Zhaffal and Salame
Middle East Fertility Society Journal (2023) 28:6
https://doi.org/10.1186/s43043-023-00131-z

Middle East Fertility Society Journal

REVIEW

Open Access

Semen human papillomavirus (HPV) shedding in males: frequency, clinical significance, and reproductive outcomes—literature review

Mokhamad Zhaffal[1] and Anastasia Salame[2*]

Abstract

Background The interest in the HPV status of the male has risen after the discovery of HPV shedding in the semen. To date, there is no consensus on the true prevalence of male HPV infection, yet there is a rising body of evidence suggesting that male HPV infection might negatively affect the sperm parameters.

Main body The concern that HPV can lead to a couple's infertility and affect reproductive outcomes had increased after the multiple publications of semen criteria perturbations specifically the asthenospermia associated with HPV infection. An extensive literature review was performed to define the actual frequency of male HPV infection as well as the true extent of sperm analysis perturbations related to the HPV illness. We also intended to define the impact of these infections on reproductive outcomes and to highlight any treatment plans for affected couples.

Conclusion HPV is a prevalent disease with a rising concern among the male populations given the suggested impact on sperm motility as well as the pregnancy and miscarriage rates post-ART treatment. Vaccines are being studied now as a possible infertility adjunct treatment for males who are already infected.

Keywords HPV, Male infertility, Assisted reproductive techniques, Vaccine, Spermatozoa, Asthenozoospermia

Introduction

Human papillomavirus (HPV) is a small non-enveloped icosahedral virus with a double-stranded circular DNA, which multiplies in the basal layer of the stratified epithelium [1, 2]. More than 150 types of HPV have been identified, sequenced, and divided into high and low-risk types depending on their association with cancerous or benign lesions [3]. Although studies have shown a 40% prevalence worldwide in males and females, the true prevalence awaits to be determined since the gold standard diagnostic test for detecting subclinical infections is lacking [4, 5].

Extensive research revealed the presence of HPV DNA in the male genital tract as well as in the seminal fluid and sperm cells [6, 7]. Although the influence of viral shedding on sperm parameters remains poorly understood, there is a growing body of evidence suggesting a negative effect on sperm motility and male fertility overall [8, 9]. Also, based on assisted reproductive technique (ART) studies, it is speculated that when HPV-infected sperm is used in intracytoplasmic sperm injection (ICSI), fertilization, implantation, and embryo development is negatively affected [8, 10]. Hence, suspected semen infection

*Correspondence:
Anastasia Salame
dranastasiasalame@hotmail.com
[1] Obstetrics and Gynecology Department, Department of Obstetrics and Gynecology of Medicine and Health Sciences, Kanad Hospital, Adjunct Assistant ProfessorintheUAE University, Al Ain, United Arab Emirates
[2] Reproductive Endocrinology and Infertility Department, Fakih Fertility Center, Villa No. 2, Tawam Roundabout - Al Markhaniya, P.O. Box 31453, Al Ain, Abu Dhabi, United Arab Emirates

may lead to female partner inoculation, unexplained male infertility, fertilization failure, post-implantation failure, and increased miscarriage rates. Given the rising interest in male HPV infection and the growing concern about the potential negative impact on the reproductive outcomes of the affected couple, this review of the literature was performed. The aims of this review were to define the actual prevalence of male HPV infection, highlight the possible implications of the infection on the sperm parameters, and characterize the effect of that infection on reproductive outcomes whether through natural conception or through ART. We also aimed at drawing attention to the possible safety measures as well as treatments that can be implemented in case of male HPV infection to optimize treatment results.

Prevalence

HPV infects both males and females. Even though the bulk of the research done earlier focused on the female population, the interest in the male HPV status has risen after the discovery of HPV shedding in the semen. HPV DNA is believed to be generally bound to the equatorial region of the sperm head surface with approximately 25% of the sperm population can be found infected in one semen sample [7, 11]. There is no consensus on the true prevalence of male HPV infection as different studies used different HPV DNA detection techniques as well as sampled different male populations. One meta-analysis has shown that the method used to detect HPV DNA does affect the rate of positive results significantly especially in the infertile male population. It has been found that using type-specific primers in conjunction with the PCR techniques provided a higher detection rate when compared with the consensus type primers [12]. The numbers vary widely between the high-risk population with unsafe sexual practices where the average prevalence was found to be almost 31% and the general population with an average frequency of 7.8–12.4% [13, 14]. Other reports demonstrated that the infertile male population has a higher prevalence of HPV infection when compared to the general fertile population with a frequency of approximately 10.2–16% versus 2.2–10%, respectively [8, 15, 16]. It was noted that in the general male population, the frequency of high- and low-risk HPV infections was almost the same, contrary to the infertile male population where high-risk HPV infections were more prevalent. The highest prevalence of HPV infection in the general population was noted among European males (15.2%), while in the infertile male population, the highest frequency was noted among Latin American males (38.2%) [12] The prevalence of such infections has been found to be independent of the age of the male as the incidence of HPV infection remained stable above the age of 24 years [17]. Table 1 summarizes the articles included in this review.

HPV-positive status and semen parameters

Given that HPV was found to be more prevalent in the infertile population as already discussed in paragraph 3, a negative effect on the semen parameters could be anticipated. In that sense, a study performed by Schillaci et al. found no association between the HPV status of the male and the different abnormalities of the semen parameters [13]. Luttmer et al. supported the former's findings [16]. On the other hand, Damke et al. in a more recent study reported that HPV infections reflect negatively on the parameters of the semen analysis. The authors found that HPV-infected samples had a higher incidence of hypospermia and increased seminal viscosity ($p=0.01$ and 0.0002, respectively); however, the sperm motility was found to be unaffected ($p=0.5$) [19]. Nevertheless, multiple recent metanalyses did document an increased rate of asthenospermia in HPV-infected males especially in the infertile male population. Foresta et al. conducted a review on 1920 patients which showed that males suffering from idiopathic infertility not only had a higher incidence of HPV infection but also a significant deterioration of sperm motility [9]. In another meta-analysis, Weinberg et al. recently revealed a significantly increased incidence of asthenospermia, supporting the findings of Foresta et al. [9, 22]. As per Muscianisi et al. in the most recent systematic review, 11 out of the 14 studies included in the analysis concluded that HPV male infection was associated with an impairment in sperm parameters whether it is oligospermia, asthenospermia, teratozoospermia, or a combination of the three [21]. In addition, Boeri et al. found an increased DNA fragmentation index in HPV-infected semen contradicting the previously published reports [23–25]. Given the published data, there is a growing concern regarding the reproductive outcomes of ART treatment cycles especially since a meta-analysis by Lyu et al. in recent years suggested a strong association between a positive male HPV status and male infertility (OR = 2.93, 95% CI = 2.03–4.24) [12]. HPV infection however was not shown to eliminate the fertilization capacity of the sperm, and thus, the risk of transmission of HPV virions or DNA into the oocyte remains a possible risk [26].

HPV-positive status and reproduction/ART outcomes

Other than affecting semen parameters and potentially causing male infertility, the main concern is whether infected sperm can transfect oocytes upon fertilization, negatively affecting the reproductive potential of embryos and thus jeopardizing pregnancy outcomes. Despite that the debate is still ongoing on whether the

Table 1 Summary of the articles included in the review

Article	Type of article	Sample size	Groups assessed	Incidence of HPV infection	HPV effect on semen analysis	Reproductive outcomes
Foresta et al. (2010) [7]	Cross-sectional	290	General population, high-risk male population, and infertile patients	2.2% in the general population 10.2% in the infertile population	Reduced motility	Not available
Schillaci et al. (2013) [13]	Cross-sectional	308	Patients undergoing IVF treatment	7.8% in the general population	No significant impairment noted	Not available
Hebnes et al. (2014) [14]	Meta-analysis	8291/31	General and high-risk male population	12.4% in the general population 30.9% in the high-risk population	Not available	Not available
Laprise et al. (2014) [15]	Meta-analysis	4029/18	General population and fertility clinic attendees	10% in the general population 16% in clinic attendees	Not available	Not available
Garolla et al. (2016) [18]	Cross-sectional	226	Patients undergoing IUI/IVF treatment	23.9% in the infertile population	No significant impairment noted	Decreased pregnancy rate Increased miscarriage rate
Luttmer et al. (2016) [16]	Cross-sectional	430	Fertility clinic attendees	14.9% in the infertile population	No significant impairment noted	Not available
Damke et al. (2017) [19]	Cross-sectional	229	Fertility clinic attendees	16.6% in the infertile population	Hypospermia, abnormal seminal viscosity, higher mean pH, and higher mean numbers of leukocytes	Not available
Lyu et al. (2017) [12]	Meta-analysis	5194/31	General population and fertility clinic attendees	11.4% in the general population 20.4% in clinic attendees	Not available	Increased risk of infertility
Xiong et al. (2018) [20]	Meta-analysis	1955/8	Infertile males	Not available	Not available	Increased risk of infertility
Weinberg et al. (2020) [21]	Meta-analysis	2750/16	Patients undergoing IVF treatment	Not available	Motility significantly affected	Decreased pregnancy rate Increased miscarriage rate

incorporation of viral DNA takes place early on during spermatogenesis or later during the maturation stages of the sperm, there is an agreement that HPV-positive males can harbor the DNA material in the sperm. Thus, the apprehension that infected male gametes might transmit viral DNA to oocytes upon penetration at fertilization still exists. The repercussions on the embryos resulting from oocyte fertilization with infected sperm remain to be elucidated [27, 28]. In an attempt to highlight the effects of HPV DNA on embryos, scientists have cultured murine embryos in HPV DNA-containing media. A study published a while ago by Henneberg et al. showed that embryonic exposure to HPV DNA during the early stages of embryonic development (2 cells stage embryos) resulted in embryonic demise. The authors also reported that the blastulation rate decreased by a quarter when the embryos were cultured with HPV 16 and/or 18 DNA fragments [29]. Hong et al. cultured murine embryos in HPV-16-rich media. In comparison with the control group, the exposed murine embryos were found to form less adhesions, affecting the trophoblast function thus possibly preventing normal implantation without affecting the embryonic development per se [30]. The presumed decreased implantation potential is thought to be due to the accelerated HPV transfection-induced apoptosis in infected cells when compared to non-infected cells [10, 31]. The question that arises here is whether the findings with murine embryos could be extended to the human race. In humans, Perino et al. showed that when the male is HPV positive, while pregnancy rates were equal with the controls, the chances of miscarriage of the IVF-treated couple were higher (66.7% vs 15%) [32]. Garolla et al. demonstrated that HPV-positive semen samples were associated with a significant decline in the success rates of both intra-uterine insemination (IUI) and ICSI cycles which were reduced by half. It was also noted that cumulative pregnancy rates whether spontaneous or with ART were decreased as

well. The authors hypothesized that the isolated presence of HPV DNA in the semen in the setting of unexplained infertility might be the hindering factor [33]. This could be explained in part by the anti-sperm antibodies (ASA) as multiple reports highlighted a relationship between HPV infection and ASA in infected infertile males [21]. In the most recent metanalysis published by Weinberg et al., the results also supported the negative impact of male HPV infection on fertility treatment outcomes leading to lower pregnancy rates and higher miscarriage rates [22]. The exact mechanism leading to the reduced reproductive potential of human blastocysts resulting from HPV-infected sperm remains to be fully understood. It is worth mentioning that at this point, the life-long risks of fetal exposure to HPV infection whether in utero or upon delivery remain to be elucidated.

HPV status and partner/recipient safety

On another level, concern with seminal HPV infection is increasing especially in case the female partner of the infertile couple is HPV naive or when using donor semen for intra-uterine insemination. This poses health risks to the recipient patient other than fertility treatment failure particularly if the donor carries infectious agents that are contagious such as HIV, hepatitis B virus, CMV, and possibly HPV. As per the societies' recommendations, it is necessary to screen all donor semen samples for dangerous contagious agents. HPV, which can be harbored in the semen of clinically asymptomatic donors, is notorious for inducing a well-known range of medical conditions from benign warts to anogenital cancers. Given the presence of such theoretical risks screening for HPV in donors of semen might be valid and attempts at its eradication then should be implemented [15]. The previously suggested method that has been found to eradicate the viral DNA from the sperm was the modified swim-up technique at the expense of the decline of the sample quality [34]. Newer approaches with the addition of hyaluronidase enzyme to the modified swim-up technique have been evaluated. This method was shown to eliminate the HPV virions completely from an infected sperm without negatively affecting the quality of the sperm [18].

HPV prevention/management

In a trial to decrease the burden of HPV infections, Foresta et al. documented that introducing the quadrivalent HPV vaccine to males including those who already had HPV DNA in their semen had promising results. They demonstrated that the prophylactic HPV vaccination reduced the mean time for viral clearance which provides a new therapeutic approach for infertile HPV-infected males or donors who are already carriers of HPV infections [35]. Garolla et al. reported in a retrospective study, the improvement of the sperm parameters of HPV-infected males who received the vaccine in comparison with those who did not (79 vs 71). An improvement in the reproductive outcomes concerning the pregnancy and the miscarriage rates was also noted [36]. It is believed that in men, as in women, the active HPV infection is cleared from the system where the mean clearance time is estimated to be about 6 months; however, the new data suggests that HPV vaccine administration accelerated the rate of clearance [35]. Muscianisi et al. suggested using it as part of HPV-infected males' treatment to increase the chances of natural conception [21].

Limitations and recommendations

One of the main limitations of the findings of this review was that the studies that were included lacked standardized HPV detection methods. This might have contributed to the discrepancies between the different studies concerning the sperm parameters as well as the reproductive outcomes. Without standardization, screening of asymptomatic males would not be efficient due to the lack of sensitivity. The other point to keep in mind was the actual impact of these infections on reproductive outcomes as there was no consensus among the studies. Until we have more consistent evidence, we would assume that the application of standardized HPV testing in males who are at risk might be cost-effective. This category would include males with a history of unprotected sexual intercourse with multiple partners, males whose female partners were diagnosed with HPV, being a partner in a couple suffering from unexplained infertility, or if the male were found to have asthenospermia.

Conclusion

HPV is a prevalent disease with a rising concern among the male populations given the suggested impact on sperm motility as well as the pregnancy and miscarriage rates post-ART treatment. Vaccines are being studied now as a possible infertility adjunct treatment for males who are already infected.

Abbreviations

ART	Assisted reproductive techniques
ASA	Anti-sperm antibodies
DNA	Deoxyribonucleic acid
HPV	Human papillomavirus
ICSI	Intra-cytoplasmic sperm injection
IUI	Intrauterine insemination

Acknowledgements

None

Authors' contributions

AS did the literature review and wrote the manuscript. MZ helped write the manuscript. The authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Received: 13 October 2022 Accepted: 1 March 2023
Published online: 10 March 2023

References

1. Quint WGV et al (2006) Results of the first World Health Organization international collaborative study of detection of human papillomavirus DNA. J Clin Microbiol 44(2):571–579
2. Schiller JT, Day PM, Kines RC (2010) Current understanding of the mechanism of HPV infection. Gynecol Oncol 118(1):S12–S17
3. Ochsendorf FR (2008) Sexually transmitted infections: impact on male fertility. Andrologia 40(2):72–75
4. Barzon L, Militello V, Pagni S, Franchin E, Dal Bello F, Mengoli C, Palù G (2010) Distribution of human papillomavirus types in the anogenital tract of females and males. J Med Virol 82(8):1424–1430
5. Nasseri S, Monavari SH, Keyvani H, Nikkhoo B, Roudsari RV, Khazeni M (2015) The prevalence of human papilloma virus (HPV) infection in the oligospermic and azoospermic men. Med J Islam Repub Iran 29:272
6. Švec A, Mikyšková I, Hes O, Tachezy R (2003) Human papillomavirus infection of the epididymis and ductus deferens: an evaluation by nested polymerase chain reaction. Arch Pathol Lab Med 127(11):1471–1474
7. Foresta C, Pizzol D, Moretti A, Barzon L, Palù G, Garolla A (2010) Clinical and prognostic significance of human papillomavirus DNA in the sperm or exfoliated cells of infertile patients and subjects with risk factors. Fertil Steril 94(5):1723–1727
8. Garolla A, Pizzol D, Foresta C (2011) The role of human papillomavirus on sperm function. Curr Opin Obstet Gynecol 23(4):232–237
9. Foresta C, Noventa M, De Toni L, Gizzo S, Garolla A (2015) HPV-DNA sperm infection and infertility: from a systematic literature review to a possible clinical management proposal. Andrology 3(2):163–173
10. Gomez LM, Ma Y, Ho C, McGrath CM, Nelson DB, Parry S (2008) Placental infection with human papillomavirus is associated with spontaneous preterm delivery. Hum Reprod 23(3):709–715
11. Foresta C, Patassini C, Bertoldo A, Menegazzo M, Francavilla F, Barzon L, Ferlin A (2011) Mechanism of human papillomavirus binding to human spermatozoa and fertilizing ability of infected spermatozoa. PLoS ONE 6(3):e15036
12. Lyu Z, Feng X, Li N, Zhao W, Wei L, Chen Y, Yang W, Ma H, Yao B, Zhang K, Hu Z (2017) Human papillomavirus in semen and the risk for male infertility: a systematic review and meta-analysis. BMC Infect Dis 17(1):1–9
13. Schillaci R, Capra G, Bellavia C, Ruvolo G, Scazzone C, Venezia R, Perino A (2013) Detection of oncogenic human papillomavirus genotypes on spermatozoa from male partners of infertile couples. Fertil Steril 100(5):1236–1240
14. Hebnes JB, Olesen TB, Duun-Henriksen AK, Munk C, Norrild B, Kjaer SK (2014) Prevalence of genital human papillomavirus among men in Europe: systematic review and meta-analysis. J Sex Med 11(11):2630–2644
15. Laprise C, Trottier H, Monnier P, Coutlee F, Mayrand MH (2014) Prevalence of human papillomaviruses in semen: a systematic review and meta-analysis. Hum Reprod 29(4):640–651
16. Luttmer R, Dijkstra MG, Snijders PJ, Hompes PG, Pronk DT, Hubeek I, Berkhof J, Heideman DA, Meijer CJ (2016) Presence of human papillomavirus in semen in relation to semen quality. Hum Reprod 31(2):280–286
17. Desai S, Chapman R, Jit M, Nichols T, Borrow R, Wilding M, Linford C, Lowndes CM, Nardone A, Pebody R, Soldan K (2011) Prevalence of human papillomavirus antibodies in males and females in England. Sex Transm Dis 38(7):622–629
18. Garolla A, Engl B, Pizzol D, Ghezzi M, Bertoldo A, Bottacin A, Noventa M, Foresta C (2016) Spontaneous fertility and in vitro fertilization outcome: new evidence of human papillomavirus sperm infection. Fertil Steril 105(1):65–72
19. Damke E, Kurscheidt FA, Balani VA, Takeda KI, Irie MM, Gimenes F, Consolaro ME (2017) Male partners of infertile couples with seminal infections of human papillomavirus have impaired fertility parameters. Biomed Res Int. 2017:4684629
20. Xiong YQ, Chen YX, Cheng MJ, He WQ, Chen Q (2018) The risk of human papillomavirus infection for male fertility abnormality: a meta-analysis. Asian J Androl. 20(5):493
21. Weinberg M, Nahshon CSS, Feferkorn I, Bornstein J (2020) Evaluation of human papilloma virus in semen as a risk factor for low sperm quality and poor in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil Steril 113(5):955–969
22. Lai YM, Lee JF, Huang HY, Soong YK, Yang FP, Pao CC (1997) The effect of human papillomavirus infection on sperm cell motility. Fertil Steril 67(6):1152–1155
23. Muscianisi F, De Toni L, Giorato G, Carosso A, Foresta C, Garolla A (2021) Is HPV the novel target in male idiopathic infertility? A systematic review of the literature. Front Endocrinol 12:643539
24. Lee CA, Huang CT, King A, Chan PJ (2002) Differential effects of human papillomavirus DNA types on p53 tumor-suppressor gene apoptosis in sperm. Gynecol Oncol 85(3):511–516
25. Boeri L, Capogrosso P, Ventimiglia E, Pederzoli F, Cazzaniga W, Chierigo F, Pozzi E, Clementi M, Viganò P, Montanari E, Montorsi F (2019) High-risk human papillomavirus in semen is associated with poor sperm progressive motility and a high sperm DNA fragmentation index in infertile men. Hum Reprod 34(2):209–217
26. Kaspersen MD, Bungum M, Fedder J, Bonde J, Larsen PB, Ingerslev J, H. and Höllsberg, P. (2013) No increased sperm DNA fragmentation index in semen containing human papillomavirus or herpesvirus. Andrology 1(3):361–364
27. Cortés-Gutiérrez EI, Dávila-Rodríguez MI, Fernández JL, de la O-Pérez, L.O., Garza-Flores, M.E., Eguren-Garza, R. and Gosálvez, J. (2017) The presence of human papillomavirus in semen does not affect the integrity of sperm DNA. Andrologia 49(10):e12774
28. Lai YM, Yang FP, Pao CC (1996) Human papillomavirus deoxyribonucleic acid and ribonucleic acid in seminal plasma and sperm cells. Fertil Steril 65(5):1026–1030
29. Kadze R, Chan PJ, Jacobson JD, Corselli JU, King A (2002) Temperature variable and the efficiency of sperm mediated transfection of HPV16 DNA into cells. Asian journal of andrology 4(3):169–174
30. Hong LJ, Oshiro BT, Chan PJ (2013) HPV-16 exposed mouse embryos: a potential model for pregnancy wastage. Arch Gynecol Obstet 287(6):1093–1097
31. Boulenouar S, Weyn C, Van Noppen M, Moussa Ali M, Favre M, Delvenne PO, Bex F, Noël A, Englert Y, Fontaine V (2010) Effects of HPV-16 E5, E6 and E7 proteins on survival, adhesion, migration, and invasion of trophoblastic cells. Carcinogenesis 31(3):473–480
32. Henneberg AA, Patton WC, Jacobson JD, Chan PJ (2006) Human papilloma virus DNA exposure and embryo survival is stage specific. J Assist Reprod Genet 23(6):255–259
33. Spandorfer SD, Bongiovanni AM, Fasioulotis S, Rosenwaks Z, Ledger WJ, Witkin SS (2006) Prevalence of cervical human papillomavirus in women undergoing in vitro fertilization and association with outcome. Fertil Steril 86(3):765–767
34. Perino A, Giovannelli L, Schillaci R, Ruvolo G, Fiorentino FP, Alimondi P, Cefalù E, Ammatuna P (2011) Human papillomavirus infection in couples undergoing in vitro fertilization procedures: impact on reproductive outcomes. Fertil Steril 95(5):1845–1848

35. Depuydt CE, Donders GGG, Verstraete L, Broeck DV, Beert JFA, Salembier G, Bosmans E, Ombelet W (2019) Infectious human papillomavirus virions in semen reduce clinical pregnancy rates in women undergoing intrauterine insemination. Fertil Steril 111(6):1135–1144
36. Gizzo S, Ferrari B, Noventa M, Ferrari E, Patrelli TS, Gangemi M, Nardelli GB (2014) Male and couple fertility impairment due to HPV-DNA sperm infection: update on molecular mechanism and clinical impact—systematic review. Biomed Res Int. 2014

Publisher's Note