cases [27].

Vaccination against HPV is most effective when administered before sexual activity as it prevents new HPV infections rather than treating existing ones [28]. Vaccines can be administered to children as young as 9 years old and to all young women up to the age of 26 years who have not been previously vaccinated [27,29]. Young males up to 21 years of age, who have not been vaccinated, should receive the complete vaccination series [30]. The HPV vaccination series should be administered to all males up to the age of 26 years who have intercourse with other men, are immunocompromised or want to protect themselves from HPV infection [31].

While preventive vaccinations have shown protective benefits for women against genital condyloma and precancerous lesions, the cost-effectiveness of HPV vaccination for male infertility treatment has received less attention. The presence of HPV in semen is a growing concern for couples seeking assisted reproductive technologies, leading to its inclusion in infertility evaluations [32]. This review aims to characterize the impact of HPV prophylactic vaccination on infertile male patients with HPV semen infection.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-analysis criteria [33]. Electronic searches were conducted in the Web of Science, Scopus and PubMed databases. In PubMed, the MeSH terms "male infertility," "human papillomavirus," "papillomavirus vaccines," "papillomavirus infections," and "HPV vaccine" were used.

The types of participants were selected using patient (P), intervention (I), comparison (C) and outcome (O) systems, wherein P, I, C, and O indicate adult male patients with HPV-related infertility, HPV vaccination, no vaccination, and male fertility, respectively. The abstracts of the selected publications were reviewed, and those that fulfilled the selection criteria were retrieved. Subsequently, a quality analysis was conducted using the Strengthening the Reporting of Observational Studies in Epidemiology Criteria.

Inclusion criteria

Articles that reported analytic epidemiological cohort design; minimal bias risk; studies assessing the impact of HPV vaccination on male fertility during infertility consultations; HPV diagnosis confirmed in males with infertility; and articles published in English five years before August 11, 2023, were compiled.

Exclusion criteria

Earlier systematic reviews, conference papers, letters to the editor, correspondences, theses and studies on the use of HPV vaccination to treat genital warts and premalignant lesions were excluded.

Three authors (FA, HG and AB) independently performed the search and removed duplicate articles. In total, 53 papers were found in the initial search. Subsequently, 49 publications that did not fulfill our eligibility criteria were removed, and four papers were finally selected.

Reviewers retrieved data from the selected articles using an established format and evaluated them to obtain data independently. The authors included the studies and submitted them for evaluation by an unbiased advisor before deciding on their final inclusion through debate and consensus in case of an issue or conflict.

RESULTS

This review included four epidemiological cohort studies, three from Italy and one from the United States, comprising 1731 males receiving infertility consultations [32,34,35]. All studies met > 90 % of the STROBE quality criteria. Table 1 summarizes the selected studies.

In the first study, Garolla *et al* examined 151 males with infertility, with 79 receiving three doses of HPV vaccine [34]. After 12 months, the vaccinated group showed increased sperm motility and presence of anti-sperm antibodies ($p < 0.05$). Pregnancy rates were higher ($p < 0.05$) in the vaccinated group (38.9 %) compared to the control group (15.3 %). The control group experienced 5.5 % deliveries and 9.7 % spontaneous abortions. Secondly, De Toni *et al*. analyzed 379 patients with seminal HPV infections who received adjuvant HPV vaccination [35]. Genital HPV DNA clearance occurred in 86 % (326) of individuals and was significantly associated with an initial serum HPV antibody titer ≥1:125. Also, Foresta *et al*. observed a decrease in the viral DNA in the semen of 179 men with HPV-related infertility post-vaccination [32]. Seropositive individuals at 12 ($p = 0.039$), 18 ($p = 0.034$), and 24 ($p = 0.034$) months had fewer multiple infections and lower semen HPV infection rates compared to HPV-negative individuals ($p < 0.05$ for all timepoints). Lastly, McInerney *et al.* reported a lower HPV vaccination rate (2.5 %) among infertile males [36]. No significant difference in vaccination status was found between study completers (5.0 %) and non-completers (7.8 %). The association between vaccination and fertility ratio among vaccinated males was not significant ($p > 0.05$).

DISCUSSION

The hypothalamic-pituitary-gonadal axis controls hormones that affect spermatogenesis, sperm storage and sperm transport in the male reproductive system [37,38]. Sexually transmitted infections (STIs) disrupt this physiology, causing infertility with 15 % of male infertility cases attributed to STIs [39,40]. While most HPV infections in males are benign, limited information is available on their impact on male fertility. However, HPV has been linked to abnormalities in semen quality parameters and a higher incidence of miscarriage in assisted reproduction [41].

Infected males who received HPV vaccination had partners with reduced rates of spontaneous abortions, higher rates of pregnancy and healthy neonatal births [13]. Patients who received vaccination showed decreased HPV detection in both exfoliated cells and sperm, as well as increased sperm motility. All reported cases of spontaneous abortion in the control group were associated with HPV-positive DNA staining in spermatozoa [12]. HPV vaccination can benefit men with HPV-related infertility by improving semen quality, facilitating conception and ensuring normal delivery [32,34–36]. Observational studies provide moderate evidence for this, but vaccination rates among men remain low and available data are limited.

Studies has revealed a clear correlation between HPV infection and male infertility, specifically asthenospermia and oligoasthenospermia [40]. In cases of oligospermia, 33 and 18 % of semen samples were positive for HPV 16 and 18, respectively. Moreover, 83 and 73 % of males with HPV 16 or HPV 18 infection had asthenospermia [42]. Punjani *et al.* found high levels of papillomavirus DNA in infertile men and reported that partners of HPV-vaccinated men had a higher rate of normal pregnancies and deliveries, which resulted in healthy newborns [43]. Notably, all observed spontaneous abortions were linked to the presence of HPV in sperm. An Italian study demonstrated that vaccination effectively prevents and treats HPV-related diseases such as genital warts and malignant tumors [44]. This positively impacts semen quality parameters, suggesting that infertile males may benefit from vaccination.

Table 1: Characteristics of studies evaluating the effect of HPV vaccines on the treatment of male infertility

Author, Year, Country	Type of study	Objective	Study population (N, Age (Mean ± SD) years, Period (months))	Included sample (Vaccinated and unvaccinated)	Main results
Foresta *et al*., 2015, Italy [32]	Retrospective Cohort	Assess the efficacy of prophylactic vaccine-induced seroconversion on clearance in males with detectable HPV-DNA in their semen.	619 infertile couples, 37.1±7.4 years, 24 months	179 (91 and 88)	Vaccine-seropositive patients showed fewer multiple infections and lower HPV semen infection rates at 12, 18 and 24 months ($p < 0.05$) compared to non-seropositive. Vaccinated seropositive patients had better healing ($p = 0.001$ at 6 months, $p < 0.001$ at 12 months) and clearance at 12 months compared to seroconverted.
McInerney *et al*., 2017, USA [36]	Retrospective Cohort	Study the link between HPV vaccination and fecundability in conceiving couples.	1022 infertile couples, 31.8 years, 48 months	1022 (53 and 969)	Male vaccination rate was 5.2 %. Weak association between partner fertility and male vaccination (fertility rate = 1.07, 95 % CI: 0.79–1.46; $p > 0.05$). HPV vaccination did not significantly affect overall fertility. Limited data due to 51 % male participation.
Garolla *et al.*, 2018, Italy [34]	Retrospective Cohort	Investigate the impact of HPV vaccination on reproductive outcomes in males of infertile couples with HPV semen infection.	151 infertile couples, 32.6±3.0 years, 24 months	151 (79 and 72)	Vaccine group showed improved progressive sperm motility and anti-sperm antibodies ($p < 0.05$). Higher pregnancy rate in vaccine group (38.9 % vs 15.3 %, $p < 0.05$). Vaccine group: 29 deliveries, 1 miscarriage; Control group: 4 births, 7 miscarriages. HPV in sperm predicted negative pregnancy outcomes. Adjuvant vaccination linked to higher live births, spontaneous pregnancies and improved HPV clearance in semen.
De Toni *et al.*, 2020, Italy [35]	Retrospective Cohort	Analyze the relationship between the clearance of HPV infection from the genital tract and HPV adjuvant vaccination.	700 infertile couples, 40.3±0.6 years, 6 months	379 (379 and 0)	86 % (326/379) showed genital HPV DNA clearance. HPV antibodies in semen: 19.6 % responders, 45.3 % non-responders. Seroconversion: 39.3 % responders, 33.9 % non-responders. Median serum antibody titer: responders 1:97, non-responders 1:28. Serum antibody titer >1:125 indicated good prognosis for recovery.

Note: *HPV, human papillomavirus; VSPs, vaccine-sensitive patients; CI, confidence interval*

Male vaccination may also prevent HPV-related sperm degradation in donors, especially considering the lack of efficient HPV-eradicating sperm-washing techniques. Large-scale epidemiological studies are needed to provide high-quality evidence on this subject.

Limitation of this study

This systematic review complied with 95.2 % of the PRISMA 2020 assessment criteria. However, due to the limited number of studies and their quality, this review could not provide a comprehensive overview of this topic across diverse settings.

CONCLUSION

Current evidence is insufficient to definitively determine the efficacy of HPV vaccination in treating HPV-related male infertility. However, vaccination improves semen quality parameters and has been associated with increased pregnancy and birth rates in partners of vaccinated males. Further studies are needed to fully understand the benefits of this approach in managing male infertility.

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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