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Decrease in Sperm Quality due to Infection of Human Papilloma Virus and *Chlamydia trachomatis*

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Additional information is available at the end of the chapter

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Abstract

Male infertility can have different causes, one of which may be the presence of etiologic agents that cause sexually transmitted infections. Among the most important sexually transmitted infections are human papillomavirus and *Chlamydia trachomatis*, which are associated with infertility in females – whether they cause infertility in men is controversial. The purpose of the chapter is to review the effect of these two pathogens on male fertility, the evidence suggests that the most important infertility effect is linked to the condition of the sperm. However, it is noteworthy that there are few studies with respect to infertility in regard to both pathogens, so it is important to further research this to elucidate the mechanisms by which these pathogens act on male infertility.

Keywords: Human papillomavirus, *Chlamydia trachomatis*, male infertility, sperm, infertility

1. Introduction

Sperm production is considered a complex process that can be affected by many factors, such as infections by viruses or bacteria. These may cause changes in motility, shape and sperm function. This chapter reviews the role of human papilloma virus (HPV), the bacterium *Chlamydia trachomatis* (*C. trachomatis*) single infections and co-infection by both pathogens in male infertility.

2. Human papilloma virus

HPV belongs to the family Papillomaviridae. Members of this family are small viruses of 45–60 nm in diameter with icosahedral capsid. This family includes more than 189 genotypes,

which are distributed in 29 genera [1, 2]. The main features of human papillomavirus are listed in Table 1.

	Human Papillomavirus	<i>Chlamydia trachomatis</i>
Type of biological agent	Virus	Bacteria
Size	45-60 nm	200-400 nm
Morphology	Icosahedral capsid	Body elemental body and reticulum
Genotypes	189 genotypes	15 genotypes
Cellular position	Intracellular	Intranuclear
Clinic manifestations	Sexually transmitted infection Warts Nonspecific lesions Squamous intraepithelial lesions Cervical cancer and laryngeal Infertility	Sexually transmitted infection Trachoma Pelvic inflammatory disease Lymphogranuloma venereum Infertility

Table 1. Features Human Papillomavirus and *Chlamydia trachomatis*

The HPV genome consists of double-stranded DNA and is divided into three regions: the long control region (LCR), the early region (E), and the late region (L). Late proteins L1 and L2 code for capsid proteins [3, 4]. Region E is involved in the formation of non-structural proteins (E1–E7). E1 and E2 genes are involved in viral replication and transcription. E5, E6 and E7 genes encode proteins involved in oncogenesis related to HPV. E6 and E7 are involved in the viral transformation process, binding cellular proteins p53 and Rb, respectively, interfering with the cell cycle and inhibiting apoptosis [5].

The infection of HPV in both women and men may be asymptomatic or manifest itself in different forms: typical is the wart. However, atypical squamous intraepithelial lesions may culminate in the development of cancer. This has been studied particularly well for cervical cancer [5], leading to an increased investigation in this area. Because infection with this virus can be initially hard to detect it can allow progress to a chronic persistent infection or can cause changes in the infected cell disrupting the normal cell cycle. HPV is generally associated with cancer [6].

It has been established that genital tract infections have an effect on fertility, however, the effect of infection with HPV remains uncertain. It is recognized that HPV is one of the most common sexually transmitted infections in the world. There have been various studies that show a wide range in prevalence (from 1.4% to 44%) in the general population [7, 8]. Specifically it is reported to cause 16% infertility in men [9]. A review indicated that prevalence may be between 1.3% and 72.9% [10].

Moreover, male infertility is multi-factorial, including etiologic agents. The human papilloma virus has been identified as a possible cause of male infertility, but not all studies confirm the mechanisms by which this happens.

There have been controversial studies on the role of HPV on fertility. A study reported that in infertile couples only 7.8% were positive for DNA from HPV genotypes, however, in this study it was reported that it does not have an effect on semen quality [11]. Other studies show that HPV is reported in infertile couples.

Different studies have linked infection with HPV in men with different clinical symptoms such as: genital warts, anal or penile intraepithelial lesions and different types of cancer in different regions – penis, anus, prostate and urethra [12, 13]. It has been found that human papillomavirus could be infecting and persisting in different areas, such as the male accessory glands, penis, exfoliated cells, semen and sperm. Some research into these effects is referred to below.

In a study, it was reported that patients with accessory gland infection and HPV have been diagnosed with infertility. It was observed that there are significant changes in sperm quality. Particularly, there is a slight lower sperm motility, despite to have normal morphology, indicating that the co-infection could be an additional risk factor for infertility [14]. Moreover, infection has been observed in epithelial cells and exfoliated cells [15].

Studies in men showing persistent HPV (penis and semen samples) indicated higher levels in the penis (22.5 months) than in semen (15.3 months). This may demonstrate that men can transmit the disease to women despite being asymptomatic [16]. Different genotypes have been found in infertile men such as HPV-45, HPV-52, HPV-18, HPV-59 and HPV-16, which have been recognized as high-risk genotypes [11, 17]. It has been observed that HPV can infect both sperm and cell desquamation [18]. However, another study showed that sperm have low motility [19, 20].

Different techniques have been used in the diagnosis of HVP: *in situ* hybridization, dot blot, hybrid capture, real-time PCR, ELISA peptides, fused E6/E7 [21, 22, 23]; these methods have allowed a more accurate and timely diagnosis. The description of existing diagnostic methods is not discussed here, but it is important to mention that each has its own advantages and disadvantages – new technologies have become more accurate in diagnosis.

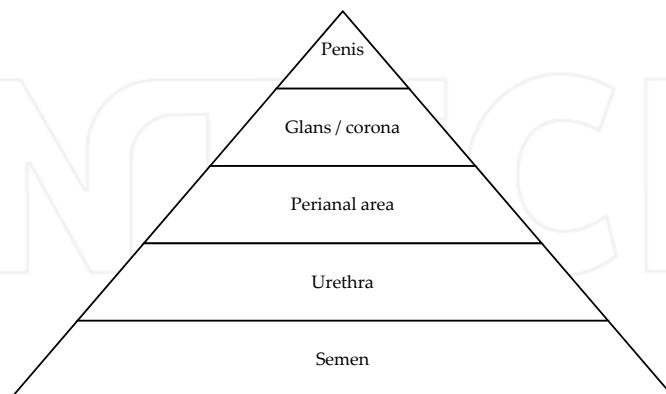


Figure 1. Pyramid showing the greatest location HPV in men, beginning with the penis at the top of the pyramid and the semen ending at the base of the pyramid.

Among the most studied area of HPV is the association with penile, larynx, head and neck cancers. It is estimated that HPV is the causative agent of 5% of human cancers [24].

In the review of Silva *et al.*, 2013 data show a prevalence in men, for different anatomical regions, in this order: penis, glans/corona, scrotum, perianal area, urethra and semen (Figure 1). This author also mentions that prevalence depends on the area, the technique used in detection and the geographical location of the patient [23].

3. *Chlamydia trachomatis*

In 1907, *Chlamydia* was first observed in the epithelium of a conjunctival scraping from an infected orangutan. This discovery is attributed to Halberstaedter and von Prowazek [25]. However, for years, trachoma was known as a blinding ocular disease in humans [26]. Although, Macchiavello reported the culture of trachoma agent in 1944, Tang and coworkers have the credit for their culture. The use of McCoy cells by Gordon and Quan was a major step to understanding chlamydial infections [27, 28]. Nowadays, it is well known that *Chlamydia trachomatis* is an intracellular pathogen and a gram-negative bacterium. In order to infect new cells, it must complete a bi-phasic developmental cycle. It contains approximately 1MB of DNA and 1000 open-reading frames (ORFs), which is considered a small genome [28]. The main features of *Chlamydia trachomatis* are listed in Table 1.

Chlamydia trachomatis can cause several clinical complications, especially in women. This bacteria not only affects the health of individuals in certain countries, it is a worldwide problem with high prevalence. For instance, it has been reported as the most common infection in the United States since 1994. The costs and the consequences of the *Chlamydia trachomatis* infection, make it a major health problem [27, 28, 29, 30]. In most cases it is asymptomatic leading to an untreated infection. It is reported that in approximately 50% of men and in 75% of women the primary infection does not show any symptoms [31]. However, it is estimated that the ratio of infected people with *Chlamydia* who develop symptoms vary depending on the study and the methodology. One major consequence in women is the pelvic inflammatory disease (PID), which is a cause of infertility. Also, there is the risk of passing the infection to the fetus in pregnant women [32, 33]. Main complications in women, which are the most affected, include: urethritis, endometritis and mucopurulent cervicitis. In men it can cause urethritis [29].

According to the World Health Organization (WHO), 101 million chlamydial infections are detected annually worldwide [34]. In adolescents and young adults between 12 and 24 years old the prevalence of *Chlamydia* is higher. For example, it was reported that in the United States the cases of *Chlamydia Trachomatis* were frequent in the young population (< 25 years old) [11]. Since young adults are in an age of sexual activity, it is a population with high-risk, therefore a higher susceptibility. In general, there are few data on the prevalence of *Chlamydia* in certain parts of the world. Most of the studies usually focus on some populations with small samples. For example, in a study carried out in Argentina (2015), 204 participants with an average age of 19 were screened for *Chlamydia trachomatis*. It was found that the prevalence was of 3.5% [31].

In Germany (2012) they studied a population of 1003 sexually active volunteers, they found a prevalence of 4.3% in women and 4.6 % in men [35].

As a mention before, *Chlamydia* can be a 'silent' infection. However, symptoms can appear after several weeks of the first exposure with the bacterium. Symptomatic infected men typically present a mucoid or watery urethral discharge and dysuria. An uncommon clinical signal is the development of epididymitis with unilateral testicular pain, tenderness and swelling. In women, some clinical signs include mucopurulent endocervical discharge, pyuria, dysuria and urinary frequency. If the infection spreads to the upper reproductive tract, the typical symptom is abdominal and/or pelvic pain, along with signs of cervical motion tenderness and uterine or adnexal tenderness on examination. It is worth mentioning that *Chlamydia* can also be found in the throats of women and men. Also, chlamydial conjunctivitis can be found in both men and women due to contact with infected genital secretions [28].

The effects of *Chlamydia trachomatis* infection in men have focused on semen parameters. However, the results of these studies have shown opposite outcomes. Some claim that there is not an association between the infection and the poorest semen quality. On the other hand, in some literature it has been reported that *Chlamydia trachomatis* affects semen quality. These contradictory results could be due to the different methodologies and techniques used, which can be difficult to compare [36, 37].

There are several methods available to detect *Chlamydia Trachomatis*. Cell culture is one of the traditional screening techniques to identify this pathogen. Briefly, this method consists of inoculate specimens (i.e., urethral swabs) in a monolayer cell culture. A stain is used to observe chlamydial inclusions. The specificity is 100%, however it can take up to 72 hours to observed sufficient viable microorganisms [38]. Recently, the molecular methods of detection have proved to be a useful tool in diagnosis. One of the first molecular methods was the *in situ* hybridization. However, this technique was not sensitive enough. Polymerase chain reaction (PCR) and ligase chain reaction (LCR) are useful to detect *Chlamydia trachomatis* infections in asymptomatic patients and populations with low prevalence [39]. Other methods include the identification of antibodies in serological samples. However, serological tests have several limitations, one example of these is that there is no specific *Chlamydia trachomatis* antibody test [40].

The most recent development is the real-time or quantitative PCR that detects *Chlamydia trachomatis* DNA copy numbers. The advantage of this method includes high sensitivity and specificity, also it is a less time-consuming method. It is very clear that there have been improvements in *Chlamydia* detection. However, there are still several challenges such as the creation of lower cost tests without sacrificing any accuracy or speed obtaining results [39].

4. Co-infection of HPV and *Chlamydia trachomatis*

It has been confirmed in different studies that HPV can be part of a co-infection with *Chlamydia trachomatis*. This is important since sexually transmitted diseases and there association with the development of cancerous and precancerous lesions has been shown in several studies. In Honduras, in women aged 18–35 years, the prevalence of *Chlamydia trachomatis* and HPV was

found to be 6% and 28%, respectively; 19 genotypes were detected – proving to be the most common were HPV-5 and 11 [41]. In a previous study of our working group we found that of 77 patients with squamous intraepithelial lesions 13% had a co-infection with HPV and *Chlamydia trachomatis*; 46% only HPV infection and 13% only *Chlamydia trachomatis* infection [42].

In another study, it was found that patients with *Chlamydia trachomatis* and HPV had a prevalence of 74 %. However, only 13% of patients were negative to HVP and positive to *Chlamydia trachomatis* [43]. In the case of sexually transmitted infections *Chlamydia trachomatis* was found in 50% and HPV in 30% [44]. Other studies show that *Chlamydia trachomatis* infection is associated with multiple HPV genotypes and changes in signaling mechanisms in cancer and precancerous lesions [45, 46].

As mentioned in the above paragraphs the relationship between infection of HPV and *Chlamydia trachomatis* is confirmed, however, few studies exist regarding infertility in men with high prevalence. It has been found that men who have HPV present *Chlamydia trachomatis* 82.8% compared to a negative HPV of 17.2% [47]. In another study a prevalence of HPV in the semen of men with conjugal infertility was of 38.5 %, meanwhile the prevalence of *Chlamydia trachomatis* with HSV (types 1 and 2) was 9.6 % [48].

There are few studies showing the association of the two pathogens as co-factors with male infertility, however, there are multiple studies showing their coexistence, so it is important to know how each of these pathogens affects infertility.

5. HPV and *Chlamydia trachomatis* co-infection in the decrease of sperm quality

It has been written that the cause of infertility may be multifactorial and its etiology – viral and bacterial agents – is of particular interest because of its prevalence. HPV and *Chlamydia trachomatis* are common sexually transmitted infections that could be associated with infertility.

Infection with HPV has been identified as one of the possible causes associated with male infertility, although the mechanisms that may be using this virus are not yet clear. However, it was found that HPV can act both at conception and gestational development. Although there are different places where HPV may be infecting, as mentioned in the first section, the main concern linked to infertility is regarding the quality of sperm [18].

Other studies confirm this last statement which demonstrates a significant reduction in sperm motility while other parameters were not affected (semen volume, pH, normal morphology, viability, sperm concentration) [49] and cell desquamation. Sperm infected by HPV can go on to introduce the virus to the oocyte when being fertilized, which can have different consequences such as underdevelopment of the fetus. It has been observed that couples undergoing *in vitro* fertilization and abortion are at high risk of HPV from semen samples [18]. Therefore, diagnosis of HPV should be included in the diagnosis of infertility especially when considering cases of pregnancy loss [20] (Figure 2).

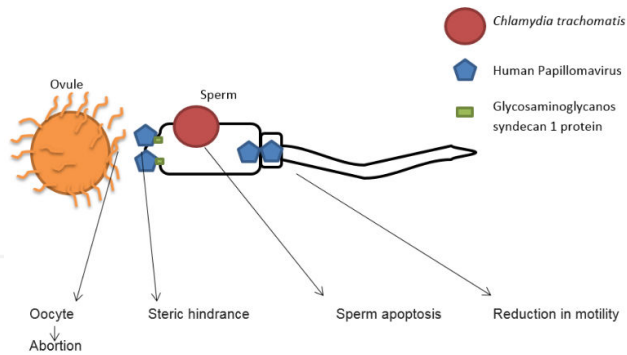


Figure 2. Effect of human papillomavirus and *Chlamydia trachomatis* in sperm

Currently, molecular techniques have detected HPV in different samples (i.e. semen, scrape of the epithelium in different parts of the masculine reproductive apparatus) in heterosexual men with a maximum prevalence of 21 % [50]. Another molecular technique, fluorescent *in situ* hybridization has allowed location of HPV on the sperm head and on the surface of sperm cells. The presence of the virus on the surface of sperm suggests that glycosaminoglycans, or soluble factors similar in chemical structure, could be involved in the binding of the sperm and HPV [49, 51]. Another study demonstrated that glycosaminoglycans syndecan-1 protein may be the unifying factor, particularly HPV L1 capsid protein because it has been unable to locate these two molecules in the sperm head [18]. We suggest that this may be a feature that explains infertility due to the fact that HPV on the head of the sperm, and on its surface, may prevent entry of the sperm to the egg because of steric hindrance since receivers can be occupied by HPV. On the other hand if fertilization is accomplished then infection of the embryo may occur. HPV in this manner could affect male fertility and that of the couple.

Despite this evidence understanding has not been achieved fully regarding the role of HPV in male infertility so the study of *Chlamydia trachomatis* as a co-factor was suggested.

With respect to *Chlamydia trachomatis* they have been reported in several studies as a major cause of female infertility [52, 53, 54]. However, male infertility has not been investigated as thoroughly.

Chlamydia trachomatis, as a sexually transmitted disease, is suggested as a factor that may be involved in the infertility of the couple. Recent studies have shown that *Chlamydia trachomatis* infection has shown an important role in chronic prostatitis [55] that could allow *Chlamydia trachomatis* to move to different areas of the male reproductive system allowing the infection to reach areas of sperm production.

It has been suggested that the cause of apoptosis of sperm is the lipopolysaccharide of the *Chlamydia* cell wall [56, 57] (Figure 2). This effect is even more serious because it would kill the sperm, preventing fertilization due to a lack of sperm, giving the bacteria a central role in male infertility.

There is little research studying the effect of these two infections as co-factors in regard to male infertility. In a study of men from Denmark it was reported that *Chlamydia trachomatis* infection may be a risk factor that allows the acquisition of an additional type of a genotype of HPV [57]. In a multivariate analysis, it was found that infection with *Chlamydia trachomatis* is significantly associated with HPV [59].

It is proposed that co-factors such as genital tract infections could have an important role in the evolution and outcome of HVP. For example, the association of HVP with *Chlamydia trachomatis* could be associated with increased risk of cervical cancer and with the reduction in cell mediated immunity [60]. This was reported in the cervix, but the same could be happening in the male reproductive system. Therefore, *Chlamydia trachomatis* infection could be a predisposing factor for the acquisition of HPV factor, which becomes more relevant if we consider that more than 50% of *Chlamydia trachomatis* infections are asymptomatic in men [61]. It has been observed that men with *Chlamydia trachomatis* infection are at increased risk of contracting an HPV infection [47].

In a study, it was found that heterosexual men, with prostatitis symptoms attributable to *Chlamydia trachomatis* and with papillomavirus had a lower motile sperm motility. Also, the morphology was lower compared with patients that were infected only with *Chlamydia trachomatis*. However, the results did not show any significant relationship depending on the HPV genotype presented [62].

Both HPV and *Chlamydia trachomatis* are sexually transmitted infections that have become important because of their prevalence, and it has been suggested that their association may be related to the development of other complications, as in the case of sperm quality.

In conclusion, the presence of *Chlamydia trachomatis* plays an important role in male infertility as well as sperm production and also facilitates entry of HPV, which contributes to a large degree the affectation of sperm. Therefore, HPV and *Chlamydia trachomatis*, and their associations, are two important pathogens that should be included in diagnostic tests for male infertility and the infertility of couples.

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