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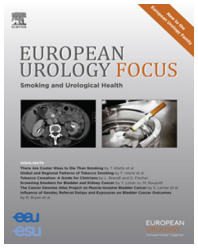

Review – Andrology

Sexually Transmitted Disease and Male Infertility: A Systematic Review

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Abstract

Context: Theoretically, sexually transmitted diseases (STDs) have the potential to disrupt male fertility; however, the topic remains controversial.
Objective: To describe the possible association between STDs and male infertility and to explore possible pathophysiologic mechanisms.
Evidence acquisition: We performed a systematic literature review in accordance with the PRISMA guidelines. PubMed, Embase, and the Cochrane Library were searched for articles published before January 1, 2016, using the MeSH terms for a variety of STDs and infertility. The search was restricted to human studies performed in men and published in English. Studies were included if they contained original data on a possible association or a cause-and-effect relationship between STD and male infertility. Studies were considered only if they included an appropriate control group and/or comprehensive laboratory data. Due to heterogeneity in the literature, a qualitative analysis was performed.
Evidence synthesis: Relevant studies on *Chlamydia trachomatis*, genital mycoplasmas, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and viral infections were identified. For all pathogens, the studies were contradictory and generally of limited quality. In studies confirming an association, there was a tendency for authors to perform multiple analyses without appropriate corrections and to subsequently focus solely on outcomes that seemed to suggest a positive association; however, the body of literature that does not confirm an association between STDs and male infertility is also of inadequate quality. The data regarding possible pathophysiologic mechanisms are inconclusive.
Conclusions: There may be an association between STDs and male infertility of unknown genesis and possibly with different pathogenic mechanisms for different pathogens. Alternatively, some STDs may cause male infertility, whereas others may not; however, there is hardly a strong correlation. High-quality studies of the subject are needed.
Patient summary: Sexually transmitted diseases may cause male infertility through unknown mechanisms; however, from the available research, we cannot be sure that there is an association, and more studies are needed.

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1. Introduction

Infertility is defined as the inability of a couple to achieve pregnancy despite unprotected intercourse for a period of >12 mo [1]. Approximately 15% of all couples are infertile, and it is estimated that a male factor plays a role in about half of the cases [2]. The components of male reproductive function include hormonal regulation of the hypothalamic–pituitary–gonadal axis, complete spermatogenesis, and unobstructed normal sperm transport and storage. Theoretically, sexually transmitted diseases (STDs) have the potential to disrupt several of these steps. Nevertheless, the main focus in studied STD-induced infertility tends to be on the female partner. This review aimed to describe the possible association between various STDs and male infertility. In addition, possible mechanisms by which STDs may influence male fertility have been explored and discussed.

2. Evidence acquisition

We performed a systematic literature review in accordance with the PRISMA guidelines. PubMed, Embase, and the Cochrane Library were searched for articles published before January 1, 2016, using the MeSH terms for a variety of STDs and infertility (Fig. 1). The search was restricted to human studies performed in men and published in English. Studies were included if they contained original data on a possible association or a cause-and-effect relationship between STD and male infertility. To reduce bias, studies were considered only if they included an appropriate control group and/or comprehensive laboratory data. Titles and abstracts were screened, and the full text of relevant articles was subsequently reviewed before inclusion. The primary author (M.F.) performed the initial screening, and all authors approved the final selection. Results of the literature search are illustrated in Figure 2. We extracted data regarding the prevalence of relevant STDs, fertility status, and traditional semen parameters as well as any data on seminal functional status or presence of antisperm antibodies. When nothing else was mentioned in the text, *infertility* was defined as the inability to conceive for a period of at least 12 mo, and *fertility* was defined as a history of parenthood and/or a currently pregnant partner. In studies in which participants were reported to have symptomatic urinary tract infections, this detail is specifically mentioned. Due to heterogeneity of the study methods and data, no meta-analyses were performed.

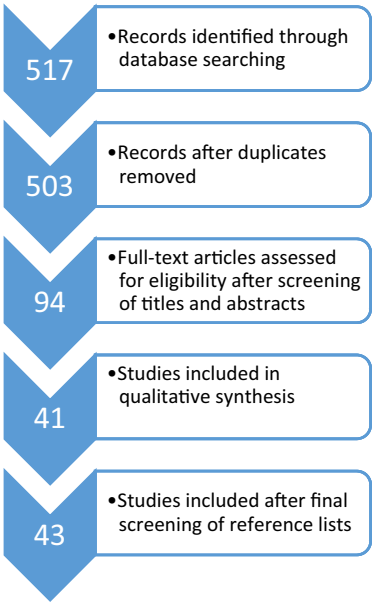

Fig. 2 – Flow diagram illustrating results of the literature search.

3. Evidence synthesis

Studies investigating STDs and fertility status and/or semen quality are summarized in Tables 1–4 according to pathogenic agents. The studies are further described in the text. Studies investigating possible causative links between STDs and infertility are described in the text only.

3.1. *Chlamydia trachomatis*

3.1.1. *Chlamydia trachomatis: studies investigating association with infertility*

Some studies have indicated that the incidence of chlamydia may be higher in infertile men compared with those with normal fertility. In one such study, serum samples were obtained from men from 52 couples with unexplained infertility and from 72 expectant fathers [3]. Men from the infertile couples were significantly more likely to be seropositive for chlamydia antibodies at a high titer; however, there was no difference between groups in the

((((((((((("Sexually transmitted diseases"[Mesh]) OR "Chlamydia trachomatis"[Mesh]) OR "Neisseria gonorrhoeae"[Mesh]) OR "herpes genitalis"[Mesh]) OR "Ureaplasma urealyticum"[Mesh]) OR "Mycoplasma hominis"[Mesh]) OR "hepatitis B"[Mesh]) OR "hepatitis C"[Mesh]) OR "HIV"[Mesh]) OR "Treponema pallidum"[Mesh]) OR "herpes simplex"[Mesh]) OR "cytomegalovirus"[Mesh]) OR "Trichomonaas vaginalis"[Mesh]) AND "infertility"[Mesh]

Fig. 1 – The full search strategy of MeSH terms used for searching PubMed.

Table 1 – Studies investigating *Chlamydia trachomatis* and fertility status and/or semen quality

Study (year)	Study characteristics	Main findings	Major limitations
Greendale et al (1993) [3]	• Case–control study • 52 men from infertile couples and 72 fertile men • Questionnaires and blood samples	• Infertile men were more likely to be seropositive for chlamydia antibodies at a titer ≥1:64 (OR: 3.4; 95% CI, 1.3–9.1)	• The titer of 1:64 was not predefined • Multiple analyses performed without corrections
Joki-Korpela et al (2009) [4]	• Case-control study • 90 men from infertile couples and 190 fertile men • Blood samples	• Chlamydial IgG (27.8% vs 6.3%) and IgA (22.2% vs 6.2%) were elevated in men from infertile couples ($p < 0.001$)	• 67/90 couples had confirmed female factor infertility
Mazzoli et al (2010) [5]	• Cohort study • 454 men with prostatitis resulting from chlamydia and 707 men with prostatitis resulting from other bacteria • Blood samples and semen samples	• 68.5% in the chlamydia group vs 1.9% in the nonchlamydia group were subfertile according to WHO criteria ($p < 0.003$)	–
Veznik et al (2004) [6]	• Cross-sectional study • 627 healthy sperm donors • Semen samples	• Chlamydia detected in 21.7% • Sperm morphology and motility reduced in samples with chlamydia • 37.0% vs 43.2% normal forms ($p = 0.01$) and 48.4% vs 52.0% vs 48.4% motility ($p = 0.05$)	• Multiple analyses performed without corrections
Ouzounova-Raykova et al (2015) [7]	• Case–control study • 281 infertile men and 100 fertile controls • Semen samples	• PCR detected chlamydia in 13.9% of infertile men vs 2% of fertile men (no p value given)	• No definition of fertility or description of how participants were included • Unclear if groups were otherwise comparable
Ouzounova-Raykova et al (2009) [9]	• Case–control study • 60 men from infertile couples and 40 healthy controls • Urethral swabs from infertile men	• Chlamydia was found in 5 men from the infertile couples and in 1 fertile man: RR 3.3 (95% CI, 0.4–27; $p = 0.26$)	• Unclear how chlamydia infections were assessed in healthy controls • Authors conclude that chlamydia infection is associated with infertility, although this is not supported by results
Al-Sweih et al (2012) [10]	• Case–control study • 127 men from infertile couples and 188 fertile men • Semen samples	• Chlamydial DNA detected in semen of 3.9% of men from infertile couples vs 3.7% of fertile controls ($p > 0.05$)	–
Abusarah et al (2013) [11]	• Case–control study • 93 infertile men and 70 fertile men • Urine samples	• PCR detected chlamydia in 4.3% of infertile men and 1.4% of fertile men ($p = 0.284$)	–
Trei et al (2008) [12]	• Retrospective cohort study • 17 764 men who received chlamydia testing between in 2001 and 2002 • Review of medical databases from 2001 to 2005	• Infertility was diagnosed in 1.27% of chlamydia-positive and 1.00% of chlamydia-negative men • Adjusted HR 1.36 (95% CI, 0.93–2.00; $p > 0.05$)	• Individual medical records not assessed • Chlamydia status before 2001 unknown • Likely presence of unrecognized chlamydia
Karinen et al (2004) [13]	• Nested case–control study analysis of a prospectively followed birth cohort ($n = 12\,231$) • 181 men with self-reported time to pregnancy of ≥12 mo and 2 controls with normal fertility for each case • Questionnaires and blood samples	• No differences in genital infections • No differences in presence of chlamydia IgG antibodies • Subanalyses showing differences in specific antibody serotypes	• Multiple analyses performed without corrections • Few participants with specific serotypes • Conclusion not in line with results
Karinen et al (2004) [14]	• Nested case–control analysis of a prospectively followed birth cohort ($n = 12\,231$) • 52 men with self-reported time to pregnancy of ≥12 mo and 2 controls with normal fertility for each case • Questionnaires and blood samples	• Higher titers of IgA antibodies to chlamydia Hsp10 in fertile men ($p = 0.048$) • No differences in other titers	• Multiple analyses performed without corrections
Samra et al (1994) [15]	• Case–control study • 135 men recruited at male infertility clinics and 88 fertile men • Blood samples, semen samples, and urethral smears	• Chlamydia was found in 9.6% of infertile men and 5.7% of fertile men ($p = 0.29$)	• Several other potential causes of infertility present in both men and women
Liu et al (2014) [16]	• Case–control study • 621 men from infertile couples and 615 fertile men • Semen samples	• Chlamydia found in 2.58% of infertile men and 2.28% of fertile men ($p = 0.732$)	• Multiple analyses performed without corrections

CI = confidence interval; HR = hazard ratio; Hsp = heat shock protein; Ig, immunoglobulin; OR = odds ratio; PCR = polymerase chain reaction; RR = relative risk; WHO = World Health Organization.

Table 2 – Studies investigating genital mycoplasma species and fertility status and/or semen quality

Study (year)	Study characteristics	Main findings	Limitations
Samra et al (1994) [15]	• Case–control study • 135 men recruited at male infertility clinics and 88 fertile men • Blood samples, semen samples, and urethral smears	• Mycoplasma species were found in 31.8% of infertile men and 28.4% of fertile men (not significant) • Considered alone, MH was found in 13.3% of infertile men and 1.1% of fertile men ($p < 0.0015$) • No difference in prevalence when considering UU alone	• Multiple analyses performed without corrections
Liu et al (2014) [16]	• Case–control study • 621 men from infertile couples and 615 fertile men • Semen samples	• MH found in 5.98% of infertile men and 4.88% of fertile men ($p = 0.472$) • UU found in 26.57% of infertile men and in 24.88% of fertile men ($p = 0.496$)	• Multiple analyses performed without corrections
Lee et al (2013) [26]	• Case–control study • 50 men from infertile couples and 48 fertile men • Semen samples	• MH found in 48% of infertile men and 25% of fertile men ($p = 0.022$) • UU found in 14% of infertile men and 6.3% of fertile men ($p = 0.318$)	• Multiple analyses performed without corrections
Xu et al (1997) [27]	• Case–control study • 1461 men with idiopathic infertility and 375 fertile controls • Semen samples	• UU found in 38.77% of infertile men and 9.06% of fertile men ($p < 0.001$)	–
Zeighami et al (2007) [28]	• Case–control study • 100 infertile men and 100 healthy controls • Semen samples	• UU found in 12% of infertile men and 3% of fertile men ($p < 0.05$) • An increased incidence of UU in infertile men (12% vs 3%, $p < 0.05$)	• No definition of fertility or description of how participants were included • No demographic information on participants
Wang et al (2006) [29]	• Cross-sectional study • 346 men attending andrology clinics • Questionnaires and semen samples	• UU found in 12% • UU infection associated with higher semen viscosity, lower semen pH, and reduced sperm concentration (all p values <0.05) • UU infection was not significantly related to other semen parameters	• Multiple analyses performed without corrections
Plecko et al (2014) [30]	• Case–control study • 145 infertile men and 49 fertile controls • Questionnaires and urine samples	• History of STD reported by 55.8% of infertile men and 24.4% of fertile men ($p = 0.0001$) • Infertile men had a higher number of lifetime sexual partners ($p < 0.0001$). • Ureaplasma species found in 30% of the infertile men and 35% of the fertile men (not significant) • MH found in 21% of the infertile men and 20% of the fertile men (not significant)	• Risk of recall bias

MH = *Mycoplasma hominis*; STD = sexually transmitted disease; UU = *Ureaplasma urealyticum*.

Table 3 – Studies investigating *Neisseria gonorrhoeae* and fertility status and/or semen quality

Study (year)	Study characteristics	Main findings	Limitations
Abusarah et al (2013) [11]	• Case–control study • 93 infertile men and 70 fertile men • Urine samples	• *Neisseria gonorrhoeae* found in 6.5% of the infertile men and in none of the fertile men ($p < 0.05$)	–
Osegbe (1991) [35]	• Prospective cohort study • 45 men with gonococcal epididymo-orchitis • Questionnaires, semen samples, blood samples	• 14/45 men had previously fathered children • 2 yr after the gonococcal infection, 21% of the fathers and 40% of the whole group showed normal semen parameters	• Semen parameters before infection unknown

proportions of patients who were positive for chlamydia antibodies at any titer (54% vs 52%). Furthermore, there were no significant differences in semen characteristics between antibody-positive and -negative infertile men. The authors speculated that high-level titers are a marker of the most serious infections with potential to cause long-term sequelae such as infertility. Nevertheless, there was no significant association between either previous diagnosis of genitourinary disease or self-reported genitourinary symptoms and infertility. Another study analyzed chlamydia immunoglobulin (Ig) G and IgA antibodies in the plasma of 90 men from infertile couples and from 190 healthy blood donors [4]. Both IgG (27.8% vs 6.3%) and IgA (22.2% vs. 6.2%) were elevated in men from infertile couples ($p < 0.001$). In addition, semen motility was lower in men from infertile couples with chlamydial antibodies than among men from infertile couples without antibodies. Chlamydial antibodies were not associated with other semen parameters and did not affect results of in vitro fertilization. Interpretation of the results is complicated by the report that 23 of 90 couples had male factor infertility, whereas 67 of 90 had confirmed female factor infertility, with no significant difference in the

Table 4 – Studies investigating sexually transmitted viral infections and fertility status and/or semen quality

Study (year)	Study characteristics	Main findings	Limitations
Naumenko et al (2014) [39]	• Cross-sectional study • 232 men attending infertility clinics • Semen samples including tests for EBV, CMV, and HHV-6	• CMV was more prevalent in the group of infertile men with chronic inflammatory urogenital tract diseases compared with the other groups combined (18.5% vs 5.4%, $p = 0.03$) • CMV was associated with reduced sperm count (39.5 vs 72.5 $\times$ 10^6/ml, $p = 0.036$) • HHV-6 was more prevalent in fertile men with chronic urogenital tract inflammation than in the other groups combined (19% vs 6.3%, $p = 0.018$) • No other significant relationships	• No definition of fertility • Multiple analyses performed without corrections
Foresta et al (2010) [40]	• Cross-sectional study • 200 men aged 18 yr • Semen samples	• HPV was associated with reduced sperm motility (53.7% in HPV-negative vs 37.7% in HPV-positive; $p < 0.05$) • Other semen parameters did not differ with or without HPV	• Multiple analyses performed without corrections • Authors did not investigate the presence of other viruses
Su et al (2014) [41]	• Retrospective case–control study • 5138 men with HBV and 25 690 noninfected controls • Data from the Taiwan National Health Insurance Research Database	• HBV infection associated with an increased 10-yr incidence of infertility diagnosis (HR: 1.52; 95% CI, 1.20–1.92; $p < 0.05$)	• Individual medical records not assessed • Likely presence of unrecognized HBV • Limited correction for confounders
Moretti et al (2008) [42]	• Case–control study • 15 men with chronic HBV, 13 men with chronic HCV, and 20 fertile controls • Semen samples	• No differences in sperm concentration, motility, or morphology between patients and controls • Increased incidences of sperm necrosis in infected men (43.2% for HVC, 35.86% for HBV, and 15.57% for noninfected men; $p < 0.01$) • Increased incidences of sperm apoptosis in infected men (6.76% for HVC, 7.5% for HBV, and 2.9% for noninfected men; $p < 0.05$)	• Multiple analyses performed without corrections
Hofny et al (2011) [43]	• Case–control study • 57 HCV infected men and 40 fertile controls • Semen samples	• Mean semen volume increased with HCV: 2.33 vs 2.15 ml ($p < 0.05$) • Mean sperm count reduced with HCV: 40.1 vs 75.4 10^6/ml ($p < 0.01$) • Mean sperm abnormal forms increased with HCV: 40.35% vs 12.6% ($p < 0.01$) • Mean sperm motility reduced with HCV: 39.6% vs 58.1% ($p < 0.01$)	• Control participants had confirmed fertility before enrollment, whereas the fertility status of participants with HCV was unknown
Muller et al (1998) [44]	• Case–control study • 250 HIV-seropositive men and 38 fertile controls • Semen samples	• Median semen volume reduced with HIV: 1.8 vs 2.9 ml ($p < 0.0001$) • Median sperm concentration reduced with HIV (62 vs 100 $\times$ 10^6/ml, $p < 0.001$) • Median sperm motility reduced with HIV: 52% vs 64% ($p < 0.0001$) • Median rapid and linear motility reduced with HIV: 14% vs 21% ($p < 0.05$)	• Control participants had confirmed fertility before enrollment, whereas the fertility status of participants with HIV was unknown
Umapathy (2005) [46]	• Cross-sectional study • 83 apparently healthy men attending a hospital for undisclosed reasons • Semen samples and blood samples	• 36/83 tested HIV positive • Mean sperm motility reduced with HIV: 34% vs 53% ($p < 0.02$) • No difference in sperm count and sperm morphology between infected and noninfected men	• No demographic knowledge provided • Unclear why healthy men would visit a hospital

CI = confidence interval; CMV = cytomegalovirus; EBV = Epstein–Barr virus; HBV = *Hepatitis B virus*; HCV = *Hepatitis C virus*; HHV-6 = *Human herpesvirus 6*; HIV = human immunodeficiency virus; HPV = human papillomavirus; HR = hazard ratio.

prevalence of antibodies between these groups. A larger study investigated semen quality in men with prostatitis resulting from chlamydia ($n = 454$) and from other bacteria ($n = 707$) [5]. Sperm concentration, sperm motility, and normal morphology were all significantly reduced in the chlamydia-infected group (all p values <0.001). Overall, 68.5% in the chlamydia group and 1.9% in the nonchlamydia group were considered subfertile according to World Health Organization (WHO) criteria ($p < 0.003$). Similarly, Veznik et al found that sperm morphology and motility were higher in samples without chlamydia compared with chlamydia-positive samples in 627 healthy sperm donors, with 43.2% versus 37.0% normal forms ($p = 0.01$) and 52.0% versus 48.4% motility ($p = 0.05$), respectively [6]. There were no statistically significant differences in volume of semen, density of the spermatozoa, or measured sperm motility.

Considering mixed infections, Ouzounova-Raykova et al investigated the prevalence of polymerase chain reaction

(PCR)–detected chlamydia, *Mycoplasma hominis* (MH), and *Ureaplasma urealyticum* (UU) in semen of 281 infertile men and 100 fertile controls [7]. Prevalence of all pathogens was increased in infertile men, with chlamydia, UU, and MH found in 13.9%, 19.2%, and 9.9%, respectively, versus 2%, 11%, and 3%, respectively, in fertile men (no p values given); however, the authors did not include their definition of *fertility* or how participants were included. In addition, no description of other possible discrepancies between infertile and fertile men was given. Another study investigated whether coinfection with chlamydia and human papillomavirus (HPV) affected sperm parameters in 1003 men with chronic prostatitis [8]. A total of 71.3% of the patients were infected with chlamydia only, and 28.7% were infected with both chlamydia and HPV. On semen analysis, 50.8% in the chlamydia-only group versus 66.8% in the coinfected group were subfertile according to the WHO criteria ($p < 0.001$). The finding that almost one-third of the chlamydia-infected men were coinfected with HPV underscores that STDs often coexist and may potentiate each other's detrimental effects. The study is limited by a lack of a control group infected with only HPV, which means that it is difficult to assess whether the reduced semen quality was caused by the coinfection or by HPV alone.

Other studies have been unable to identify an association between chlamydia and male infertility. A study by Ouzounova-Raykova and coworkers investigated the prevalence of chlamydia in 60 male partners of infertile couples compared with the prevalence in 40 healthy controls [9]. The authors took urethral swabs from all male participants and cervical swabs from the female partners of infertile couples and used cultures and PCR for chlamydia detection. Chlamydia was found in five men from the infertile couples and in one control participant ($p = 0.26$). Three of the female partners of chlamydia-positive men harbored signs of an infection. For a similar study of 315 participants, the investigators detected chlamydial DNA in the semen of 3.9% of men from infertile couples versus 3.7% of fertile controls ($p > 0.05$) [10]. The study showed better semen parameters in uninfected men compared with infected men in the fertile subgroup but not in the infertile subgroup. Abusarah et al also used urine PCR for detection of chlamydia in 93 infertile men with abnormal semen parameters and 70 men who had previously fathered children and/or had a normal sperm evaluation [11]. They found chlamydia in 4.3% of infertile men and 1.4% of fertile men ($p = 0.284$). It is unclear whether the groups were comparable because controls were recruited among men presenting at urology clinics for undisclosed reasons.

Although most studies are composed mainly of clients of infertility clinics who likely suffer competing causes of infertility, two database studies have looked at the association between chlamydia and the development of infertility. Trei et al used laboratory records to identify all active-duty Air Force men who received chlamydia testing between in 2001 and 2002 ($n = 17\,764$) [12]. Participants were tracked through 2005, and infertility was diagnosed in 1.27% of chlamydia-positive and 1.00% of chlamydia-negative men. The difference did not reach statistical significance. Karinen et al conducted a similar study with data from a prospectively followed Finnish cohort of 12 231 men and women [13]. Participants consisted of those who both delivered blood samples and responded to questions about their time to pregnancy at the age of 31 yr. Overall, 181 men and 298 women had self-reported time to pregnancy of $\geq$12 mo. Two random controls with normal fertility were picked for each case. The study showed no statistically significant differences in either self-reported genital infections or the presence of chlamydia IgG antibodies between the cases and controls. Only after various subanalyses of 10 different serotypes were the authors able to demonstrate an increased occurrence of antibodies in male cases demonstrating a C complex containing immunotypes C, J, H, and I (7.7% in male cases and 3.0% in controls; $p = 0.012$) and in individual serotype H among men ($p = 0.036$) and serotypes C ($p = 0.036$), J ($p = 0.022$), H ($p = 0.021$), and I ($p = 0.025$) among women. The remaining associations were insignificant. Despite the multiple analyses performed and the low absolute numbers of participants with specific serotypes, the authors still hypothesized that "chlamydia infection plays an important role in male infertility."

In a subsequent study of the same cohort, the authors looked at a possible association between infertility and antibodies to chlamydia heat shock protein (Hsp) 60 and Hsp10 [14]. Using 146 cases (94 women and 52 men) and 278 controls (188 women and 90 men), the authors found that IgA antibodies to chlamydia Hsp60 and Hsp10 were significantly higher in female partners of infertile couples compared with controls ($p = 0.002$ and $p = 0.007$, respectively), whereas there was no statistically significant difference in IgG antibodies to the two proteins. Among men, the control participants showed significantly higher titers of IgA antibodies to Hsp10 ($p = 0.048$), whereas there were no differences in the remaining titers. Taken together, the two studies in the Finnish cohort do not show a clear link between chlamydia infection and male infertility.

Regarding mixed infections, Samra et al looked at the prevalence of chlamydia, UU, and MH in infertile couples ($n = 135$) and fertile couples ($n = 88$) [15]. Among the men in infertile couples, oligoteratoasthenozoospermia was diagnosed in 62.9%, with 28.9% having a varicocele. In addition 21.5% of the men were diagnosed with prostatovesiculitis, antisperm antibodies, or both. Among women from infertile couples, ovulatory dysfunction was diagnosed in 31.8%, tuboperitoneal adhesions and/or endometriosis was diagnosed in 6.7%, and uterine adhesions or myomata were diagnosed in 5.2%. The degree of overlapping pathology in couples is unclear. Antichlamydia IgA, IgG, and IgM antibodies were tested in blood and semen, whereas semen, urethral, and cervical smears were cultured for bacteria. Chlamydia was found in 9.6% of men and 10.4% of women in the infertile group and in 5.7% of men and 4.5% of women in the fertile group ($p = 0.29$ and $p = 0.12$, respectively). More infertile women were positive for serum chlamydia IgG compared with fertile women (11.9% vs 3.4%, $p < 0.015$). Likewise, specific semen IgA was higher in infertile than in fertile men (8.9% vs 1.1%, $p < 0.015$). However, there were

no differences in the prevalence of remaining immunoglobulins, and no corrections were made for multiple comparisons. A similar study using PCR found no significant differences in the prevalence of the three pathogens in semen between 621 men from infertile couples (34.93%) and 615 fertile controls (32.03%) [16].

3.1.2. *Chlamydia trachomatis: studies investigating possible causative links to infertility*

Despite the questionable link between infertility and chlamydia, several studies have attempted to identify causative mechanisms. A direct toxic effect has been suggested by in vitro experiments. In one such study, Galdiero and coworkers showed that lipopolysaccharide extracted from chlamydia caused spermatozoa mortality of 100% within 60 min of incubation [17]. Likewise, another study found that incubating spermatozoa from normospermatic men with chlamydia elementary bodies caused a decline in motile sperm cells and an increase in dead cells [18]. When incubating sperm with dead elementary bodies, the detrimental effects were abolished, indicating that these detrimental events were caused by live bacteria only. Regarding advanced sperm function, limited data from a study of 293 infertile men of whom 13% had signs of previous chlamydia infection did not point to an association between chlamydia and reduced sperm DNA integrity [19]. Meanwhile, a study assessing the acrosome reaction in semen from chlamydia-negative ($n = 46$) and chlamydia-positive ($n = 30$) male partners of infertile couples and healthy men ($n = 53$) suggested that sperm functional capacity may be reduced with infection [20]. Other researchers have investigated a possible autoimmune response against sperm cells, with unconvincing results [21].

An alternative theory of cause and effect is that chlamydial infections may cause damage to the ductal system. To test this theory, Sripada et al used PCR to detect chlamydia DNA in testicular/epididymal biopsies and aspirate of 14 men with idiopathic obstructive azoospermia and 22 men seeking vasectomy reversal [22]. No chlamydia-specific DNA was detected in any of these participants, making the hypothesis that asymptomatic chlamydial infection can lead to obstruction of the male genital tract unlikely. However, this lack of causation may not apply to men with symptomatic chlamydia infections. In addition, the prevalence of chlamydia in the background population was uncertain, and the authors did not perform a power analysis, meaning that the study could have been underpowered. Looking for more subtle signs of damage, Gonzalez-Jimenez et al found that infertile men with free stereocilia in semen had increased prevalence of chlamydia, MH, and UU on semen culture [23]. This result was taken as indirect evidence that infections may cause damage to the ductal system. However, the small number of highly selected participants makes the study prone to bias, and the authors concluded that prospective trials are needed to confirm the hypothesis.

Yet another theory revolves around the female partner. Eggert-Kruse et al found a significant relationship between the presence of chlamydia antibodies in men's semen and tubal infertility in their female partners ($n = 197$) [24]. The finding was confirmed in a subsequent study with 1303 couples consulting for infertility treatment [25]. There was no relation between chlamydia antibodies and general semen quality, sperm functional capacity, or the presence of antisperm antibodies in either of the studies. The findings suggest that chlamydia does not have a direct effect on male fertility but rather has an indirect effect through infection of the female partner.

3.2. *Genital mycoplasma and ureaplasma species*

3.2.1. *Genital mycoplasma and ureaplasma species: studies investigating association with infertility*

In the study by Samra et al, described above, mycoplasma species were found in 31.8% of men and 25.9% of women in infertile couples and in 28.4% of men and 26.2% of women in fertile couples [15]. Neither difference was statistically significant. However, when considered alone, MH was found in 13.3% of infertile men and 10.4% of infertile women and in only 1.1% each of fertile men and women ($p < 0.0015$ and $p < 0.01$, respectively). In contrast, Lee et al found that UU was more frequent in semen from the men from 50 couples with idiopathic infertility (48%) compared with 48 fertile men (25%; $p = 0.022$), whereas there were no significant differences between the occurrence of MH [26].

A larger study looked at UU in 1461 men with idiopathic infertility and 375 fertile controls, all with normal semen parameters according to WHO 1987 criteria [27]. There was a significantly higher frequency of UU infection among infertile men compared with fertile controls (38.77% vs 9.06%, $P < 0.001$). Examination of eight specimens from infertile men and eight specimens from fertile participants by electron microscopy, immunogold, and immunofluorescence techniques demonstrated adhesion of UU to the membranes of spermatozoa and exfoliated germ cells, which the authors proposed as a possible cause of the infertility. An increased incidence of UU in semen from 100 infertile men compared with 100 healthy controls (12% vs 3%, $p < 0.05$) analyzed using PCR was also found by Zeighami et al [28]. In the UU-positive infertile patients, semen volume, count, and normal morphology were reduced compared with UU-negative infertile men. Unfortunately, the study did not provide demographic information on the participants, and the study definitions of *infertile* and *fertile* men were not provided. These findings are somewhat contradicted by an earlier study in which the relationship between UU and semen quality was assessed in 346 men attending Chinese andrology clinics [29]. In this study, 39.3% had positive semen UU cultures, and on multivariate analysis, this was associated with higher semen viscosity, lower semen pH, and reduced sperm concentration (all p values <0.05). However, UU infection was not significantly related to other semen parameters. Another study compared the occurrence of genital mycoplasmas in first-void urine samples from 145 infertile men with reduced semen quality and 49 fertile controls [30]. The infertile men were significantly more likely to report a

history of STD ($p = 0.0001$) and had a higher number of lifetime sexual partners ($p < 0.0001$). Nevertheless, the study revealed no statistically significant differences in the occurrence of MH and UU between the groups.

3.2.2. Genital mycoplasma and ureaplasma species: studies investigating possible causative links to infertility

As with chlamydia, the possible pathophysiology behind MH- or UU-related infertility has been investigated in in vitro studies. Díaz-García and coworkers showed that clusters of MH attach to spermatozoa and locate intracellularly [31]. Interestingly, the MH–spermatozoa interaction reached a maximum within the first hour and then started to decline. Sperm viability did not decline significantly compared with uninfected spermatozoa. Likewise, Nunez-Calonge et al found a significant reduction in sperm motility as well as signs of membrane alterations when incubating spermatozoa with UU [32]. Scanning electron microscopy showed that clusters of UU attached to the deformed spermatozoa. In a more complex study, Reichart et al further confirmed that UU adhere to sperm cells in vitro and that infection caused dose- and time-dependent chromatin decondensation and DNA damage [33]. Surprisingly, infected cells exhibited higher rates of viability and motility than uninfected cells. The study also investigated sperm chromatin stability and DNA integrity in semen from eight men with UU-positive cultures. Initially, the sperm cells exhibited a low percentage of stable chromatin, as determined by nuclear chromatin decondensation assay (42%, $n = 8$), and a high percentage of denatured DNA, as determined by sperm chromatin structure assay (60.9%, $n = 7$). A significant improvement in both parameters was observed following 10 d of doxycycline treatment. Contrary to this finding, another study measured susceptibility of DNA strand breaks in sperm nuclear chromatin to in situ denaturation in 293 men and found no overall association with chlamydia, UU, and MH infection [19]. Antibiotic therapy was initiated and followed up in 47 of the infected men with no apparent effect on semen parameters.

A different approach was taken by Shi and coworkers who recruited healthy donors and infertile patients infected with UU [34]. Using western blot analyses, the authors confirmed the existence of possible cross-reactive antigens between UU and human sperm membrane proteins. The authors were able to purify one of the cross-reactive antigens and identify a common pentapeptide between urease complex component UreG and human nuclear autoantigenic sperm protein. The clinical significance of this finding is unclear.

3.3. Neisseria gonorrhoeae and Treponema pallidum

Our search yielded only two studies demonstrating a possible association between *Neisseria gonorrhoeae* and male infertility. In the Jordanian study, previously described, involving 93 infertile men and 70 fertile controls, *Neisseria gonorrhoeae* DNA was detected in semen from 6.5% of infertile men and in none of the fertile men ($p < 0.05$) [11]. In another study, the fertility status of 45 men who developed gonococcal urethritis and subsequent epididymo-orchitis were followed prospectively [35]. Fourteen of the men had previously fathered children; however, 2 yr after the gonococcal infection, only 21% of these fathers and 40% of the whole group showed normal semen parameters. Although severe syphilis infections can likely cause ductal obstruction and/or testicular damage, no studies on *Treponema pallidum* were deemed appropriate for this review. The lack of studies on the two pathogens is likely due to the rarity of infections in developed countries.

3.4. Trichomonas vaginalis

Limited evidence from in vitro studies suggests that *Trichomonas vaginalis* may have detrimental effects on sperm motility [36,37]. Only a single study investigating possible in vivo effects was identified, but the authors selected an inappropriate control group with confirmed normal semen parameters [38].

3.5. Sexually transmitted viral infections

3.5.1. Epstein–Barr virus, cytomegalovirus, human herpesvirus, and human papillomavirus

Naumenko et al looked at Epstein–Barr virus (EBV), cytomegalovirus (CMV), and *Human herpesvirus 6* (HHV-6) DNA in semen samples of 232 men attending infertility clinics [39]. This cohort consisted of infertile men with varicocele, men with idiopathic infertility, infertile men with chronic urogenital tract inflammation, fertile men with chronic urogenital tract inflammation, and men whose partners had a history of pregnancy loss. The total prevalence of PCR-detected viral DNA was 17.7%. CMV was more prevalent in the group of infertile men with chronic inflammatory urogenital tract diseases compared with the other groups combined (18.5% vs 5.4%, $p = 0.03$). Furthermore, CMV infection was associated with reduced sperm count (39.5 vs 72.5 $\times$ 10^6/ml, $p = 0.036$). In contrast, HHV-6 was more prevalent in fertile men with chronic urogenital tract inflammation than in the other groups combined (19% vs 6.3%, $p = 0.018$), but the infection was not associated with any differences in semen parameters compared with the remaining groups. No associations between EBV and infertility or urogenital tract inflammation were found. The study is limited by the fact that the authors failed to describe how *fertile* men were defined and why fertile men would visit an infertility clinic. No corrections for multiple comparisons were performed. In a better designed study, Foresta and coworkers investigated the prevalence of HPV in 200 volunteers aged 18 yr, 100 of whom had previously had sexual intercourse [40]. Not surprisingly, none of those without intercourse had HPV DNA in their semen. The prevalence was 10% in the sexually active participants. Seminal volume, pH, sperm concentration, viability, and normal morphology did not differ between HPV-infected and noninfected participants; however, HPV was associated with significantly reduced sperm motility (53.7% in HPV-negative vs 37.7% in HPV-positive participants; $p < 0.05$). Although the authors excluded

bacterial infections by microbiological sperm culture, it is important to note that they did not investigate the presence of other viruses, meaning that coinfection could be present in some of the participants.

3.5.2. Hepatitis

Su et al used data from the Taiwan National Health Insurance Research Database to compare the incidence rates of male infertility in 5138 men with newly diagnosed *Hepatitis B virus* (HBV) and 25 690 noninfected controls [41]. With a follow-up period of 10 yr, the study found a 1.59-times increased crude incidence rate of infertility in the HBV patients, corresponding to an overall risk in the infected group of 1.83% versus 1.15% in the noninfected group ($p < 0.05$). The association remained significant on multivariate analysis (hazard ratio: 1.52; 95% confidence interval, 1.20–1.92). In a much smaller study, the sperm quality from patients with chronic HBV ($n = 15$) or *Hepatitis C virus* (HCV; $n = 13$) and unknown fertility status was compared with that of 20 fertile controls [42]. There were no statistically significant differences in traditional semen parameters, but increased incidences of apoptosis and necrosis were observed in infected men by electron microscopy. Another study looked at the possible effect of HCV on semen parameters in 57 infected men and 40 fertile controls [43]. In that study, the duration of HCV infection was negatively correlated with semen volume and sperm motility, and the viral load was negatively correlated with sperm count and sperm motility. HCV-infected patients also had significantly lower total serum testosterone and higher serum E2 and prolactin levels compared with healthy controls.

3.5.3. Human immunodeficiency virus

A possible effect of human immunodeficiency virus (HIV) was assessed by Muller and coworkers through semen analyses in 250 HIV-seropositive men and 38 fertile controls [44]. The fertile controls had significantly greater semen volume (2.9 vs 1.8 ml, $p < 0.0001$), sperm concentration (median 100 vs 62×10^6/ ml, $p < 0.001$), percentage of motility (median 64% vs 52%, $p < 0.0001$), and percentage of rapid and linear motility (median 21% vs 14%, $p < 0.05$) than HIV-seropositive men. Nevertheless, there was no difference between the groups in the proportion of sperm with normal morphology and the number of leukocytes in semen. In the group of HIV-positive men, $CD4^+$ values $<200/mm^3$ were associated with significantly lower proportions of motile spermatozoa, strictly normal morphology, and total morphologically normal spermatozoa. Likewise, based on clinical categories, healthier men had significantly higher proportions of strictly normal morphology, and fewer had azoospermia. The authors concluded that HIV-seropositive men with low $CD4^+$ cell counts or severe symptoms had reductions in semen quality that were similar to those of other men with chronic diseases. Similar findings were made in a subsequent study that investigated the effects of different patient characteristics on fertilizing capacity in 33 HIV-seropositive men [45]. Sperm vitality, motility, and penetration rates assessed by the zona-free hamster oocyte penetration test were all correlated with $CD4^+$ cell number, and the parameters were significantly higher in patients whose $CD4^+$ counts were at least $350/mm^3$ compared with those whose $CD4^+$ counts were $<350/mm^3$ (all p values <0.05). Interestingly, sperm penetration rate in patients receiving antiretroviral therapy was significantly higher than in those not receiving antiviral therapy, implying that the treatment could be beneficial for fertility ($p < 0.05$). A simpler study was performed in Zimbabwe by collecting sperm and blood from 83 apparently healthy men attending a hospital for undisclosed reasons [46]. Sperm motility was impaired (34% vs 53%, $p < 0.02$) in HIV-positive men, whereas neither sperm count nor sperm morphology differed significantly between the groups. The paper did not provide information on clinical fertility status.

4. Conclusions

The available literature exploring a possible association between STDs and male infertility is of limited quality, and the results are contradictory. Studies confirming an association more frequently tended to have significant drawbacks. There was a tendency for authors to perform multiple analyses without appropriate corrections and to subsequently focus solely on outcomes that seemed to suggest a positive association; however, the body of literature that does not confirm an association between STDs and male infertility is also of inadequate quality to draw any final conclusions. A significant limitation in the literature is that only a few studies have investigated symptomatic STDs. Serum analysis for IgG, for example, may reflect an interaction with a pathogen but not necessarily a relevant inflammatory response that can alter the anatomy or physiology of the genital tract. This might contribute to the wide differences found in the literature. For these reasons, we cannot expect the existing literature to unequivocally reveal whether STDs really cause male infertility. In summary, there may well be an association of unknown genesis and possibly with different pathogenic mechanisms for different pathogens. Alternatively, some STDs may cause male infertility, whereas others may not; however, there is hardly a strong correlation. To reach more firm conclusions on the subject, higher quality studies are needed.

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Study concept and design: Fode, Fusco, Lipshultz, Weidner.
Acquisition of data: Fode.
Analysis and interpretation of data: Fode, Fusco, Lipshultz, Weidner.
Drafting of the manuscript: Fode.
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