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SYSTEMATIC REVIEW

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# Papillomavirus infection and male infertility: A systematic review and meta-analysis

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## Abstract

**Background and Aims:** Increasing attention is being paid to the role of human papillomavirus (HPV) in men and specifically reproduction. Growing evidence suggests an association between HPV infection with many adverse effects including the impairment of semen parameters, the increase of blastocyst apoptosis, the reduction of endometrial implantation of trophoblastic cells, as well as the increase rate of miscarriages and spontaneous preterm birth.

**Methods:** We systematically searched PubMed/MEDLINE, Scopus, Embase, Web of Science, CINHAL, PsycINFO, and ERIC from inception to 2nd of July 2024, for studies that investigated the association between HPV infection with sperm parameters and fertility outcomes. The meta-analysis was conducted on mean data and standard deviations.

**Results:** We included 25 studies with a total of 6942 patients. Sperm morphology was lower in HPV positive groups versus HPV negative control groups (SMD = -0.52 95% CI −0.84; −0.21; $p = 0.001$). Sperm motility was also significantly lower in HPV positive groups when compared to HPV negative controls (SMD = −0.82 95% CI −1.07; −0.57; $p = <0.001$). Sperm volume, concentration, and pH were not significantly different between the two groups. The other 15 studies included in the systematic review for which it was not possible to conduct a meta-analysis showed strong associations between HPV infection and impairment of sperm parameters, reduced couple fertility and increased risk of pregnancy loss.

**Conclusions:** The current evidence highlights the link between HPV infection and sperm parameters, male fertility and reproductive outcomes, which has the potential to lead to a decreased couple fertility, increased risk of pregnancy loss, re-infection and increased treatment costs.

KEYWORDS

sperm quality, sperm parameters, male infertility, HPV

## 1 | INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted viral infection worldwide affecting both males and females.[1] There are more than 200 known subtypes including High-Risk-HPV (HR-HPV) and Low-Risk HPV based on their oncogenic potential.[2] It has been shown that most sexually active men and women acquire at least one HPV infection at some point in their lives and, some of them, could be repeatedly infected although most infections remain asymptomatic.[3] Interestingly, the global prevalence of HPV infection in women with normal cytology is around 11–12%, with the highest prevalence in sub-Saharan Africa at 24%, Eastern Europe 21% and Latin America 16%. Moreover, HPV prevalence peaks in adolescence and those under 25 years old.[4] Although HPV infection in men is less investigated than in woman, the global prevalence in men is estimated to be ~30% with the infection peak between the ages of 25 and 29 years and a HR-HPV prevalence of 21%.[1] In general, HPV clinical manifestation in men includes anogenital warts and penile, anal, and oropharyngeal cancers and recurrent respiratory papillomatosis.[5,6] For women, The World Health Organization (WHO) guidelines recommend using HPV DNA detection every 5–10 years as a primary screening test for those aged between 30 and 50 years and, when HPV DNA is not available, visual inspection after acetic acid application or cytology every 3 years.[7] Although sexually active men are at risk of HPV-related morbidity and represent a reservoir for HPV, there is no standardized approach for screening in men.[8] However, increasing attention is being paid to the role of HPV in men also due to its role in reproduction. Indeed, growing evidence suggests associations between HPV infection with multiple adverse effects including the impairment of semen parameters, the increase of blastocyst apoptosis, the reduction of endometrial implantation of trophoblastic cells, the increase rate of miscarriages, and spontaneous preterm birth.[9] Interestingly, men affected by idiopathic infertility show a higher prevalence of HPV infection, asthenozoospermia and anti-sperm antibodies (ASAs) compared with the general population.[10] Moreover, HPV in semen has been demonstrated to also have an impact on reproductive outcomes.[11] To date, the role of HPV in male and couple fertility it is not fully understood and the scientific literature addressing male aspects remains less documented than for females. The aim of this review and meta-analysis was to assess associations between HPV infection with sperm parameters and its correlation with couple fertility.

## 2 | METHODS

This systematic review adhered to the PRISMA[12] and MOOSE[13] statements and followed a structured protocol registered on PROSPERO (CRD42024510030).

### 2.1 | Data sources and literature search strategy

Two investigators (MT and DP) independently conducted a literature search using PubMed/MEDLINE, Scopus, CINAHL, Embase, PsycINFO, Web of Science and ERIC from inception until July 2nd, 2024. Any inconsistencies were resolved by consensus with a third author (LS).

In PubMed, the following search strategy was used: ("Human Papillomavirus" OR "Papillomaviridae" OR HPV) AND ("male fertil*" OR "male infertil*" OR "male subfertil*" OR "fertil* men" OR "infertil* men" OR "subfertil* men" OR "Sperm" OR "Sperm quality" OR "Sperm count" OR "Sperm volume" OR "Sperm motility" OR "Sperm vitality" OR "Sperm antibodies" OR "Sperm pH" OR "Sperm viscosity" OR "Sperm morphology" OR "Sperm DNA" OR "sperm DNA fragmentation" OR "Sperm DNA integrity" OR "semen quality" OR "semen parameters"). Conference abstracts and reference lists of included articles were hand-searched to identify any potential additional relevant work.

### 2.2 | Study selection

Following the PICOS (participants, intervention, controls, outcomes, study design) criteria, we included studies assessing the influence of HPV infection on sperm parameters and fertility outcomes in observational (case-control, cross-sectional, cohort) studies.

The WHO sperm parameters values were considered as reference values.[14]

Studies were excluded if the data were not analyzable; in vitro studies; if it was not possible to consider separated groups (HPV positive and negative) or if they did not clearly report data regarding sperm parameters or fertility outcomes. No language restriction was a priori applied.

### 2.3 | Data extraction

For each eligible study, two independent investigators (MT and DP) extracted: name of the first author and year of publication, setting, sample size, mean age of the population, mean body mass index (BMI), HPV status and genotype, sperm parameters, and fertility outcomes. Data about matching and method (i.e. propensity score) were planned to be extracted between infected and controls, but no study included this information. Any inconsistencies were resolved by consensus with a third author (LS).

### 2.4 | Outcomes

The primary outcomes considered regarded sperm parameters investigated as sperm count, volume, concentration, motility, vitality, morphology, ASAs, DNA fragmentation, chromatin damage and reproductive outcomes. All parameters were reported in the original papers as mean with standard deviations (SDs).

### 2.5 | Assessment of study quality

Two independent authors (MT and DP) carried out the quality assessment of included studies' using the Newcastle-Ottawa Scale

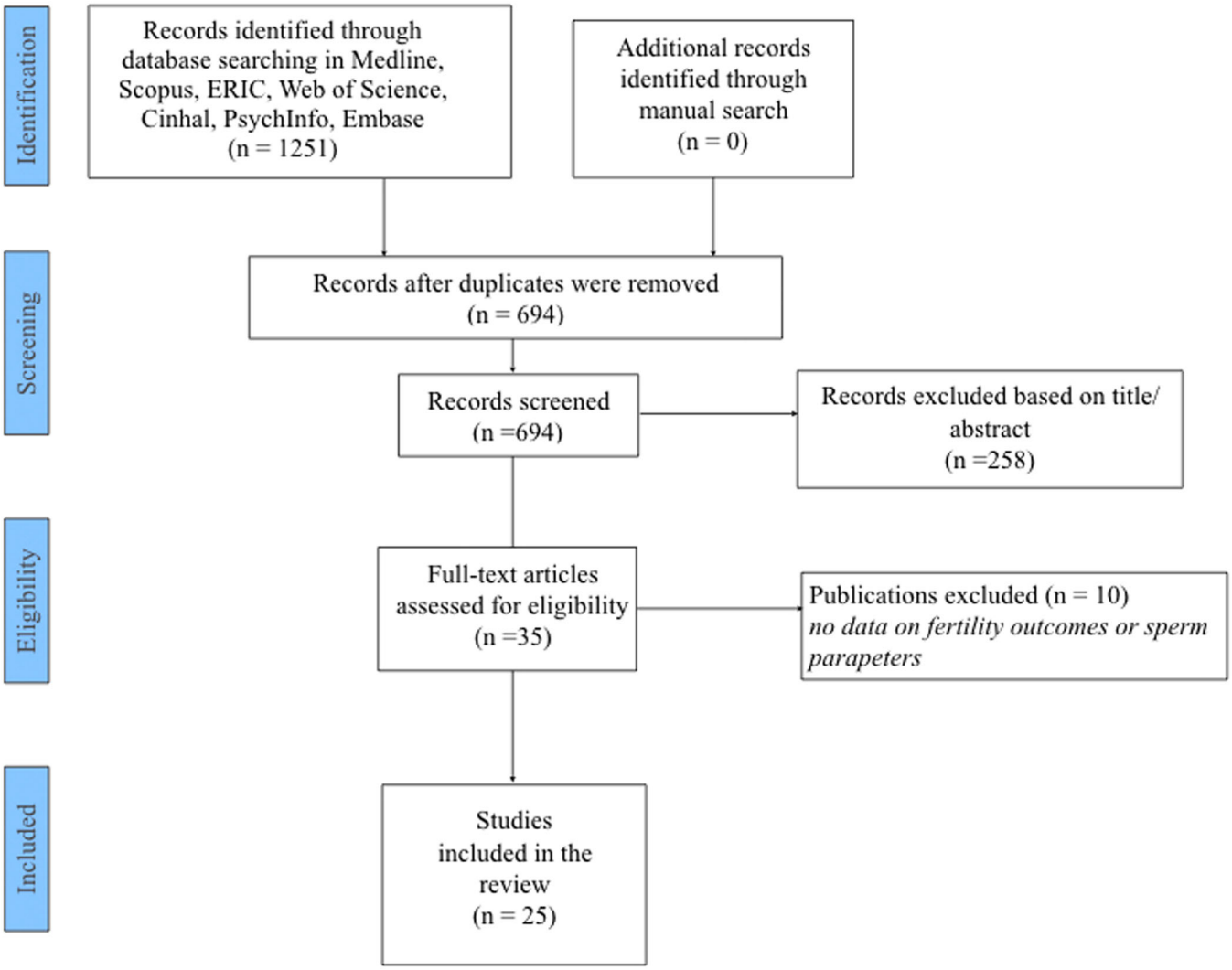


**FIGURE 1** PRISMA flow chart.

(NOS).[15] The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome.[16] Any inconsistencies were resolved by consensus with a third author (LS).

## 2.6 | Data synthesis and statistical analysis

All analyses were performed using the meta package inR.[17] For all analyses, a two-sided *p* value less than 0.05 was considered statistically significant. Studies were eligible for inclusion in the meta-analysis if mean data and standard deviations were available for variables in both the H PV+ and HPV- groups. If studies had more than one outcome within the same domain (e.g., two outcomes relating to sperm volume), both the HPV+ and control groups were required to be independent to be included (e.g. the outcomes could not share the same control group).

For all analyses, a random effects meta-analysis using the DerSimonian method[18] was employed, with studies weighted on their inverse variance. Publication bias was assessed using the Egger's test.[19] Heterogeneity was assessed using the $I^2$ statistic.

### 2.6.1 | Sensitivity analyses

To determine the robustness of results, a sensitivity analysis was performed using the one-study removed method.

### 2.6.2 | Credibility of evidence

The credibility of all results was classified according to the GRADE criteria, initially based on guidelines proposed by Schünemann et al.[20]

# 3 | RESULTS

## 3.1 | Literature search

As shown in Figure 1, 694 articles were initially screened and 35 full texts were retrieved. Among them, 25[21–45] studies were finally included in the systemic review.

**TABLE 1** Main information and findings of sperm parameters of included studies.

| Study | Country | Sample size | Detection | HPV positive | | | | | | HPV negative | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Count | Volume | Concentration | Motility | pH | Morphology | Count | Volume | Concentration | Motility | pH | Morphology |
| Boeri, 2018[22] | Italy | 729 | PCR | NA | 3,0 | 10,9 | 16 | NA | 1,0 | NA | 3,0 | 12,4 | 22,0 | NA | 2,0 |
| Cannarella, 2021[24] | Italy | 40 | PCR | 67,4 | NA | 24,8 | 50,25 | NA | 18,5 | 73,0 | NA | 25,7 | 58,8 | NA | 20,5 |
| Capra, 2022[25] | Italy | 117 | PCR | 116,5 | 3 | 38,3 | 43,7 | NA | 4,4 | 123,5 | 2,8 | 49,6 | 46 | NA | 8,5 |
| Damke, 2017[26] | Brazil | 229 | PCR | 46 | 2,9 | NA | 42,4 | 7,8 | NA | 48 | 3,5 | NA | 49,8 | 7,7 | NA |
| De Lima Bossi, 2019[27] | Brazil | 25 | PCR | NA | NA | 62,3 | 65 | NA | NA | NA | NA | 65,9 | 46,6 | NA | NA |
| Didelot-rousseau, 2007[29] | France | 62 | PCR | 3,2 | NA | NA | NA | NA | NA | 16 | NA | NA | NA | NA | NA |
| Faja, 2024[31] | Italy | 177 | PCR | 98 | 2,5 | 37,5 | 40 | NA | 10 | 108 | 3 | 42 | 45 | NA | 10 |
| Foresta, 2010[32] | Italy | 26 | PCR e FISH | NA | 2,6 | 53,5 | 36,2 | 7,7 | 32,6 | 177,1 | 0,8 | NA | 56,2 | 7,4 | 36,3 |
| Foresta, 2010[32] | Italy | 66 | PCR e FISH | NA | 2,8 | 48,5 | 38,4 | 7,6 | 31,8 | 178,4 | 2,5 | NA | 53,8 | 7,7 | 31,8 |
| Foresta, 2010[32] | Italy | 108 | PCR e FISH | NA | 2,9 | 30,0 | 33,9 | 7,7 | 32,9 | 102,9 | 3,0 | NA | 51,7 | 3,0 | 33,1 |
| Foresta, 2010[32] | Italy | 90 | PCR e FISH | NA | 2,5 | 60,5 | 55,5 | 7,6 | 33,5 | 176 | 2,6 | NA | 54,2 | 7,7 | 33,0 |
| Garolla, 2012[33] | Italy | 35 | PCR e FISH | 87,7 | 3,1 | 29,0 | 29,6 | 7,6 | 19,0 | 98,8 | 3,3 | 30,5 | 42,4 | 7,5 | 21,1 |
| Garolla, 2013[34] | Italy | 165 | Inno-Lipa, FISH | 94,2 | NA | 32 | 29,0 | NA | 18,8 | 108,8 | NA | 34.6 | 47,8 | NA | 18,5 |
| Garolla, 2015[35] | Italy | 226 | FISH | 145,6 | 2,3 | 58,9 | 25,9 | NA | 16,2 | 131,9 | 2,7 | 52,2 | 34,3 | NA | 14,8 |
| Jaworek, 2021[33] | Czech Republic | 97 | PCR | 161,5 | 4,8 | 31,2 | 50 | 7,3 | 10,5 | 167,2 | 3 | 56,5 | 51,5 | 7.4 | 11 |
| Jaworek, 2021[36] | Czech Republic | 328 | PCR | 33 | 2 | 13 | 53 | 8 | 5 | 71,8 | 3 | 26 | 58,5 | 8 | 7 |
| Lai,1997[37] | China | 24 | PCR | NA | NA | NA | 40,4 | NA | 75 | NA | NA | NA | 62,7 | NA | 79,3 |
| Luttmer, 2016[38] | The Netherlands | 430 | PCR | 157,5 | 3,1 | 52,1 | 60,2 | 8,1 | NA | 189,3 | 3,4 | 57,5 | 57,9 | 8,1 | NA |

TABLE 1 (Continued)

| Study | Country | Sample size | Detection | HPV positive | | | | | | HPV negative | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Count | Volume | Concentration | Motility | pH | Morphology | Count | Volume | Concentration | Motility | pH | Morphology |
| Moghimi, 2019[39] | Iran | 70 | PCR | NA | NA | 51,38 | 23,50 | NA | 7,13 | NA | NA | 60,71 | 32,21 | NA | 15,18 |
| Niakan, 2023[40] | Iran | 140 | PCR | NA | 4,26 | 49,33 | 47,28 | 7,76 | 1,55 | NA | 3,91 | 58,96 | 50,72 | 7,69 | 2 |
| Rintala, 2004[42] | Finland | 65 | PCR | 297,1 | 3,7 | 96,5 | 54,2 | 7,37 | NA | 412,1 | 4,4 | 108,7 | 56,5 | 7,51 | NA |
| Tongal, 2019[43] | Turkey | 117 | PCR | NA | NA | 24 | NA | NA | 4 | NA | NA | 20 | NA | NA | 4 |
| Yang, 2013[44] | China | 615 | PCR | NA | 2,67 | 111,31 | 20,55 | 7,3 | 4,66 | NA | 2,65 | 120,96 | 29,11 | 7,26 | 8,15 |
| Yang, 2013[44] | China | 523 | PCR | NA | 2,31 | 114,42 | 32,25 | 7,03 | 8,51 | NA | 2,72 | 117,52 | 39,22 | 7,3 | 13,01 |

## 3.2 | Descriptive findings and quality assessment

The 25 included studies were carried out mainly in Europe ($n = 16$), Asia ($n = 6$), South America ($n = 2$) and Middle-East ($n = 1$). Overall, 6942 participants (range: 24–1173) were included having a mean age, for studies with available data, of 35 years (range: 31.16–39.2).

The median quality of the studies was 5.32 (range: 4–7), indicating an overall good quality of the studies, according to the NOS.

## 3.3 | Influence of HPV infection on sperm parameters

Table 1 reports the main information and findings of sperm parameters of included studies. A total of 10 studies with 14 independent outcomes had enough data to be included in the meta-analysis. A total of 10 studies (with 14 independent outcomes) examined sperm motility and sperm morphology, eight studies (nine outcomes) examined sperm concentration, five studies (ten independent outcomes) examined sperm volume, and four studies (eight independent outcomes) examined sperm pH.

Full meta-analysis results can be found in Table 2 and Figures 2–6. Sperm morphology was significantly lower in HPV+ groups versus HPV- control groups (SMD = −0.52 95% CI −0.84; −0.21; $p = 0.001$). Sperm motility was also significantly lower in HPV+ groups when compared to HPV-controls (SMD = −0.82 95% CI −1.07; −0.57; $p = <0.001$). Sperm volume, concentration, and pH were not significantly different. Sensitivity analyses revealed that the removal of any one study did not affect the significance of any outcome.

## 3.4 | Fertility and reproductive outcomes

Table 3 reports the main information and findings on fertility and reproductive outcomes of included studies. Female HPV infection was associated with lower rates of implantation, biochemical pregnancy, and clinical pregnancy as well as with a slightly higher frequency of biochemical miscarriage and clinical miscarriage.[21] The presence of HPV infection in sperm impacts negatively on assisted reproduction with a reduction of clinical pregnancies[28,30,45] and increase in pregnancy loss.[23,41]

# 4 | DISCUSSION

The findings of our systematic review and meta-analysis suggest a role of HPV infection in men both in impairing sperm parameters and in affecting pregnancy outcomes. In terms of sperm parameters, sperm morphology and motility were lower in HPV positive males compared to HPV negative. These results are in line with one previous review focusing on sperm quality.[46] However, sperm volume, concentration, and pH did not show significant differences between HPV infected males and those not infected. Possible mechanisms

**TABLE 2** Full meta-analysis results.

| Outcome | *k studies* (*n* outcomes) | Meta-analysis SMD (95% CI) | *p* value | Heterogeneity $I^2$ | Publication bias Egger's *p* value | Level of certainty |
|---|---|---|---|---|---|---|
| Sperm volume | 5 (10) | 0.14 (−0.11; 0.40) | 0.266 | 67.9 | 0.30 | NS |
| Sperm concentration | 9 (8) | −0.33 (−0.67; 0.01) | 0.057 | 85.3 | NA | NS |
| Sperm motility | 10 (14) | −0.82 (−1.07; −0.57) | <0.001 | 73.6 | 0.54 | Moderate[a] |
| Sperm pH | 4 (8) | 0.53 (−0.16; 1.22) | 0.133 | 93.6 | NA | NS |
| Sperm morphology | 9 (14) | −0.52 (−0.84; −0.21) | 0.001 | 84.2 | 0.96 | Moderate[a] |

Abbreviations: SMD, standardized mean difference; NA, not applicable due to number of studies under 10; NS, not significant

[a]Downgraded due to high heterogeneity.

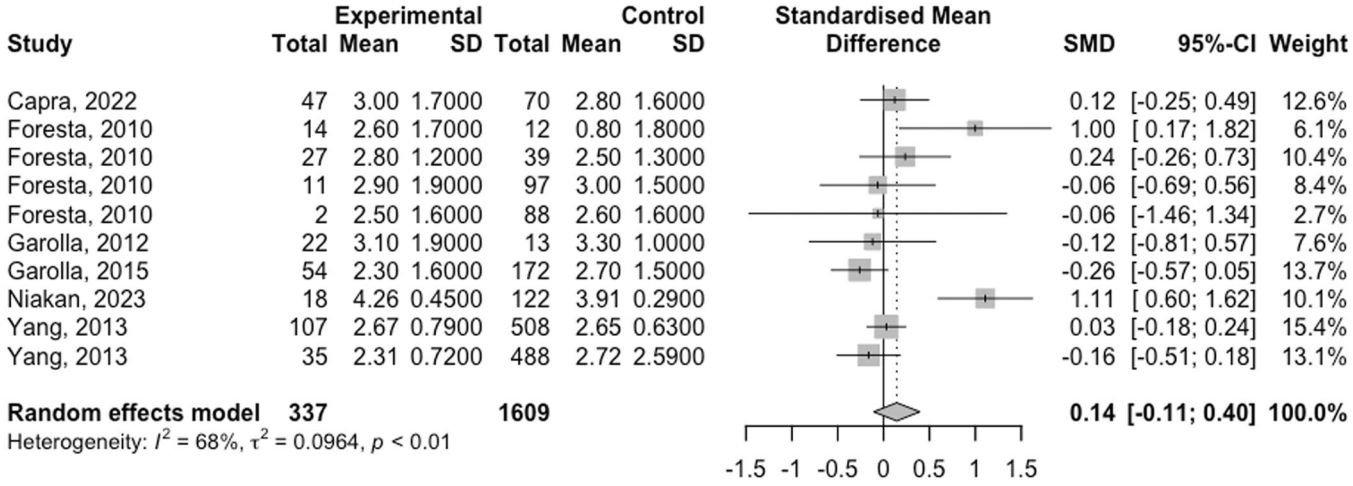


**FIGURE 2** Sperm volume levels in HPV+ populations vs. HPV- controls.

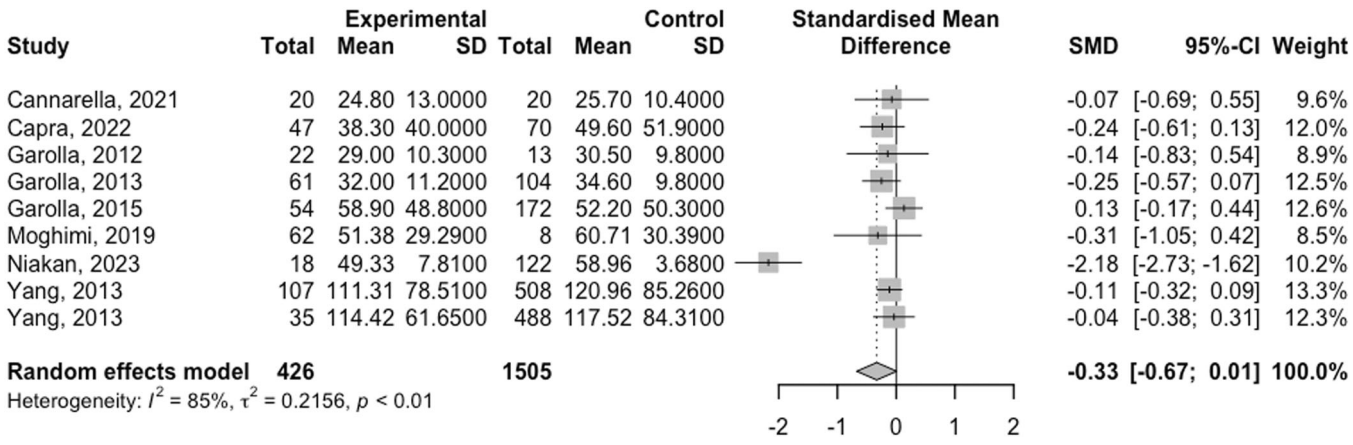


**FIGURE 3** Sperm concentration levels in HPV+ populations vs. HPV- controls.

hypothesized for explaining impairment in parameters is likely owing to the presence of HPV itself and the highest presence of ASA.[34] Indeed, previous literature has demonstrated an interaction between HPV with sperm receptors localized in the equatorial region of the sperm head.[47] Moreover, the presence of HPV in the sperm is frequently associated with ASAs in infertile patients.[34,38] Moreover, ASAs may affect male fertility through sperm agglutination and impaired cervical mucus penetration, complement-mediated sperm injury through the female genital tract, and interference with gametes interaction.[34] Considering that autoimmune infertility is often treated by assisted reproduction techniques (ART) and that these procedures can be ineffective in the presence of HPV sperm infection, it is

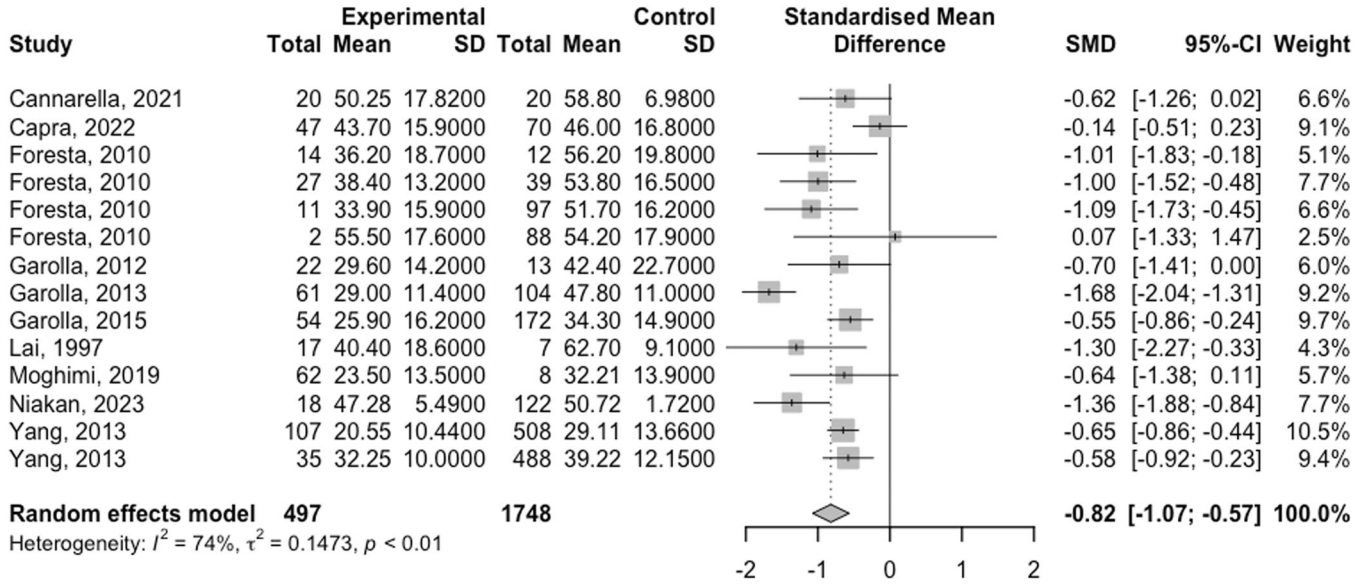


**FIGURE 4** Sperm motility levels in HPV+ populations vs. HPV- controls.

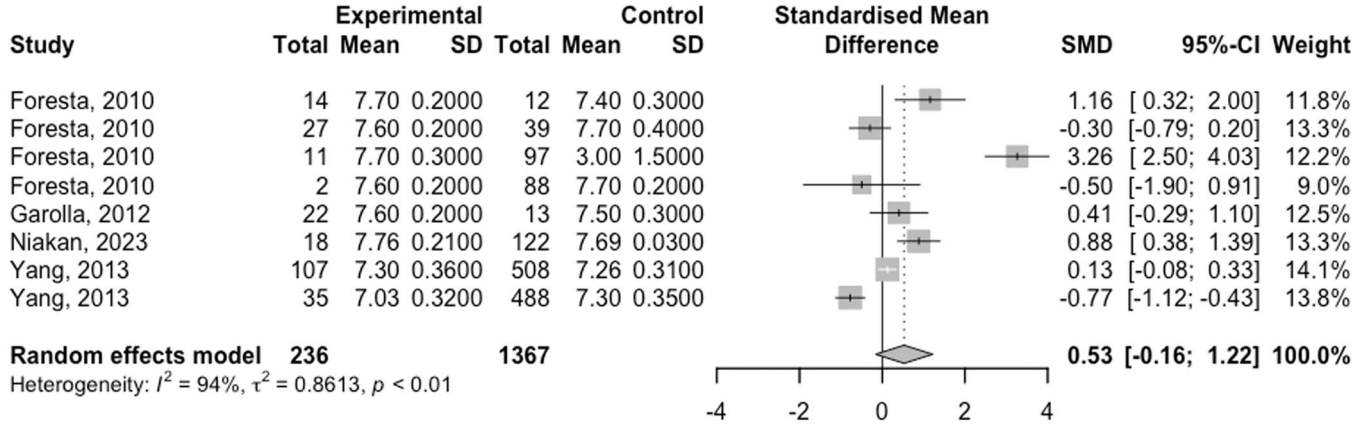


**FIGURE 5** Sperm pH levels in HPV+ populations vs. HPV- controls.

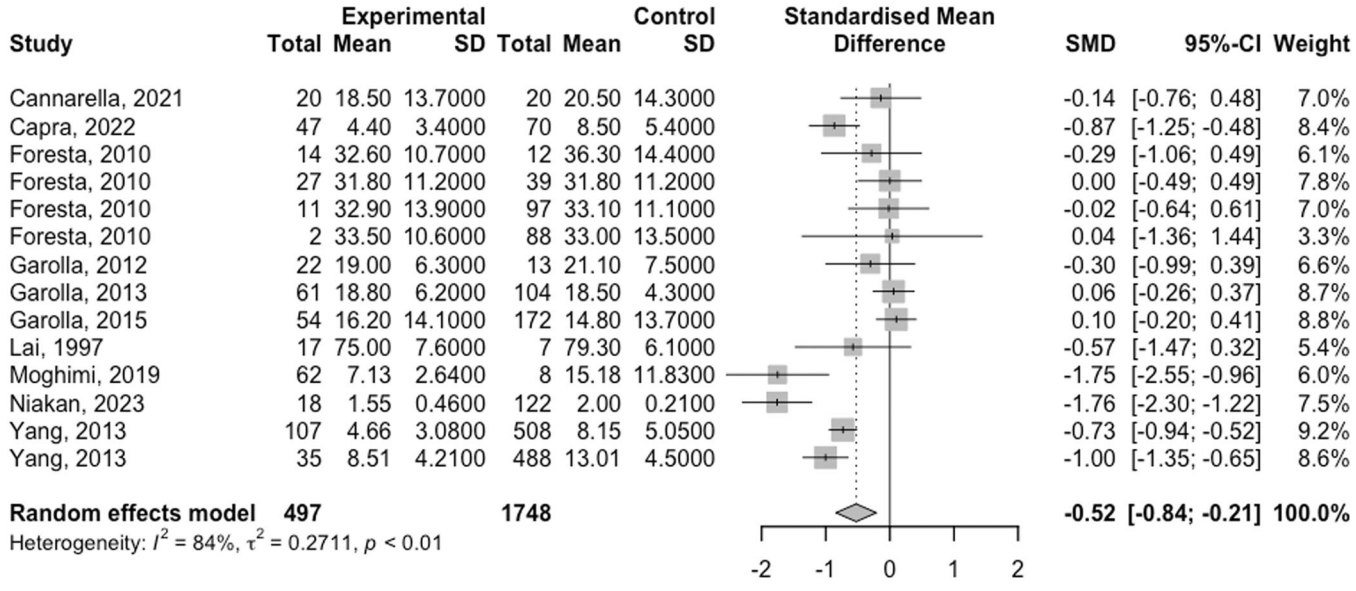


**FIGURE 6** Sperm morphology levels in HPV+ populations vs. HPV- controls.

**TABLE 3** Main information and findings on fertility and reproductive outcome of included studies.

| Author and date | Aim | Study type | Sample size and characteristics | Outcome measures | Findings |
|---|---|---|---|---|---|
| Bai, 2024[21] | To assess the effects of intrauterine HPV on ART outcomes in infertile couples | Cohort Study | 4153 infertile women undergoing IVF or ICSI treatment | Pregnancy and clinical miscarriage rates in the transfer cycle underwent HPV detection | Uterine cavity HPV infection resulted in lower rates of ongoing, implantation, biochemical pregnancy, and clinical pregnancy compared with HPV negative group. The infertile female with positive HPV also had a slightly higher frequency of biochemical miscarriage and clinical miscarriage. |
| Busnelli, 2023[23] | To assess the association between HPV sperm infection and idiopathic recurrent pregnancy loss | Case-control | 117 cases were men of couples affected by first trimester idiopathic recurrent pregnancy loss. 84 controls were men of couples with proven fertility | The association between HPV sperm infection and recurrent pregnancy lost | The prevalence of HPV sperm infection was significantly higher in couples affected by recurrent pregnancy lost than in their controls. The semen sample was infected by HPV in approximately 1 out of 5 patients. |
| Depuydt, 2019[28] | To study the influence of HPV in sperm of male partners of women undergoing IUI | Cohort study | 7320 infertile couples undergoing 1753 IUI cycles | Biochemical and clinical pregnancy rate in IUI | Women inseminated with HPV positive sperm had 4 times fewer clinical pregnancies compared with women who had HPV negative partners. |
| Depuydt, 2021[30] | To determine the sperm DNA fragmentation and HPV infection impact on clinical pregnancies in women undergoing IUI | Cohort study | 161 infertile couples going through 209 cycles of IUI | Clinical pregnancies in women undergoing IUI | Both the sperm DNA fragmentation and HPV infection negatively impacted IUI. When HPV was present in sperm, no clinical pregnancies were observed. |
| Perino, 2011[41] | To assess the relationship between HPV infection in and ART outcome | Cohort study | Of 199 couples, 33 underwent oocyte insemination, and 166 intracytoplasmic sperm injection. | Clinical pregnancy rate and pregnancy loss rate | A highly statistically significant correlation between pregnancy loss rate and positive HPV DNA testing in the male was observed. No statistically significant differences in term of pregnancy rate. |
| Zhang, 2019[45] | To demonstrate the association of HPV infection and pregnancy, delivery and neonatal outcome in women undergoing IUI | Cohort study | 329 women undergoing IUI | Clinical pregnancy rate, miscarriage rate, live birth rate, gestational weeks, neonatal weight, sex, and delivery mode | HPV infection could reduce clinical pregnancy rate and live birth rate significantly of women undergoing IUI. There was no significant difference for miscarriage rate. Gestational weeks showed significant difference between two groups while no difference was noted in neonatal weight, sex or delivery mode. |

Abbreviations: ART, assisted reproduction technologies; HPV, Human Papillomavirus; ICSI, intracytoplasmic sperm injection; IVF, In vitro fertilization.

recommended screening for HPV in all asymptomatic subjects with ASAs.

Studies assessing pregnancy and ART outcomes related to HPV infection are still too limited to perform any statistical analysis, but important considerations can be drawn from existing literature. Indeed, Perino et al. found a significant increased risk of pregnancy loss in couples who underwent ART when HPV was present in sperm.[41] Another study reported the reduction in both natural and assisted cumulative pregnancy rate and an increase in miscarriage rate in association with the presence of HPV at sperm level.[35] Interestingly, women underwent intra uterine insemination with HPV positive sperm showed 4 times fewer clinical pregnancies compared with those with negative partners.[28] Recently, another study revealed that the prevalence of HPV sperm infection is significantly higher in couples affected by recurrent pregnancy loss compared to controls.[23] Similar results have been observed also in cases of positive women. Indeed, women with HPV infection are associated with lower rates of implantation, biochemical pregnancy, and clinical pregnancy as well as with a slightly higher frequency of biochemical miscarriage and clinical miscarriage.[21,48] Again, in one study HPV positive women which underwent intrauterine insemination had six times less pregnancies than those wo were HPV negative.[49]

Several mechanisms have been hypothesized by which HPV infection can lead to infertility and its negative impact on the success of spontaneous and assisted reproduction could be related to the alteration of sperm parameters, induction of DNA damage, and genomic instability.[50] Moreover, in vitro studies found that HPV-transfected trophoblast cells have an increased rate of stage-specific maturation arrest and apoptosis and a reduced placental invasion into the uterine wall compared with control cells.[35] Moreover, HPV can compromise trophoblast engraftment and embryo development, leading to pregnancy loss.[9] Finally, anti-HPV immune response could cause infertility rejecting the HPV-infected embryo caused by maternal graft-versus-host disease against HPV infected fetus.[9] Importantly, host immune responses and vaginal microbiome have a natural role in HPV infection, although HPV use different immune evasion mechanisms to limit antiviral activity of immune response inducing tolerance in the host's immune system and reducing the natural clearance.[51]

Independent from the mechanism, it is urgent to find integrated and multidisciplinary solutions which consider the complexity of reproductive care. Although it is not possible from our results to draw final conclusions, we can make some recommendations.

First, HPV DNA testing, also considering its low cost compared to a failed ART procedure, in male partners of infertile couples, even if asymptomatic, could be useful to find this possible infertility cause and, thus, find the best solution. Considering that the estimated clearance for the virus in sperm is >60% at 6 months, in the case of young couples there is the possibility for waiting for spontaneous healing to restore normal sperm parameters and aim for spontaneous pregnancy or to improve the ART outcomes. Instead, in case of aged couples with no possibility for waiting for spontaneous clearance, specific enzymatic washing procedure of infected semen have been shown to be effective for HPV removal.[33,52] Moreover, HPV vaccination has been suggested, showing promising findings, not only in preventing clinical manifestations but also in speeding up the clearance.[53,54] In particular, the nonavalent HPV vaccine seems to offer wider protection especially in men with positive HPV partners, which would play a role in the transmission of the infection and relapse. However, considering that a significant reduction in HPV related infections can be achieved only through vaccination coverage above 80%, extensive vaccination programs should be planned also in a public health economically viable approach.[55]

In addition to these considerations, counseling should be tailored for infected couples paying particular attention to the hygiene of the reproductive tract and of the hands, strict use of personal underwear and personal towels, a complete abstinence from oral and anal sex, smoking reduction or cessation, the practice of protected intercourse only, and, in the case of HPV-related lesions, the treatment and the monitoring of the genital area.[56]

Findings from this meta-analysis must be considered in light of its limitations: I) not all studies considered all sperm parameters; II) some important confounding factors, such as male age and environmental exposures were not always noted; and III) despite the clear negative impact on sperm and pregnancy outcomes, the exact pathophysiological mechanisms are not fully understood.

In conclusion, the present work identified associations between HPV and sperm parameters and reproductive outcomes, which has the potential to lead to a decreased couple fertility, increased risk of pregnancy loss, re-infection and increased treatment costs. Counseling and vaccination are two pillars for the management of infected couples, However, it is urgent for reproductive specialists, health professionals, researchers and policy makers to collaborate to develop the best models of HPV management. Such models should be tailored to male and female infected patients to prevent infection transmission, reinfection, speed up clearance, and ultimately to improve and increase reproductive outcomes.

## FUNDS

None to declare.

## AUTHOR CONTRIBUTIONS

**Andrea Garolla**: Conceptualization; Supervision. **Silvia Mereu**: Investigation; Writing—original draft. **Damiano Pizzol**: Writing—review and editing; Investigation. **Dong Keon Yon**: Writing—review and editing; Methodology. **Masoud Rahmati**: Visualization; Formal analysis. **Pinar Soysal**: Writing—original draft; Data curation. **Petre Cristian Ilie**: Methodology; Data curation. **Alessandro Bertoldo**: Data curation; Investigation; Formal analysis. **Mike Trott**: Software; Data curation; Visualization. **Lee Smith**: Writing—review and editing; Funding acquisition.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The data are available upon request. Available from DP (damianopizzol8@gmail.com)

## TRANSPARENCY STATEMENT

The lead author Damiano Pizzol affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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