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REVIEW ARTICLE

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Seminal human papillomavirus infection and reproduction: a systematic review and meta-analysis

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Abstract

Background: The impact of human papillomavirus (HPV) on male fertility and associated reproductive outcomes has not been clarified.

Objectives: To elucidate the prevalence of seminal HPV infection and assess the associated effects on seminal parameters, male infertility, and reproductive outcomes.

Materials and methods: A systematic review and meta-analysis was performed in accordance with PRISMA guidelines. A search was performed using PubMed, MEDLINE, SCOPUS, and Cochrane databases. Studies published until November 2019 were included. HPV prevalence, risk of infertility, seminal parameters, and reproductive outcomes were evaluated among the general population and infertile men.

Results: Fifty studies met the inclusion criteria. The prevalence of seminal HPV infection is significantly higher in infertile compared to the general population (20.9% versus 8.2%). A significant association between seminal HPV infection and male infertility (OR 3.30, 95% CI 1.87–5.84), even when adjusting for female infertility (OR 3.02, 95% CI = 2.11–4.33) was founded. In addition, HPV infection is related to a significant decrease in progressive motility (DM −10.35, IC −13.75, −6.96), a low sperm morphology score (DM −2.46, 95% CI −3.83, −1.08), and a significant increase in the sperm DNA fragmentation index (7.24, 95% CI 4.44.10.03) compared with HPV-negative patients. It was also observed an increased risk of miscarriage (OR 5.13, 95% CI 2.40,10.94), and a reduced chance of ongoing pregnancy (OR 0.33, IC 95% 0.13,0,82) in patients undergoing ART with seminal HPV infection.

Discussion: Infertile men have a higher prevalence of seminal HPV infection compared to the general population, regardless of the HPV genotype detected.

Conclusions: HPV in semen may have an impact in sperm quality and reproductive outcomes. Additional well-designed studies are warranted to improve the quality of evidence.

KEYWORDS
human papillomavirus, male infertility, semen infection, sperm analysis, semen parameters, sperm DNA fragmentation

1 | INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted virus worldwide, and over 180 genotypes of the virus have been reported. According to its association with different malignancies, HPV can be divided into two groups: high-risk HPV (HR-HPV) and low-risk HPV (LR-HPV).[1,2]

Although the vast majority of infections resolve within two years, if HR-HPV genotypes are not controlled immunologically or through screening, they cause virtually all cervical, a fraction of anogenital, and an increasing proportion of oropharyngeal cancers.[3,4]

HPV infection in men has been considered to be transient,[5] with a main clinical expression being warts in the external genitals. However, the presence of HPV has also been documented in the testicles, epididymis, vas deferens, prostate, urethra, and semen.[5–8]

Furthermore, the prevalence of HPV has been shown to be highly variable and depends on geographical region, age, sexual behavior, host control of the virus, and effects of screening and treatment. Nonetheless, infection rates approach 40% worldwide.[2,9]

One of the first studies focusing on seminal HPV infection reported the presence of HPV DNA sequences using nested polymerase chain reaction (PCR) in 10% of semen samples from asymptomatic young adult males who had unprotected sex.[10] A subsequent study of patients with risk factors for HPV, including subjects with genital warts, partners of women with HPV infection, and infertile patients, reported that seminal HPV infection can be detected in both spermatozoa and exfoliated cells.[11]

HPV virions can bind to different sites including ones on the sperm head, probably due to glycosaminoglycans,[12] or on the sperm surface, due to other soluble factors of similar chemical structure.[13]

Recent research has focused on elucidating the consequences of seminal HPV infection; however, this research has presented conflicting results. While some studies have associated this infection with alterations in seminal parameters,[10,14,15] infertility,[11,16] and adverse reproductive outcomes, blaming the potential transfer of HPV virions to the oocyte during fertilization,[17] other studies have not confirmed these findings.[18,19]

Sperm DNA fragmentation has progressively gained clinical significance in the field of reproductive medicine and also has been included in current research related to seminal HPV infection.[20,21] However, the few studies on this topic present contradictory results.[22–25]

Moreover, there are controversies about the possible harmful effects of seminal HPV infection over the outcome of assisted reproductive therapies (ART).[26] There are animal studies indicating the specific effects of HR-HPV infection at the embryo level, including a decrease in blastocyst formation (HPV 16) and an inhibition of the blastocyst hatching process (HPV 18).[27] Human studies have reported the effect of HPV infection on rates of clinical pregnancy, miscarriage, ongoing pregnancy, and home-based delivery of a child.[28–32]

The aim of this review is to gather the available published evidence related to seminal HPV infection, determine its prevalence in the general and infertile population, and assess its effect on seminal parameters, infertility, and reproductive outcomes of ART.

2 | METHODS

2.1 | Protocol and registration

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[33] We registered this study in the International Prospective Register of Systematic Reviews (PROSPERO) with the ID CRD42020091102. This study was exempted from the institutional review board approval, as it was a meta-analysis.

2.2 | Search strategy

An electronic search was developed and approved by all authors. PubMed, MEDLINE, SCOPUS, and Cochrane databases were searched for studies published up to November 2019 with no restriction in language. The search terms used were "human papilloma virus" combined with "semen quality," "sperm quality," "sperm volume," "sperm concentration," "sperm count," "sperm motility," "sperm morphology," "sperm DNA fragmentation" and "male fertility," "in vitro fertilization," "intrauterine insemination," and "pregnancy." The cited references were reviewed to identify related studies. The full search strategy is illustrated in Appendix S1: Table S1.

2.3 | Eligibility criteria

Seminal HPV infection was defined as HPV DNA detected in seminal samples by PCR or other methods. The review included original studies reporting:

- Prevalence of seminal HPV infection in the general population and in men from infertile couples or studies that provided data that made it possible to calculate it.
- Seminogram parameters including volume, concentration, progressive motility, morphology, and DNA fragmentation.
- Rates of clinical pregnancy, ongoing pregnancy, spontaneous abortion, and live birth.
- Collected studies with no adequate control group to estimate effects were excluded.

2.4 | Data extraction and quality assessment

In a first screening, both authors assessed all of the abstracts retrieved from the search, and then, they obtained the full manuscripts

of citations that fit the inclusion criteria. They judged study eligibility, assessed quality, and extracted data solving discrepancies by agreement.

The quality of the case-control and cohort studies included were evaluated on selection process, comparability of cohorts, and outcomes ascertainment following the guidelines suggested by the Newcastle-Ottawa Scales (NOS).[34] In this scale, studies are scored across 3 categories: selection of subjects, comparability of study groups, and assessment of outcome/exposure. Studies of low, moderate, and high quality were defined with NOS scores of 1–3, 4–6 and 7–9 in the meta-analysis, respectively. The quality of cross-sectional studies was assessed using the Agency for Healthcare Research and Quality (AHRQ) statement (Appendix S1: Table S1).

Both authors critically appraised the summarized results and referred to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to evaluate the quality of evidence for each outcome.[35]

2.5 | Outcome measures

The main outcome measures were as follows: (a) Prevalence of seminal HPV infection, which was calculated by dividing the number of patients with HPV-positive seminal samples by the total number of patients in the study population. (b) Infertility was defined as the inability to conceive after 1 year of unprotected sexual activity.[36] Oligozoospermia was defined as a sperm count less than 15 million per ml.[37] Asthenozoospermia as progressive motility (a + b) less than 32%.[37] Teratozoospermia as a normal morphology in less than 14%.[37] A sperm DNA fragmentation index (sDFI) value of 30% was used as a cutoff to distinguish between potentially fertile and infertile men.[38]

Clinical pregnancy corresponds to those with evidence of fetal cardiac activity on ultrasound at 7 weeks gestation.[36] Spontaneous abortion corresponds to spontaneous gestational loss before 22 weeks.[36] Ongoing pregnancy corresponds to an intrauterine pregnancy of at least 12 weeks duration confirmed by ultrasound.[39] Live birth was defined as the complete expulsion or extraction from a woman of a product of fertilization, after 22 completed weeks of gestational age; which, after such separation, breathes or shows any other evidence of life, such as heartbeat, umbilical cord pulsation or definite movement of voluntary muscles.[36]

2.6 | Statistical analysis and assessment of heterogeneity

To determine the pooled effect of each variable, we used a Mantel-Haenszel model and applied the fixed-effects model. The odds ratio (OR) for dichotomous data accompanied by the 95% confidence intervals (CIs) was calculated. Statistical significance was set at a P-value <.05. We evaluated the degree of variation across studies attributable to heterogeneity with the I square statistics (I2). When the heterogeneity was greater than 50% (I2 > 50%), we applied the random effects model.[40] We used the Review Manager (RevMan Version 5.3) and Comprehensive Meta-Analysis (Version 3.3) softwares for statistical analysis.[41]

3 | RESULTS

3.1 | Search results and description of included studies

The search yielded 1590 records but 1515 were excluded at title / abstract screening. The remaining studies were considered eligible by one or both reviewers. Fifty of these met inclusion criteria. A flowchart describes in detail the selection of studies for inclusion in Figure 1. Characteristics of included studies are summarized in Table 1.

3.2 | Synthesis of results

3.2.1 | Characteristics of the study populations

The selected studies included general population (20), fertility clinics attendees (32), patients with genital warts (7), and patients with a HPV-positive partner (4).

Most of the articles focused on european populations (27/41 studies), followed by North Americans (8/47), Asians (7/41), South Americans (3/41), Africans (1/47), and Oceanians (1/47).

3.3 | Prevalence of seminal HPV infection

3.3.1 | General population

Twenty studies, with a total of 2906 patients, including 217 with seminal HPV infection, were part of this analysis. The pooled prevalence of seminal HPV infection was estimated at 8.2% (95% CI 5.8–10.5; I2 = 84% Figure 2). In the subanalysis stratified by continent, the prevalence of seminal HPV infection in the general population was higher in Europe (12.5%, 95% CI 7.7–17.4), followed by North America (4.8%, 95% CI = 3.5–6.1%) and Asia (6.2%, 95% CI = 0.6–11.8%).

3.4 | Infertile male population

Thirty-two studies, with a total of 6565 patients, including 1204 with seminal HPV infection, were used in this analysis. The pooled prevalence of seminal HPV infection in the infertile population was 20.9% (95% CI: 16.9–24.9; I2 = 96%; Figure 3). In the subanalysis stratified by continent, the prevalence was higher in North America

(31.7%, 95% CI = 0.0–64.9%), followed by Oceania (29.4%, 95% CI = 7.8–51.1%), Africa (28.6%, 95 CI = 17.4–39.7%), South America (27%, 95% CI = 11.5–42.4%), Europe (19%, 95% CI = 15–22.9%), and Asia (13.9%, 95% CI = 5.7– 22.2%).

3.5 | Men with a positive HPV Partner

Seven studies, with a total of 278 participants, including 129 with seminal HPV infection, were pooled in this meta-analysis. The estimated prevalence of seminal HPV infection was 42.3% (95% CI: 21.6–63.1; I2 = 93%; Figure 4).

3.6 | Genital warts

Four studies, with a total of 163 participants, including 87 with seminal HPV infection, were part of this analysis. The pooled prevalence of seminal HPV infection was 58.8% (95% CI: 34.4–83.1; I2 = 92%; Figure 5).

3.7 | High-risk (HR) and low-risk (LR) HPV genotypes

Studies that specifically focused on oncogenic genotypes reported HR-HPV DNA in their semen samples, with HPV-16 as the most frequent genotype. Table 2 compiles the prevalence of HR-HPV and LR-HPV genotypes in semen of the general population and infertile male.

3.8 | Seminal HPV infection and male infertility

Nine studies that included 3193 patients, 1944 infertile males and 1249 fertile controls were pooled in this meta-analysis. Seminal HPV infection was a risk factor for presenting male infertility, with an OR of 3.93 (95% CI: 2.97–5.19; I2 = 56%; Figure 6). The subgroup analysis in studies that excluded men with an infertility factor associated with their partner showed a similar association (OR 3.02; 95% CI 2.11–4.33; I2 = 0.0%). The quality of the evidence was low according to GRADE.

3.9 | Effect of seminal HPV infection on seminal parameters

The mean difference (MD) was used to estimate the effect of HPV on the seminal parameters. Subgroup analyses were performed, including general and infertile male population.

3.10 | Sperm volume

Ten studies, including 3346 patients, were used in this analysis. The random effects analysis showed a MD of −0.17 (95% CI −0.37, −0.03; I2 = 45%) when comparing the sperm volume of patients with seminal HPV infection versus patients without infection. The analysis by subgroups showed a MD of −0.14 (95% CI −0.39, 0.11; I2 = 54%) in infertile patients and a MD of −0.30 (95% CI −0.58, 0.11; −0.03; I2 = 0%) in the general population (Figure 7). The quality of the evidence was low according to GRADE.

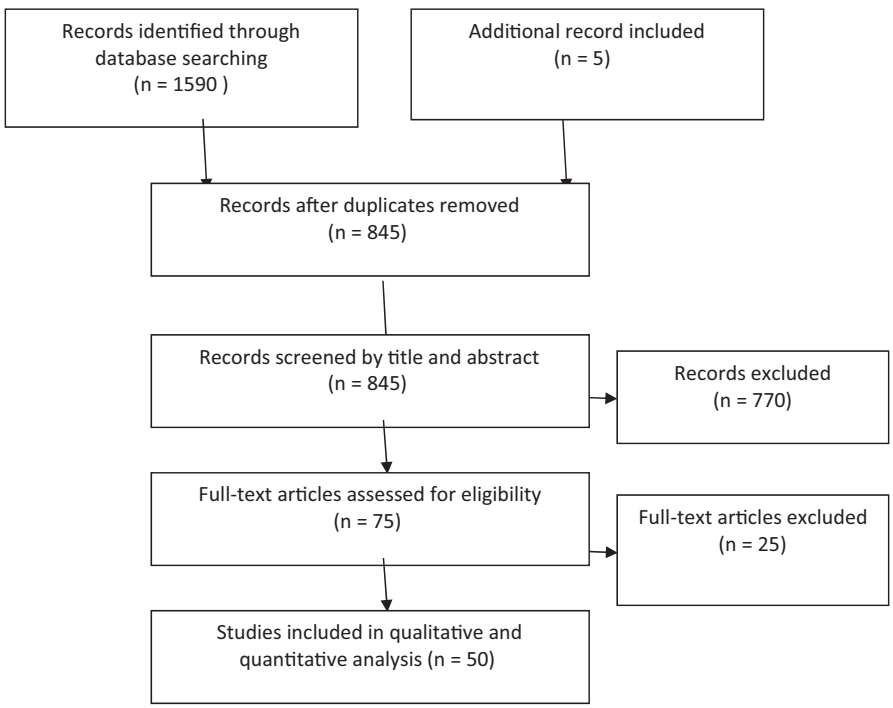


FIGURE 1 Flowchart for the study identification and selection process according to preferred reporting items for systematic reviews and meta-analysis guidelines PRISMA

TABLE 1 Characteristics of included studies

Study	Year	Study design	Country	Age	Population characteristics
Asia					
Inoue 42	1992	Cross-sectional	Japan	NR	Fertile men
Kyo 43	1994	Cross-sectional	Japan	NR	Infertile Men
Lai 15	1997	Cross-sectional	China	NR	Infertile Men
Tanaka 44	2000	Cross-sectional	Japan	NR	Male partners of women undergoing IVF
Yang 16	2013	Case Control	China	Mean: 31.2 Range: 21–48	Idiopathic infertility
					Fertile men
Nasseri 45	2015	Cross-sectional	Iran	Range: 22-55	Oligozoospermia
					Azoospermia
Kim 46	2017	Cross-sectional	South Korea	NR	Infertile Men
Moghimi 47	2019	Case control	Iran	Mean: 31.88 ± 5.18	Idiopathic infertility
				Mean: 33.61 ± 5.25	Fertile men
Europe					
Green 48	1991	Case control	UK	NR	Meatal warts
					Penile warts
					Healthy men
					Infertile Men
Astori 49	1995	Cross-sectional	Italy	NR	Partners of HPV-positive women
Rohde 50	1999	Cross-sectional	Germany	Range: 19–41	Idiopathic infertility
					Fertile men
Aynaud 51	2002	Cross-sectional	Francia	NR	Partners of HPV-positive women
Rintala 52	2002	Cross-sectional	Finland	Mean: 40.3 Range: 33–49	Fertile men
Rintala 14	2004	Cross-sectional	Finland	Mean: 28 Range: 20–43	Fertile men
Czegledy 53	2006	Cross-sectional	Hungary	NR	Male partners of women undergoing IVF
Giovanelli 115	2007	Cross-sectional	Italy	NR	Partners of HPV-positive women
Foresta 10	2010	Case control	Italy	Mean: 37.2 ± 5.5	Genital warts
				Mean: 33.9 ± 3.9	Partners of HPV-positive women
				Mean: 38 ± 5.3	Idiopathic infertility
				Mean: 34.2 ± 4.5	Healthy men
Foresta 11	2010	Case control	Italy	18	Men who had unprotected intercourse
					Men who had never had intercourse
Foresta 13	2011	Case control	Italy	Mean: 30.9 ± 7.1	Testicular cancer patients
				Mean: 33.1 ± 6.5	Healthy men

Sample size	N HPV +	Prevalence HPV %	HR-HPV	Prevalence HR-HPV %	LR-HPV	Prevalence LR-HPV %	Study quality
23	4.00	17.39	4.00	17.39	NR	NR	Moderate quality
53	12.00	22.64	12.00	22.64	NR	NR	Moderate quality
24	6.00	25.00	6.00	25.00	NR	NR	High quality
99	4.00	4.04	4.00	4.04	NR	NR	Moderate quality
615	107.00	17.40	103.00	16.75	30.00	4.88	High quality
523	35.00	6.69	21.00	4.02	17.00	3.25	
50	15.00	30.00	3.00	6.00	12.00	24.00	Moderate quality
20	8.00	40.00	3.00	15.00	5.00	25.00	
381	6.00	1.57	3.00	0.79	3.00	0.79	High quality
70	8.00	11.43	8.00	11.43	NR	NR	High quality
70	0.00	0.00	NR		NR	NR	
20	20.00	100.00	20.00	100.00	19.00	95.00	Moderate quality
7	4.00	57.14	3.00	42.86	4.00	57.14	
2	1.00	50.00	1.00	50.00			
104	43.00	41.35	35.00	33.65	23.00	22.12	
70	58.00	82.86	NR		NR	NR	Moderate quality
30	8.00	26.67	8.00	26.67	NR	NR	Moderate quality
8	2.00	25.00	2.00	25.00	NR	NR	
111	26.00	23.42	NR		NR	NR	Moderate quality
18	5.00	27.78	4.00	22.22	1.00	5.56	High quality
65	10.00	15.38	10.00	15.38	NR	NR	Moderate quality
13	6.00	46.15	3.00	23.08	NR	NR	Moderate quality
63	15.00	23.81	NR	NR	NR	NR	Moderate quality
26	14.00	53.85	NR	NR	NR	NR	High quality
66	27.00	40.91	NR	NR	NR	NR	
108	11.00	10.19	NR	NR	NR	NR	
90	2.00	2.22	NR	NR	NR	NR	
100	10.00	10.00	5.00	5.00	NR	NR	High quality
100	0.00	0.00	NR	NR	NR	NR	
98	6.00	6.12	NR	NR	NR	NR	High quality
60	2.00	3.33	NR	NR	NR	NR	

(Continues)

TABLE 1 (Continued)

Study	Year	Study design	Country	Age	Population characteristics
Perino 26	2011	Cross-sectional	Italy	Mean: 38.0 ± 6.4	Male partners of women undergoing IVF
Kero 54	2011	Cross-sectional	Finland	Median: 28 Range: 19–46	Healthy men
					Partners of HPV-positive women
Kaspersen 55	2011	Cross-sectional	Denmark	Mean: 25 ± 6.1	Healthy donors
Garolla 17	2012	Case control	Italy	Mean: 31.2 ± 5.4	Testicular cancer patients
				Mean: 30.8 ± 4.7	Fertile men
Kaspersen 23	2013	Cross-sectional	Denmark	Median: 27 Range 18–40 years	Healthy donors
Schillaci 56	2013	Cross-sectional	Italy	Mean 38.7 ± 5.9	Male partners of women undergoing IVF
Golob 18	2014	Cross-sectional	Slovenia	Mean: 32.91 ± 5.15	Infertile Men
La Vignera 57	2015	Case control	Italy	Mean: 32.0 ± 6.0	Infertile men with an inflammatory MAGI
					Infertile men with an microbial MAGI
				Mean: 34.0 ± 4.0	Fertile men
Foresta 58	2015	Prospective cohort	Italy	HPV (-) Mean: 38.2 ± 8.1 HPV (+) Mean: 37.1 ± 7.4	Idiopathic infertility
Luttmer 59	2015	Cross-sectional	Netherlands	Median: 22.1 Range: 18-64	Fertile men
Luttmer 19	2016	Cross-sectional	Netherlands	Mean: 36.2 Range: 35.6 - 36.8	Infertile Men
Garolla 60	2016	Cross-sectional	Italy	Mean: 34.2 ± 4.1	Male partners of women undergoing IVF
Depuydt 61	2018	Cross-sectional	Belgium	NR	Healthy donors
Boeri 62	2018	Cross-sectional	Italy	Median: 37 Range: 34–40	Idiopathic infertility
Fedder 63	2018	Cross-sectional	Denmark	Mean: 40	Healthy men
Depuydt 64	2019	Prospective cohort	Belgium	Median: 34.5 Range: 33.8–35.0	Idiopathic infertility
Jersoviene 65	2019	Cross-sectional	Lithuania	Mean: 36.4 ± 5.12	Male partners of women undergoing IVF
Tangal 66	2019	Cross-sectional	Turkey	Mean: 36 ± 5.4	Infertile men with two previous IVF failure
North America					
Chan 67	1994	Cross-sectional	USA	NR	Infertile Men
Olatunbosun 68	2001	Case control	Canada	Median: 27 Range: 20-41	Sperm donors, pre-swim-up
					Sperm donors, post-swim-up
					Genital warts, pre-swim-up
					Genital warts, post-swim-up
Nielson 69	2007	Cross-sectional	USA	NR	Fertile men
Giuliano 70	2007	Cross-sectional	USA	Mean: 27.2 ± 6.5"	Healthy men
Bezold 71	2007	Cross-sectional	USA	Range: 22-55	Infertile men with leukocytospermia
					Infertile men without leukocytospermia
Hernandez 72	2008	Cross-sectional	USA	Mean: 28.8 ± 11.9	Healthy men
Flores Sanchez 73	2010	Cross-sectional	Mexico	Mean: 37.27 ± 7.27	Idiopathic infertility
Cortes 24	2017	Case control	Mexico	NR	Fertile men
					Idiopathic infertility
					Genital warts

Sample size	N HPV +	Prevalence HPV %	HR-HPV	Prevalence HR-HPV %	LR-HPV	Prevalence LR-HPV %	Study quality
199	19.00	9.55	NR	NR	NR	NR	Moderate quality
67	20.00	42.55	NR	NR	NR	NR	High quality
22	8.00	36.36	NR	NR	NR	NR	
188	30.00	15.96	20.00	10.64	15.00	7.98	High quality
155	15.00	9.68	NR	NR	NR	NR	High quality
84	2.00	2.38	NR	NR	NR	NR	
76	20.00	26.32	NR	NR	NR	NR	High quality
308	24.00	7.79	20.00	6.49	4.00	1.30	High quality
316	43.00	13.61	16.00	5.06	34.00	10.76	High quality
48	10.00	20.83	7.00	14.58	3.00	6.25	High quality
52	15.00	28.85	9.00	17.31	6.00	11.54	
20	2.00	10.00	0.00	0.00	2.00	10.00	
619	179.00	28.92	NR	NR	NR	NR	High quality
213	58.00	27.23	45.00	21.13	44.00	20.66	High quality
430	64.00	14.88	47.00	10.93	26.00	6.05	High quality
226	42.00	18.58	NR	NR	NR	NR	High quality
514	20.00	3.89	NR	NR	NR	NR	High quality
729	113.00	15.50	78.00	10.70	35.00	4.80	High quality
43	15.00	34.88	NR	NR	NR	NR	High quality
732	170.00	12.48	143.00	10.50	NR	NR	High quality
100	20.00	20.00	20.00	20.00	NR	NR	High quality
117	9.00	7.69	6.00	5.13	3.00	2.56	High quality
42	15.00	35.71	NR	NR	NR	NR	High quality
40	3.00	7.50	NR	NR	NR	NR	High quality
	2.00	5.00	NR	NR	NR	NR	
45	24.00	53.33	NR	NR	NR	NR	
	23.00	51.11	NR	NR	NR	NR	
337	18.00	100.00	12.00	36.36	6.00	18.18	High quality
463	18.00	3.89	NR	NR	NR	NR	High quality
70	3.00	4.29	NR	NR	NR	NR	High quality
109	5.00	4.59	NR	NR	NR	NR	
197	12.00	6.09	3.00	1.52	11.00	5.58	High quality
149	89.00	59.73	89.00	59.73	NR	NR	High quality
9	0	0	0	0	NR	NR	High quality
22	6.00	27.27	3.00	13.64	3.00	13.64	
7	2.00	28.57	2.00	28.57	3.00	42.86	

(Continues)

TABLE 1 (Continued)

Study	Year	Study design	Country	Age	Population characteristics
South America					
Gimenes 74	2014	Cross-sectional	Brazil	Mean: 33.4 ±: 7.2 Range: 19-51	Infertile Men
Damke 75	2017	Cross-sectional	Brazil	Mean: 32.87 ± 6.6 Range 18–52	Infertile Men
Bossi 76	2019	Cross-sectional	Brazil	Mean: 39.2 ± 8.36 Range: 27- 68	Infertile Men
Oceania					
Reich 77	2012	Cross-sectional	Australia	NR	Infertile Men
Africa					
Didelot 78	2007	Cross-sectional	Ivory Coast	Median: 36 IQR: 32–45	Infertile Men

Abbreviations: MAGI, Male accessory gland infection; NR, Not registered.

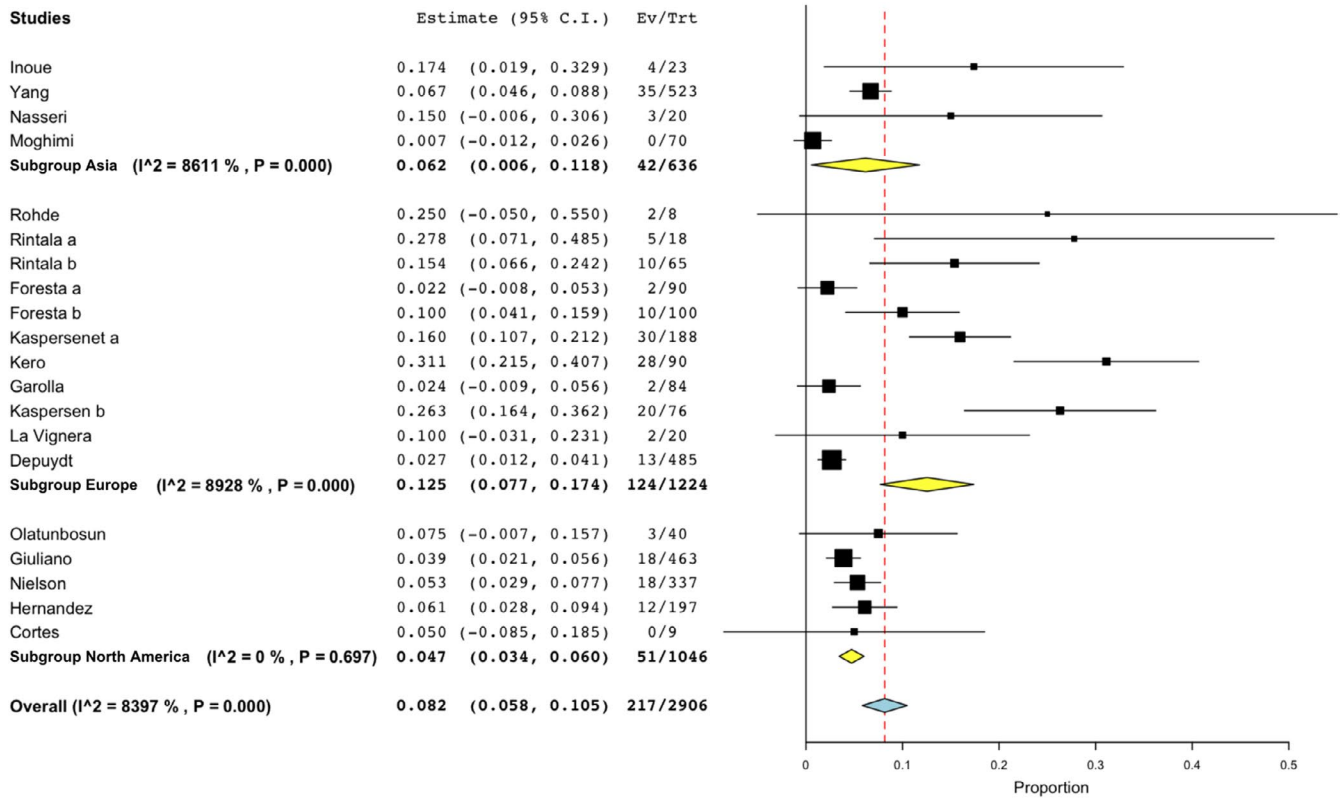


FIGURE 2 Prevalence of seminal HPV infection in the general population

3.11 | Sperm concentration

Twelve studies, including 3062 patients, were part of this analysis. The random effects analysis showed a MD of −8.51 (95% CI −18.96, −1.94; I2 = 96%) when comparing the sperm concentration of patients with seminal HPV infection versus patients without infection. The analysis by subgroups showed a MD of −8.98 (95% CI −21.35, 3.40; I2 = 97%) in infertile patients and a MD of −2.13 (95% CI −8.55, 4.29; I2 = 0%) in the general population (Figure 8). The quality of the evidence was low according to GRADE.

A subanalysis was performed to determine the effect of seminal HPV infection on the risk of presenting oligozoospermia and azoospermia.

Overall, no difference in the risk of oligozoospermia (three studies, 484 patients; OR 1.13, 95% CI 0.80, 1.60; I2 = 0%, Figure 9A) or azoospermia (two studies, 20 patients, OR 2.90, 95% CI 0.92, 9.11; I2 = 0%, Figure 9B) was noted among the patients with seminal HPV

Sample size	N HPV +	Prevalence HPV %	HR-HPV	Prevalence HR-HPV %	LR-HPV	Prevalence LR-HPV %	Study quality
76	29.00	38.16	23.00	30.26	11.00	14.47	High quality
229	38.00	16.59	13.00	5.68	14.00	6.11	High quality
25	7.00	28.00	NR	NR	NR	NR	High quality
17	5.00	29.41	2.00	11.76	2.00	11.76	High quality
63	18.00	28.57	8.00	12.70	10.00	15.87	Moderate quality

infection and patients without infection. The quality of the evidence was low according to GRADE.

3.12 | Sperm progressive motility

Thirteen studies, which included 4157 patients, provided data on the sperm progressive motility. The random effects analysis showed a MD of −10.35 (95% CI −13.75, −6.96; I2 = 90%) when comparing the progressive motility of patients with seminal HPV infection versus patients without infection. The analysis by subgroups showed a MD of −10.33 (95% CI −14.27, 6.39; I2 = 92%) in infertile patients and a MD of −9.54 (95% CI −15.07, −4.01; I2 = 29%) in the general population (Figure 10). The quality of the evidence was low according to GRADE.

A subanalysis was performed to determine the effect of seminal HPV infection on the risk of developing asthenozoospermia. Two studies, including 583 patients, were included in this analysis. Patients with seminal HPV infection have an increased risk of asthenozoospermia (OR 1.69 95% CI 1.13, 2.51; I2 = 0%) compared to patients without infection (Figure 11). The quality of the evidence was low according to GRADE.

3.13 | Sperm morphology

Eleven studies, including 3498 patients, provided information on sperm morphology. The random effects analysis showed a MD of −2.46 (95% CI −3.83, −1.08; I2 = 72%) when comparing the sperm morphology of patients with seminal HPV infection versus patients without infection. The analysis by subgroups showed a MD of −2.11 (95% CI −3.85, −0.38; I2 = 78%) in infertile patients and a MD of −4.14 (95% CI −5.49, −2.79; I2 = 0%) in the general population (Figure 12). The quality of the evidence was low according to GRADE.

A subanalysis, including two studies and 537 patients, was performed to determine the effect of seminal HPV infection on the risk of teratozoospermia. The overall risk of teratozoospermia was not significantly different among the patients with seminal infection and patients without infection (OR of 1.15 95% CI 0.77, 1.72; I2 = 0%) (Figure 13). The quality of the evidence was low according to GRADE.

3.14 | Sperm DNA fragmentation index

Two studies, including 926 patients, were used in this analysis. The random effects analysis showed a MD of 7.24% (95% CI 4.44, 10.03; I2 = 0%) when comparing the sDFI of patients with seminal HPV infection versus patients without infection (Figure 14). The quality of the evidence was low according to GRADE.

A subanalysis was performed to evaluate the effect of seminal HPV infection on the risk of having a sDFI higher than 30%. Only two studies, including 373 patients, were pooled in this analysis. Overall, there was no difference in the risk of presenting a sDFI higher than 30% in patients with seminal HPV infection (OR 1.52, 95% CI 1.02, 2.27; I2 = 0%) compared with patients without infection (Figure 15). The quality of the evidence was low according to GRADE.

Table 3 summarizes the findings regarding the association between seminal HPV infection and seminal parameters.

3.15 | Reproductive outcomes

3.15.1 | Effect of seminal HPV infection on reproductive outcomes in spontaneous pregnancies

Clinical pregnancy

Only one study,[60] including 226 patients, evaluated the clinical pregnancy rates. No difference was noted in the clinical pregnancy rates

between couples with seminal HPV infection and couples without seminal infection.

No studies were found that provided data on the miscarriage, ongoing pregnancy, and live birth rates in spontaneous pregnancies.

3.15.2 | Effect of seminal HPV infection on the reproductive outcomes of patients undergoing ART

3.15.3 | Clinical pregnancy

Four studies, including 1890 patients, provided information on the clinical pregnancy rates. There was no significant difference between the seminal HPV infection and no infection group (OR 0.61 95% CI 0.29–1.28, I2 = 61%; Figure 16). The subgroup analysis in patients undergoing IUI (two studies; 203 patients) indicated that the seminal HPV infection increased the clinical pregnancy rate with an OR of 0.36 (IC 95% 0.20–0.67, I2 = 0%). However, in patients undergoing IVF (two studies; 173 patients) there was no significant difference between groups considering clinical pregnancy rate (OR 0.86 95% CI 0.28–2.63, I2 = 69%; Figure 16). The quality of the evidence was low according to GRADE.

3.15.4 | Miscarriage

Four studies, including 446 patients, evaluated the miscarriage rates. The overall risk of miscarriage in patients undergoing ART was significantly higher in the seminal HPV infection group than patients without infection (OR 5.13; 95% CI 2.40–10.94, I2 = 0%, Figure 17). We also performed subanalysis considering the technique used. Seminal HPV infection was associated with an increase in miscarriage risk for patients undergoing IUI (OR 2.81, 95% CI 0.78–10.14) as in patients undergoing IVF (OR 6.47, 95% CI 2.00–20.87, I2 = 0%) compared with patients without infection. The quality of the evidence was low according to GRADE.

3.15.5 | Ongoing pregnancy

Three studies, including 1752 patients, were pooled in this meta-analysis. Seminal HPV infection in patients undergoing ART was associated with a lower ongoing pregnancy rate (OR 0.33 95% CI 0.13–0.82, I2 = 50%, Figure 18) compared to couples without infection. The subgroup analysis in patients undergoing IUI revealed similar differences between the groups as regards to ongoing pregnancy rate (OR 0.24 95% CI 0.10–0.60, Figure 18). The quality of the evidence was low according to GRADE.

No studies were found that provided data on the live birth rates in patients undergoing ART. Table 4 summarizes the findings regarding the effect of seminal HPV infection on the reproductive outcomes of patients undergoing ART.

3.16 | Sensitivity analysis

Funnel plots with respect to the association between Seminal HPV infection and the risk of male infertility, clinical pregnancy, and ongoing pregnancy did not demonstrate asymmetry which was typically associated with publication bias; Begg's adjusted rank correlation test suggested a low probability of publication bias. Funnel plot related to seminal HPV infection and the risk of miscarriage demonstrates asymmetry, but a sensitivity analysis was performed by omitting one study at a time, demonstrating no significant impact on the pooled effect size (Appendix S1: Table S2, Figures S1-S4).

4 | DISCUSSION

4.1 | Main findings

Our current results provide enhanced insight into seminal HPV infection and its connection to male infertility. They confirm that HPV infection is frequently detected in the semen of both asymptomatic and infertile men.

Furthermore, the prevalence of seminal HPV infection is significantly higher in infertile men when matched to the general population (20.9% versus 8.2%). The results also highlight that HR-HPV is more common than LR-HPV (11.9% versus 7.2%) and that HPV 16 is the most commonly detected genotype.

Our meta-analysis revealed a significant association between seminal HPV infection and male infertility (OR 3.30, 95% CI = 1.87–5.84), even after adjusting for female infertility (OR 3.02, 95% CI = 2.11-4.33).

Furthermore, our results point out that HPV infection may cause detriment to seminal parameters, including a significant decrease in progressive motility and sperm morphology, and a significant increase in the sperm DNA fragmentation index (sDFI) when compared to HPV-negative patients. In addition, an increased risk of asthenozoospermia and a sDFI greater than 30% in patients with seminal HPV infection was found.

Moreover, couples undergoing ART with a seminal HPV infection have an increased risk of miscarriage and a decreased likelihood of maintaining an ongoing pregnancy compared to negative patients. However, the overall quality of evidence was rated low, mainly due to several limitations of the included studies and imprecision of the results; therefore, the findings of this study should be interpreted with caution.

4.2 | Comparison with other studies

The meta-analysis performed shows the prevalence of seminal HPV infection to be 20.9% in infertile patients, which is consistent with a recent meta-analysis that reported a prevalence of 20.4% in the same population.[79]

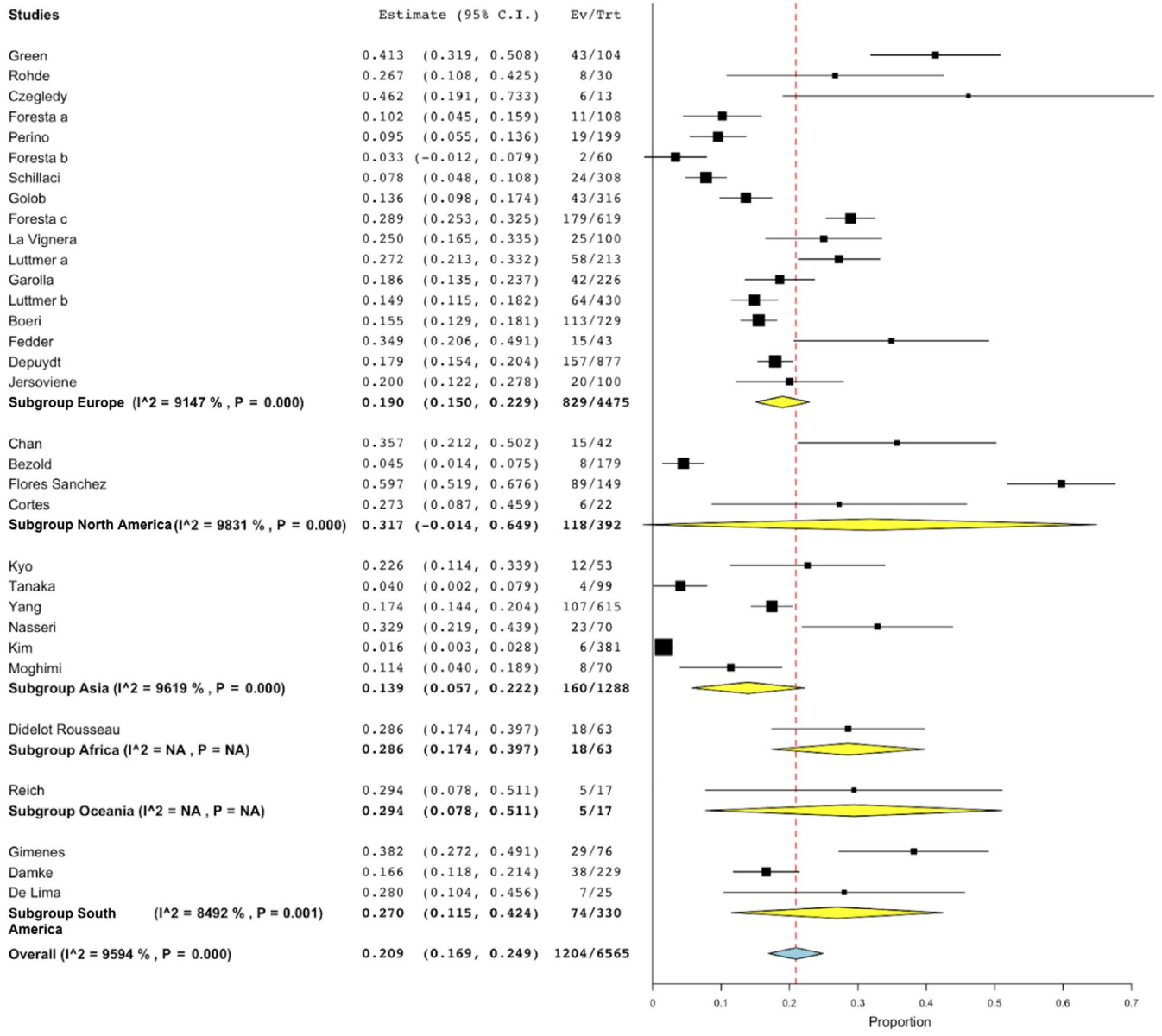


FIGURE 3 Prevalence of seminal HPV infection in infertile males

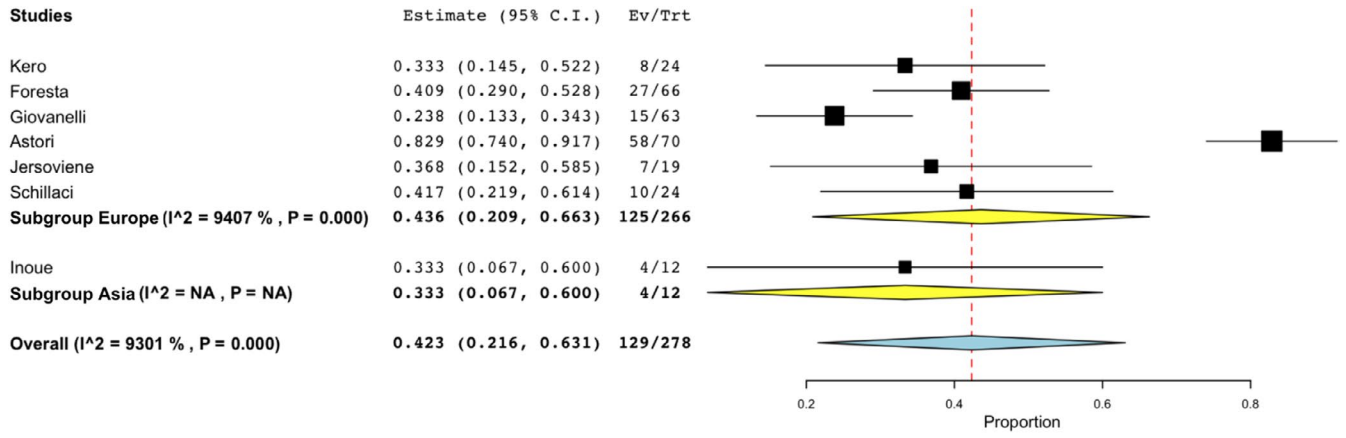


FIGURE 4 Prevalence of seminal HPV infection in males with a positive HPV partner

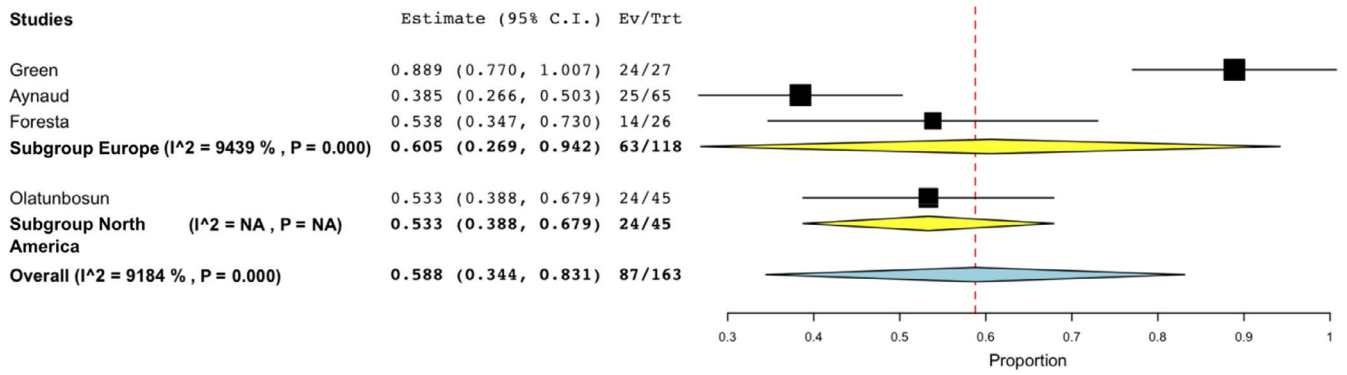


FIGURE 5 Prevalence of seminal HPV infection in patients with genital warts

Our review includes recently published studies that used larger sample sizes; however, it maintains a high heterogeneity (I2 = 95%).

In relation to the HPV genotype distribution, our study indicated that HPV 16 is the most frequent genotype, with a prevalence of 5.9% in the infertile population and 4.7% in the general population. These results are in accordance with one study that reported prevalences of 6% and 4.8% respectively.[79] Moreover, recent evidence has also shown that HPV 16 is the predominant genotype in the male anogenital area, prostate, bladder, and oropharynx.[80,81]

Two recent meta-analyses have shown that seminal HPV infection is a risk factor for male infertility, reporting an OR 2.93 (95% CI = 2.03-4.24)[79] and OR 3.02 (95% CI = 2.11-4.32),[82] which is confirmed by our findings. By performing a subanalysis excluding studies that involved couples with female factors, the effect was maintained and an optimal heterogeneity was obtained (OR 3.02, 95% CI 2.11 - 4.33, I2 = 0%).

On the other hand, few studies have reported the effects of HPV infection on seminal parameters, and the available data are conflicting. Some studies had reported an association between seminal HPV infection and decreased progressive sperm motility,[10,11,83] while others did not observe any clinically significant alterations of these parameters.[18,19,56] In addition, only two small cross-sectional studies have analyzed the specific impact of HR-HPV or LR-HPV genotypes on semen parameters and their results showed no significant association.[19,75] One recent study involving a large number of patients, which included a specific evaluation of the effect of HR/LR-HPV genotypes, confirmed the potentially harmful impact of seminal HPV infection on progressive motility.[63] Our meta-analysis, which combines the results of the aforementioned studies, showed an increased risk of asthenozoospermia (OR 1.70 95% CI = 1.14-2.52) and a significantly lower progressive motility in patients with HPV infection (MD −10.35 95% CI −13.75, −4.01). However, the heterogeneity observed for the latter result is high (I2 = 90%).

Unlike some in vivo studies that failed to find any association between seminal HPV infection and sperm DNA integrity,[23,24] our results demonstrate that patients with seminal HPV infection have a significantly higher risk with a sDFI greater than 30% (OR 1.52 95% CI 1.02-2.27) compared to patients without infection. Our analysis includes two recently published studies, obtaining an optimal heterogeneity (I2 = 0%).[63,66]

Furthermore, recent reports suggest that seminal HPV infection has a potentially harmful effect on reproductive outcomes of ART.[25,26,31,60,64] These authors found a reduced ongoing pregnancy rate and an increased abortion rate in HPV-infected couples compared to uninfected ones. One study confirmed an increased risk when HPV DNA tests were positive in the female partner, and the risk was even greater when the semen samples were also positive for HPV.[25] In accordance with these results, our systematic review and meta-analysis found a negative effect of the seminal presence of HPV, with lower ongoing pregnancy rates and higher miscarriage rates.

Some previous studies on the impact of HPV on infertility, IVF failure, and reproductive outcomes showed conflicting results.[84–86] However, it is important to note that their investigations included the detection of HPV in the cervix and trophoblastic tissues, unlike our study that includes the seminal infection only. Both aforementioned studies focused on seminal, cervical, and trophoblast infection reported an increased risk of miscarriage.[32,86.]

4.3 | Interpretation of the results

Several pathogenic mechanisms have been proposed to explain the effects of seminal HPV infection on male infertility.

Firstly, the action of HPV virions could explain the decline of seminal parameters such as motility and DNA fragmentation.[25] The first study to investigate this mechanism reported a significantly lower performance of curvilinear velocity, straight-line velocity, and mean amplitude of lateral head displacement in HPV-infected specimens,[15] confirmed later by others.[10,11,17]

By contrast, seminal HPV infection has been associated with increased levels of anti-sperm antibodies (ASA), which, when binding to spermatozoa, release pro-inflammatory cytokines that interfere with motility and fertility.[83] Furthermore, the

TABLE 2 Prevalence of HR-HPV and LR-HPV genotypes in semen of general population and infertile male

	General population			Infertile men		
	Studies	HPV +	Prevalence DNA HPV (%) CI 95%	Studies	HPV +	Prevalence DNA HPV (%) CI 95%
HR- HPV	11	127	9.27 (7.73 – 10.81)	21	672	12.26 (11.39 – 13.13)
LR-HPV	6	85	8.54 (6.8 – 10.28)	14	2962	6.55 (5.66 – 7.44)
Individual Type						
Clade 9						
HPV16	10	74	4.7 (3.68 – 5.78)	21	238	5.9 (4.2–7.6)
HPV31	8	7	0.58 (0.15 – 1.02)	11	32	0.8 (0.4–1.2)
HPV33	7	6	0.61 (0.12 – 1.10)	6	17	0.5 (0.2–0.9)
HPV35	7	2	0.2 (0.0 – 0.48)	3	8	0.5 (0.1–0.9)
HPV52	8	9	0.68 (0.24 – 1.12)	10	61	1.6 (0.7–2.5)
HPV58	7	2	0.2 (0.0 – 0.48)	7	25	0.8 (1–1.5)
Clade 7						
HPV18	7	11	0.92 (0.38 – 1.46)	15	110	1.9 (0.9–2.8)
HPV39	7	5	0.51 (0.06 – 0.95)	4	10	0.5 (0.1–0.9)
HPV45	7	5	0.51 (0.06 – 0.95)	7	25	0.8 (0.2–1.4)
HPV59	9	10	0.65 (0.25 – 1.05)	8	33	1 (0.6–1.5)
HPV68	7	8	0.81 (0.25 – 1.37)	3	6	0.5 (0.1–1)
HPV70	8	1	0.10 (0.0 – 0.3)	8	9	0.2 (0–0.4)
Clade 10						
HPV6	9	18	1.79 (0.97 – 2.61)	11	89	2.3 (1.1–3.5)
HPV11	10	28	2.71 (1.72 – 3.70)	6	32	1.6 (0–3.2)
HPV44	8	1	0.1 (0.0 – 0.3)	7	7	0.3 (0–0.6)
Clade 3						
HPV61	8	3	0.3 (0.0 – 0.65)	7	9	0.3 (0–0.6)
HPV62	9	5	0.38 (0.05 – 0.71)	6	13	0.7 (0.1–1.2)
HPV81	8	9	0.91 (0.32 – 1.51)	5	9	0.4 (0.1–0.6)
Clade 6						
HPV53	8	8	0.81 (0.25 – 1.37)	8	20	0.8 (0.2–1.3)
HPV56	8	8	0.67 (0.21 – 1.13)	8	33	1.2 (0.5–1.9)
HPV66	8	16	1.34 (0.69 – 1.99)	13	41	0.9 (0.5–1.3)
Clade 8						
HPV40	8	1	0.1 (0.0 – 0.3)	5	4	0.1 (0–0.3)
HPV43	9	1	0.1 (0.0 – 0.29)	6	28	1.3 (0.3–2.3)
Clade 10						
HPV42	9	15	1.25 (0.62 – 1.88)	5	28	1.3 (0.8–1.8)
Clade 5						
HPV51	9	18	1.17 (0.63 – 1.71)	10	31	0.9 (0.3–1.4)
Clade 13						
HPV54	8	3	0.3 (0.0 – 0.65)	10	17	0.4 (0.1–0.8)

infection can affect sperm DNA integrity as revealed in a study where HPV type 16 and 31 caused DNA breakage characteristics.[22] In our study, a significantly higher sDFI was observed in patients with seminal HPV infection (MD 7.24 95% CI 4.44-10.03) compared to those without infection. HPV-infected cells are presumed to cause chromosome breakage and may increase cell susceptibility to DNA damage and/or defects in DNA repair. It is speculated that this is a result of diminished p53 or pRB activity.[87] However, these mechanisms have not yet been demonstrated and will need future clarification with a rigorously designed methodology and adequate sample size. In addition, the HPV infection in the male genital tract has been associated

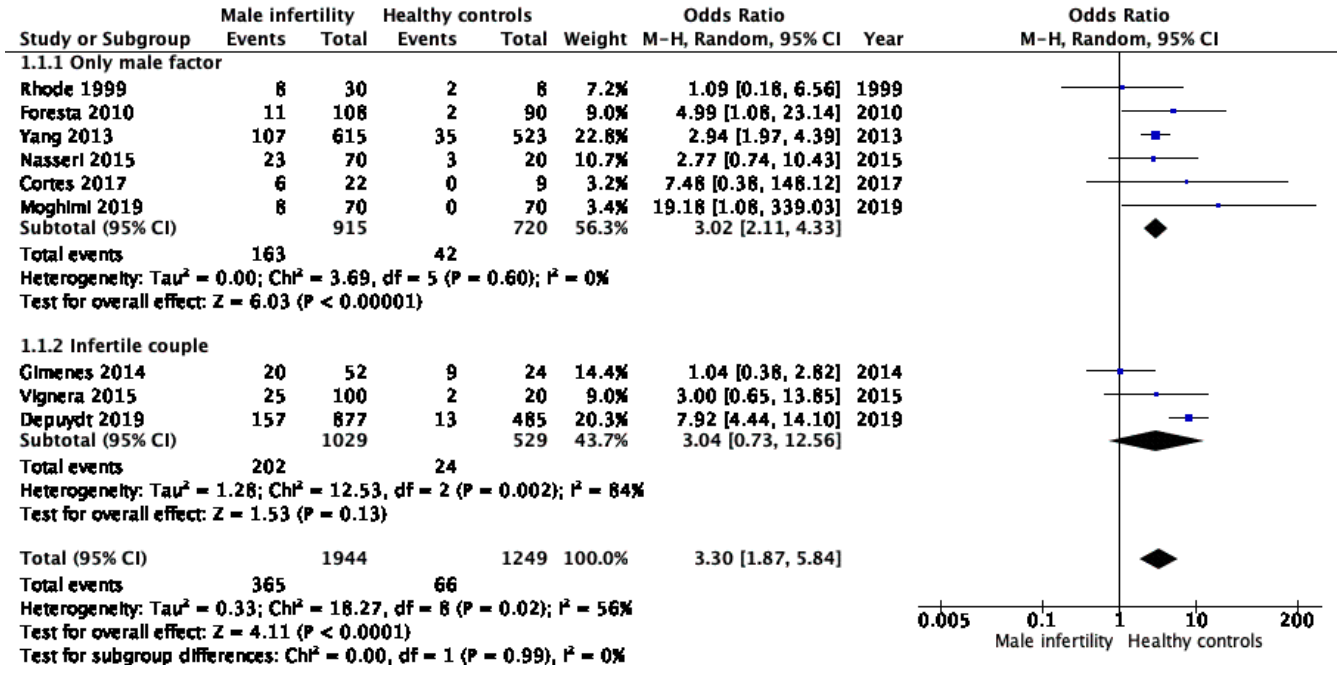


FIGURE 6 Association between male infertility and seminal HPV infection

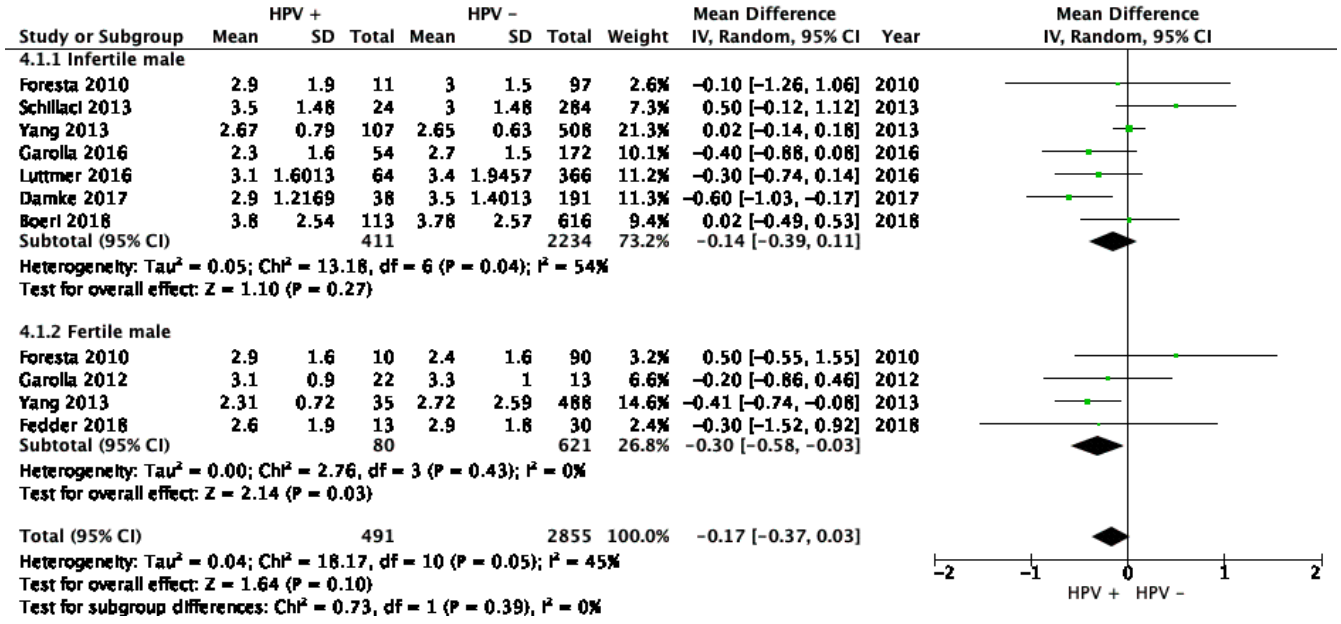


FIGURE 7 Effect of seminal HPV infection on sperm volume

with changes in the composition of prostatic secretions and seminal vesicles, which are considered essential for the proper movement of spermatozoa.[75]

Moreover, spermatozoa is able to transport the HPV genome to oocytes during fertilization.[13,88] This could result in the failure of fertilization; however, if embryo progression occurred, the viral genome would be harmful to the developing embryo, resulting in the development of aneuploidies and placental defects.[89] In addition, the possible consequences of fetal exposure to HPV are not well defined. In vitro studies have shown that trophoblastic cells infected with HPV have a higher rate of apoptosis and less placental invasion into the uterine wall compared to controls.[13] In vivo studies are required to confirm these findings.

While our study analyzed reproductive outcomes in couples with seminal HPV infection, there is also growing interest in elucidating this issue by assessing the presence of HPV in the cervix and products of conception. A recent study highlighted that HPV can be detected in the placenta and that this infection can occur not

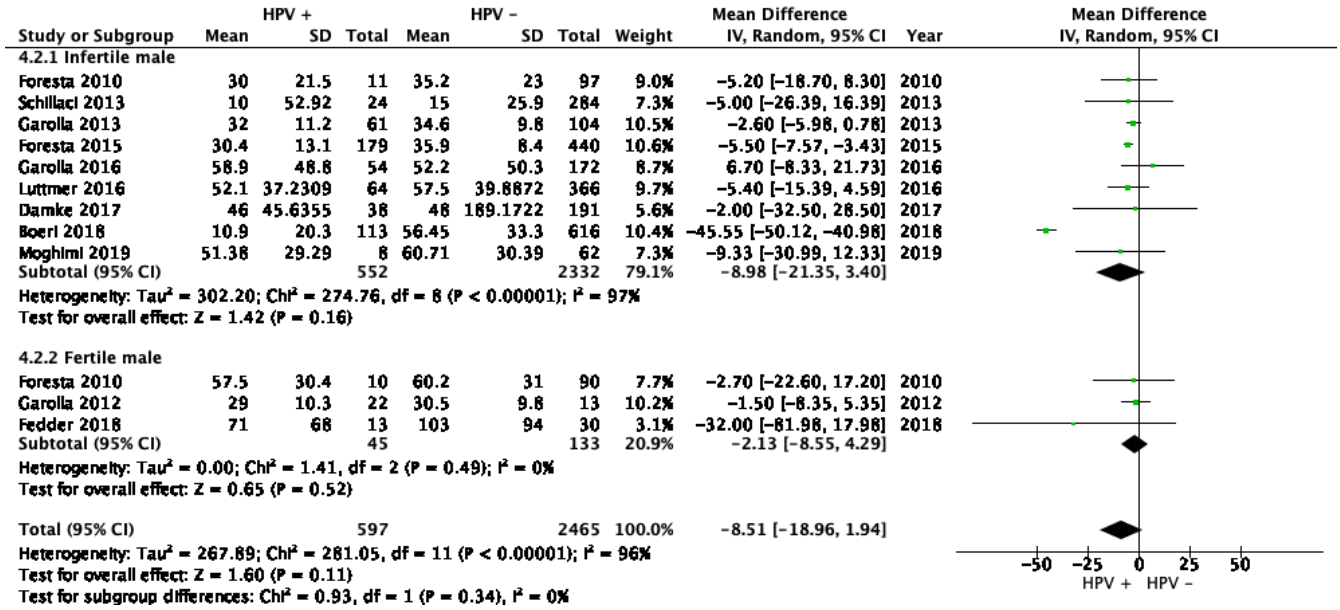
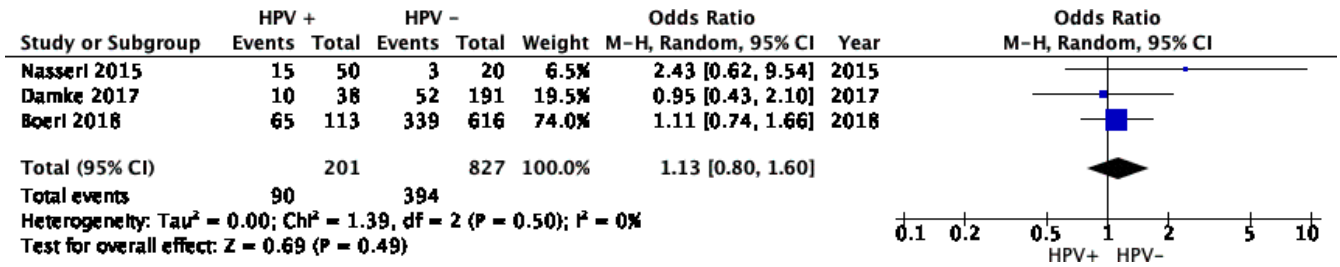


FIGURE 8 Effect of seminal HPV infection on sperm concentration

(A) Oligozoospermia



(B) Azoospermia

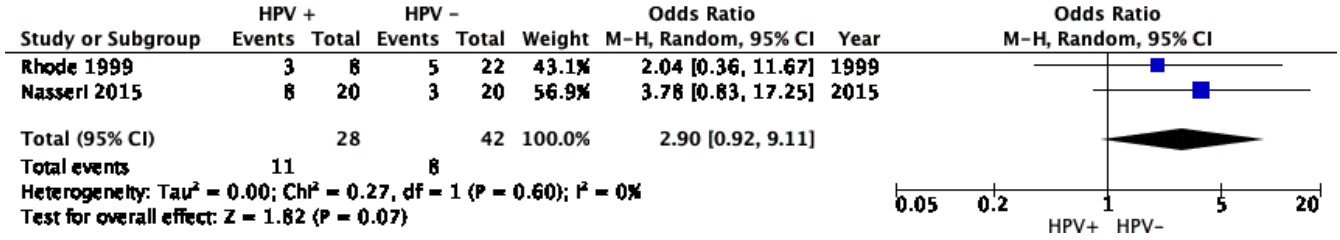


FIGURE 9 Risk of oligozoospermia and azoospermia of seminal HPV infection

only through an ascending infection of the cervix but also through infected spermatozoa.[90]

Several studies have reported that cervical HPV infection in women may reduce the pregnancy rate and increase the risk of miscarriage in couples undergoing ART.[16,26,29,42,82,91,92] The increased risk of HPV-induced miscarriage may be due to the damage caused to the structure of the chromosomes and the disruption of regulatory processes of gene function, such as early-stage apoptosis.[28,32,84] Recent studies postulate that early miscarriage is more frequent in HR-HPV infections, probably because of the high rate of replication of virions,[31] while LR-HPV genotypes could induce late-onset damage on embryonic and placental development due to a slower rate of replication.[31] The effect of HPV virions in placental tissue remains uncertain, and further studies are warranted.[31]

It is important to note that in addition to HPV, there are many sexually transmitted infections (STIs) that can result in infertility and pregnancy complications, such as chlamydia trachomatis, neisseria gonorrhoeae, viral hepatitis, and human immunodeficiency virus, which coexist with HPV in several cases.[93,94] A recent systematic review failed to confirm the association between STIs and male infertility, attributing its findings to the poor quality of the included

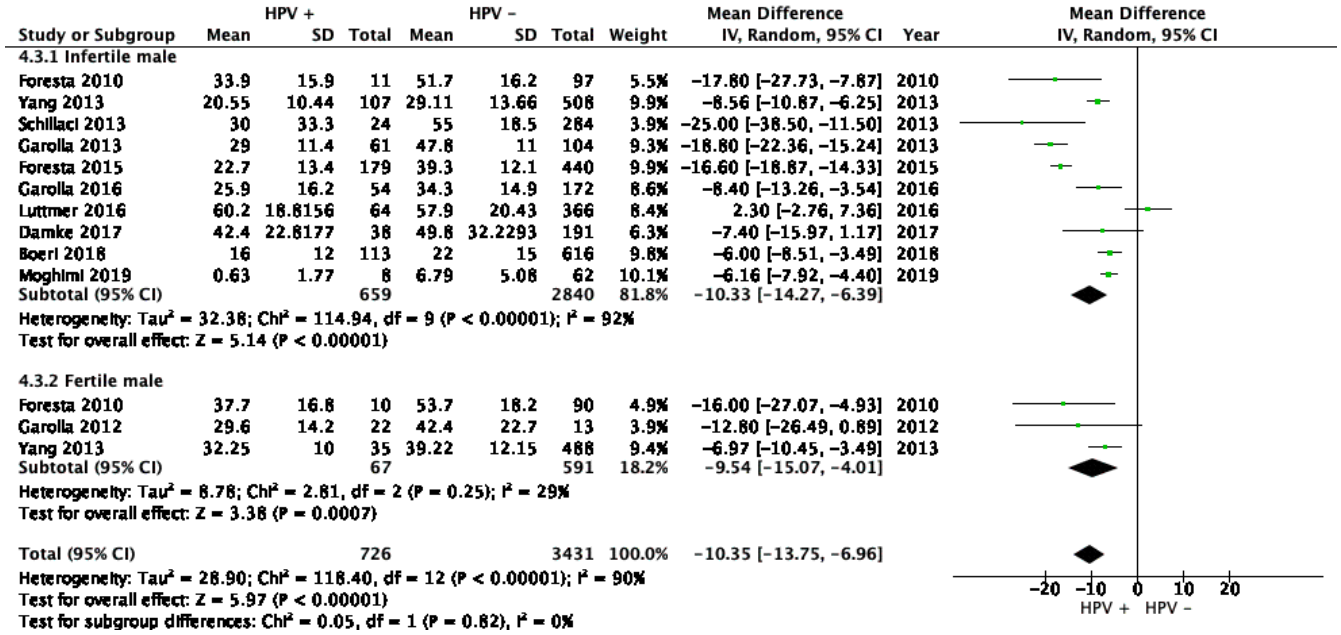


FIGURE 10 Effect of seminal HPV infection on sperm progressive motility

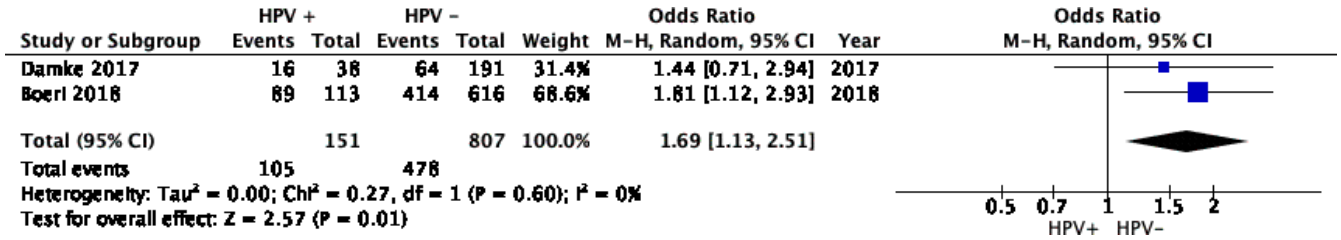


FIGURE 11 Risk of asthenozoospermia in seminal HPV infection

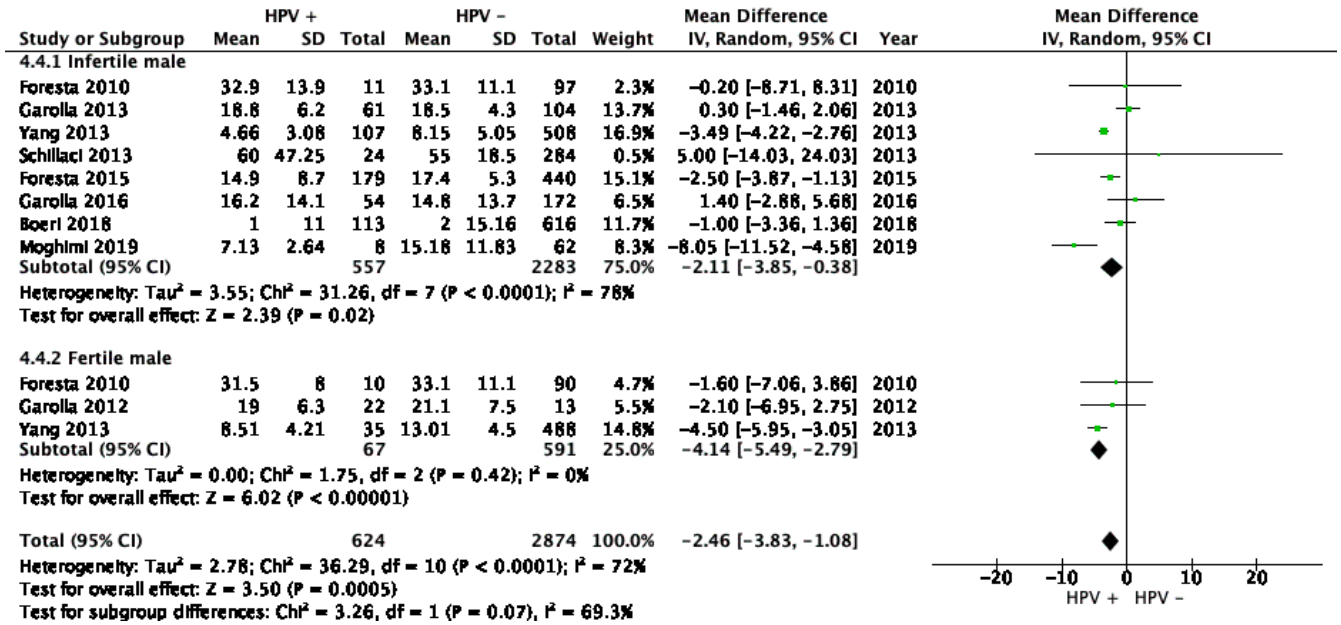


FIGURE 12 Effect of seminal HPV infection on sperm morphology

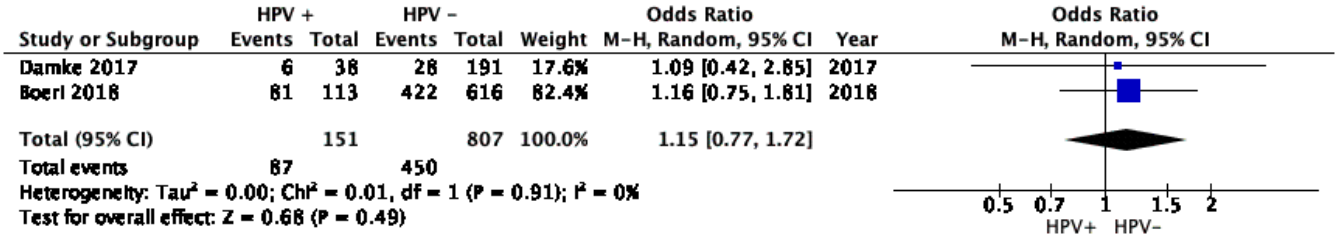


FIGURE 13 Risk of teratozoospermia in seminal HPV infection

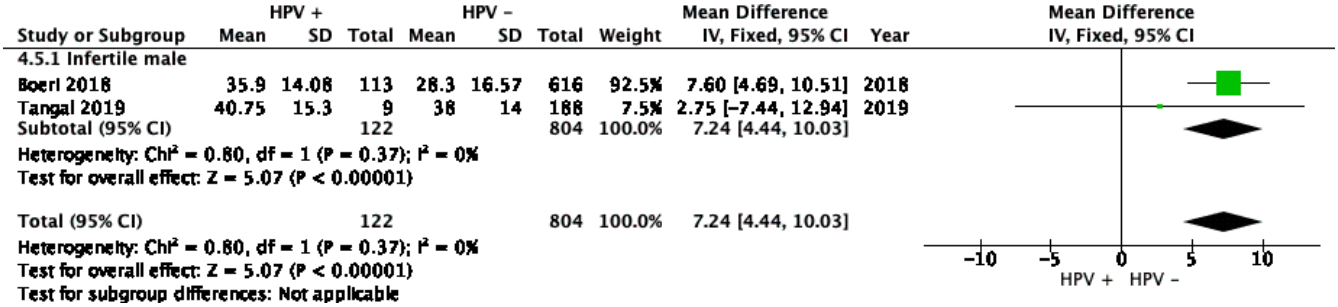


FIGURE 14 Effect of seminal HPV infection on sperm DNA fragmentation index

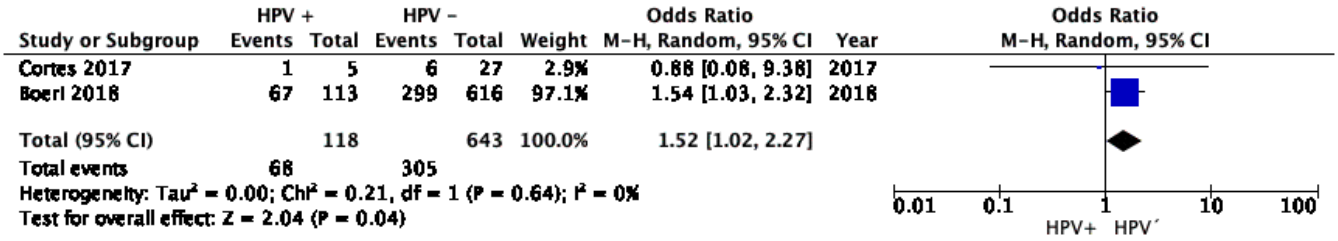


FIGURE 15 Risk of a sDFI higher than 30% in seminal HPV infection

studies. However, the systematic review suggested that future studies with adequate methodology and sample size may change the current evidence.[93]

4.4 | Strengths

This meta-analysis includes the largest number of studies involving HPV prevalence in semen, both in the general population and in infertile men. Performing subgroup analyses has made it possible to significantly reduce the heterogeneity observed, for example, in the risk of infertility in patients with seminal HPV infection.

Our research examined the geographical variation in the prevalence of seminal HPV infection and confirmed important differences between regions, for example, Europe and Latin America. This aspect has been widely confirmed by other studies carried out on women.[95] As a result of sexually transmitted virions, it is reasonable that the seminal prevalence of HPV exhibits a geographic aspect similar to cervical HPV infection.

4.5 | Limitations

Several limitations should be considered when interpreting the results of our meta-analysis. One of the main limitations are the design of the articles included. Most of them were not designed prospectively, which may reduce the reliability of the analysis.

The HR/LR-HPV genotypes should be recognized separately to determine their effects on the aspects evaluated: male fertility, seminal parameters, and reproductive outcomes. High heterogeneity across the included studies was observed, for example, in seminal parameters. However, this is not an unusual characteristic of meta-analyses related to infectious diseases. Furthermore, many of the studies included in our review that analyzed seminal parameters did not make an adequate adjustment for important confounding variables such as steroidal hormone levels and lifestyle habits, such as smoking and alcohol consumption. Also, in assessing reproductive outcomes, some studies lack adjustment for important confounding variables including co-infection with other STIs, such as chlamydia trachomatis, genetic factors, and environmental exposure. Further prospective research must be more accurate in examining the association between HPV

TABLE 3 Association between seminal HPV infection and seminal parameters

Seminal parameter	Population	N Studies	I2 (%)	MD	CI 95%	P-value	Quality of evidence (GRADE)
Sperm volume	Infertile men	6	54	−0.14	−0.39, 0.11	0.27	⨁⨁◯◯ Low
	Fertile men	4	0	−0.30	−0.30,−0.03	0.03	⨁⨁◯◯ Low
	Total	10	45	−0.17	−0.17,0.03	0.05	⨁⨁◯◯ Low
Sperm concentration	Infertile men	9	97	−8.98	−21.35,3.40	0.16	⨁⨁◯◯ Low
	Fertile men	3	0	−2.13	−8.55,4.29	0.52	⨁⨁◯◯ Low
	Total	12	96	−8.51	−18.96,1.94	0.11	⨁⨁◯◯ Low
Progressive motility	Infertile men	10	92	−10.33	−14.27,−6.39	<0.001	⨁⨁◯◯ Low
	Fertile men	3	29	−9.54	−15.07,−4.01	<0.001	⨁⨁◯◯ Low
	Total	13	90	−10.35	−13.75,−6.96	<0.001	⨁⨁◯◯ Low
Sperm morphology	Infertile men	8	78	−2.11	−3.85,−0.38	0.02	⨁⨁◯◯ Low
	Fertile men	3	0	−4.14	−5.49,−2.79	<0.001	⨁⨁◯◯ Low
	Total	11	72	−2.46	−3.83,−1.08	<0.001	⨁⨁◯◯ Low
Sperm DNA fragmentation index	Infertile men	2	0	7.24	4.44,10.03	<0.001	⨁⨁◯◯ Low

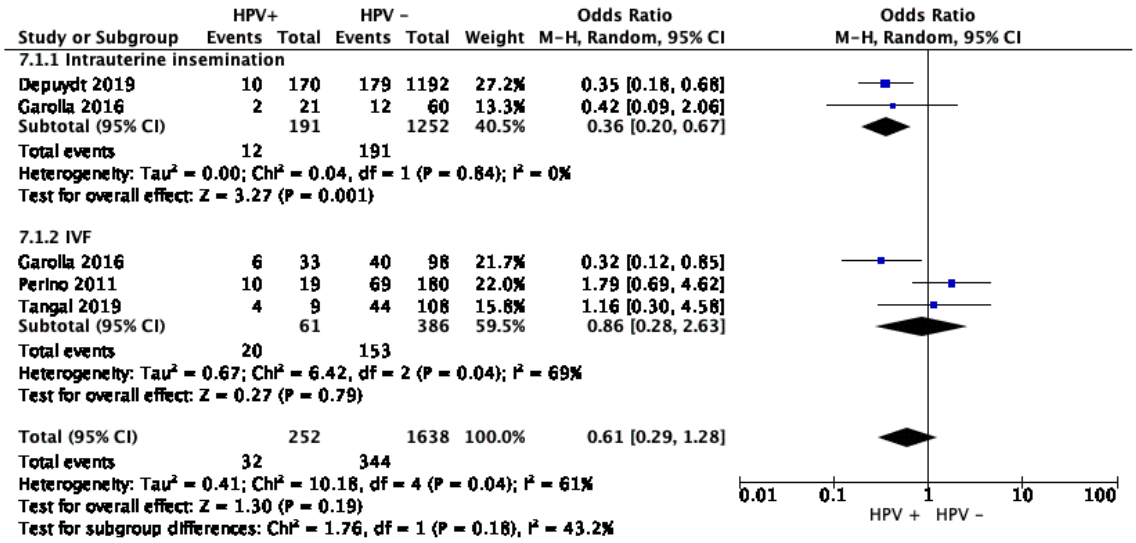


FIGURE 16 Effect of seminal HPV infection on clinical pregnancy rate in patients undergoing ART

infection and adverse pregnancy outcomes by accounting for STI co-infection.

The quality of evidence generated from our findings is low, mainly due to the factors mentioned above. This highlights the retrospective design of the majority of the included studies and a lack of adjustment for confounding variables.

4.6 | Future research

4.6.1 | Viral clearance

Considering the reported prevalence of seminal HPV infection, possible transmission to one's partner, and its oncological and reproductive

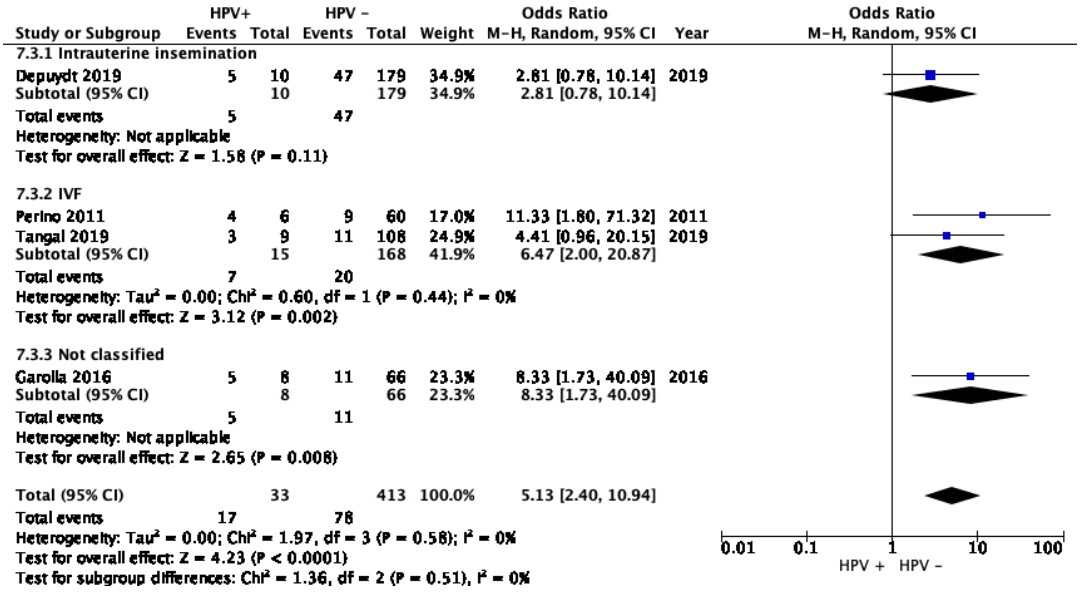


FIGURE 17 Effect of seminal HPV infection on the risk of miscarriage after ART

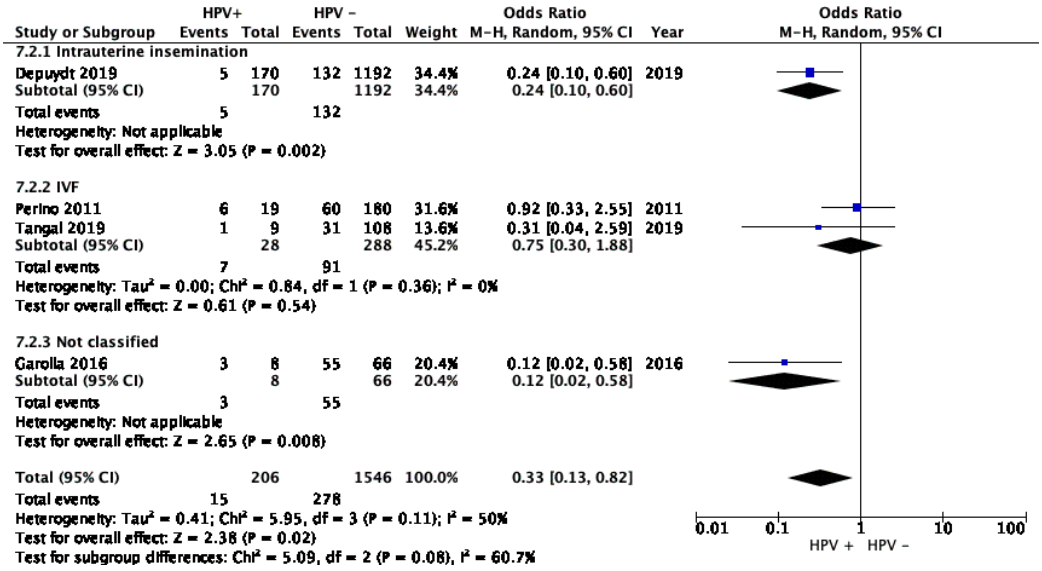


FIGURE 18 Effect of seminal HPV infection on the ongoing pregnancy rate in patients undergoing ART

consequences,[96] it is of great importance to identify the time to clearance of HPV infection in men. One study estimated the average time to clearance at 5, 9 months, and complete clearance in at least 75% of infected subjects within 12 months, regardless of HPV genotype.[70] However, this study included samples obtained not only from semen but also from the coronal sulcus, glans, penis, and scrotum.[6,70] Further studies specifically focused on seminal samples are required to determine time to clearance.

4.6.2 | Donor testing

Recent published research indicates that the prevalence of HPV infection in donor samples is similar to that of the general population and includes primarily men under 30 years old, the age group with the highest prevalence of HPV infection.[61,64] Many testing workups for other potentially transmissible semen pathogens are universally used in ART clinics, but HPV testing is not part of such protocols.

Considering the large proportion of ART cycles that are performed with donor spermatozoa and the current evidence that HPV DNA found in semen is not harmless contamination of the genital epithelial cells,[13,88] donor sperm testing strategies should be implemented because of the potential for HPV infection.

4.6.3 | Seminal wash

Since HPV virions bind to the surface of spermatozoa, sperm washing protocols prior to ART may reduce seminal infection. One study

TABLE 4 Association between seminal HPV infection and reproductive outcomes of patients undergoing ART

Reproductive outcome	Absolute effect Risk difference per 100 HPV + vs HPV- (CI 95%)	Odds ratio (CI 95%)	N Studies	Participants	Quality of evidence (GRADE)
Clinical pregnancy	8 fewer per 100 (18 fewer to 1 fewer)	0.61 (0.29-1.28)	4	1890	⨁⨁◯◯ Low
IUI	9 fewer per 100 (13 fewer to 5 fewer)	0.36 (0.20-0.67)	2	1443	⨁⨁◯◯ Low
IVF	3 fewer per 100 (29 fewer to 23 more)	0.86 (0.28-2.63)	3	447	⨁⨁◯◯ Low
Miscarriage	34 more per 100 (17 more to 51 more)	5.13 (2.40-10.94)	4	446	⨁⨁◯◯ Low
IUI	24 more per 100 (8 more to 55 more)	2.81 (0.78-10.14)	1	189	⨁⨁◯◯ Low
IVF	34 more per 100 (10 more to 59 more)	6.47 (2.00-20.87)	2	183	⨁⨁◯◯ Low
Ongoing pregnancy	9 fewer per 100 (13 fewer to 6 fewer)	0.33 (0.13-0.82)	4	172	⨁⨁◯◯ Low
IUI	8 fewer per 100 (11 fewer to 5 fewer)	0.24 (0.10-0.60)	1	137	⨁⨁◯◯ Low
IVF	7 fewer per 100 (23 fewer to 10 more)	0.75 (0.30-1.88)	2	316	⨁⨁◯◯ Low

has evaluated the effectiveness of conventional sperm selection procedures in eliminating HPV infection, noting a significant persistence of infected semen after sperm washing.[97] A later study observed that through seminal washing with the addition of heparinase III, HPV DNA was completely removed from the semen and no significant alteration in sperm quality or DNA integrity was evident.[17] New standardized seminal washing protocols should be implemented to reduce the risks of HPV transmission prior to ART.

4.6.4 | Transmission to women and associated consequences

A concordance of at least one viral type in 50% of HPV-infected couples has been reported, thus suggesting that HPV-infected men may have an important role in the transmission and maintenance of the infection in their partners. Among the consequences of HPV transmission, the development of precancerous lesions and cervical cancer is the most important.[56] Furthermore, several authors have suggested that men's sexual behavior may also contribute to an increased risk of cervical, anogenital, and oropharyngeal tract cancer in their sexual partners.[98,99] Among the reproductive consequences in women, spontaneous abortion and lower ongoing pregnancy rate are prominent. Detection of HPV in placental tissue suggests vertical transmission of HPV[85,100,101] and has been associated with adverse perinatal outcomes, including placental insufficiency, premature rupture of membranes,[102,103] and premature birth[104–106] in addition to possible transmission to the newborn during vaginal delivery or cesarean section after prolonged rupture of the membrane.[107,108] However, its impact on the newborn is uncertain, and related studies have presented conflicting results. A study of 291 pregnant women exceeding 36 weeks' gestation reported a vertical transmission rate of 18.2%; however, the absence of HPV infection at 6 months of age suggested temporary inoculation rather than vertical infection.[109] Contrary to these findings, other research has detected HPV DNA in different mucous membranes (genital, oral, or respiratory tract) of newborns from infected mothers.[110,111] Further research is still required to clarify whether certain HR/LR-HPV genotypes increase the risk of miscarriage or placental disease-related outcomes.

4.6.5 | Vaccination

There are currently three HPV vaccines available (bivalent, quadrivalent, and 9-valent); however, the actual impact of this vaccine on seminal infection and male infertility is uncertain. A recent systematic review of human studies concluded that an HPV vaccine used as an adjuvant treatment for clinically active HPV infection was associated with a decreased viral load.[112] Similarly, a controlled clinical trial of 619 patients with seminal HPV infection and one year of follow-up showed that the use of the prophylactic vaccine is effective in reducing the time to eliminate the virus.[25] A subsequent retrospective study showed that HPV vaccination in infected men is associated with increased pregnancy and live birth rates along with a decrease in miscarriages.[113] The authors also reported improved sperm motility and reduced ASA levels in vaccinated patients. Based on these findings, it is postulated that patients with seminal HPV infection who will undergo ART may benefit from prophylactic vaccination.

Currently, there is a disparity in the rate of vaccination between men and women due to the lack of data on its effectiveness and cost-effectiveness in men,[114] although universal vaccination already exists in countries such as the USA, Canada, and Australia. Further studies should confirm the effectiveness of the vaccine in eliminating seminal HPV infection and assess the potential benefits of prophylactic vaccination on reproductive outcomes in both infertile men and the general population.

5 | CONCLUSIONS

Our study suggests that seminal HPV infection is prevalent worldwide, and there is a higher prevalence in infertile men compared to the general population, regardless of the HPV genotype detected. There is a significant association between the infection and male infertility, notably an alteration of seminal parameters including a decreased progressive motility, increased sDFI, and an increased risk of asthenozoospermia and sDFI > 30%.

Considering the high prevalence in the infertile population observed in our study, couples consulting infertility specialists should be advised about this infection and the potential negative effect on seminal parameters and reproductive outcomes.

Present data should be interpreted with caution due to the low quality of the evidence. However, this information should be taken into account when evaluating infertile couples who will undergo ART, including donor sperm cycles. Available data are still insufficient to draw firm conclusions about the effect of HPV infection on the reproductive outcomes of ART patients in terms of live births, but an increased risk of miscarriage is noted.

Further studies with an adequate methodological design, sample size, control group, and adjustment for relevant confounding variables are required to confirm our findings.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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