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From infection to infertility: a review of the role of human papillomavirus-induced oxidative stress on reproductive health and infertility

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Abstract

Infertility has emerged as a significant global health concern, affecting nearby 8–12% of couples in reproductive age worldwide. Increasing evidence suggests a potential link between human papillomavirus (HPV) and infertility in both men and women. Some research indicate that HPV can infect various components of semen, potentially affecting sperm quality by decreasing motility, viability, and increasing DNA fragmentation, all of which may contribute to male infertility. The virus can attach to the equatorial region of the sperm head, enabling infected sperm to transmit the virus to the oocyte or placenta. Consequently, HPV potentially induces apoptosis in trophoblastic cells and disrupts their adhesion to endometrial cells, which raises the risk of miscarriage. HPV may also affect ovarian reserve by causing chronic inflammation, which can impair granulosa cell function and lower serum anti-Müllerian hormone (AMH) levels. Besides, HPV-related immune responses also contribute to infertility by producing anti-sperm antibodies (ASAs), which cause sperm clumping, reduce motility through cervical mucus, activate the complement system that damages sperm in the female reproductive tract and interfere with sperm–egg interactions. Moreover, HPV infection has been linked to reduced success rates in assisted reproductive technologies (ART), potentially disrupting critical processes such as the acrosome reaction, sperm–oocyte interaction, and fusion. One potential mechanism through which HPV contributes to infertility is oxidative stress (OS). Triggered OS can negatively impact sperm quality and cause damage to the female reproductive system, ultimately contributing to infertility. Despite these associations, the precise mechanisms and the strength of the relationship remain uncertain. Thus, this review seeks to investigate the potential impact of HPV on infertility, particularly its effects on the reproductive system through OS. A clearer understanding of these processes could inform future health strategies for addressing HPV-related infertility.

Keywords Human papillomavirus, Inflammation, Infertility, Oxidative stress, Reproductive health, Reproductive tract infections

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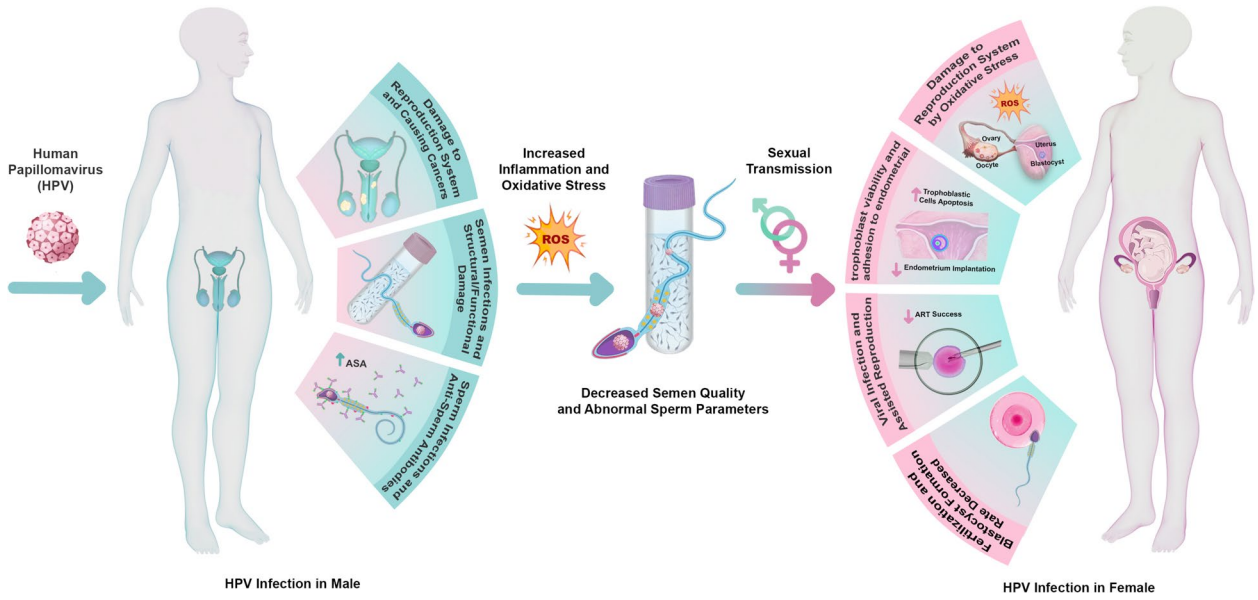
Graphical Abstract



Introduction

Infertility has become a major public health issue, with an estimated 186 million people affected worldwide [1]. Infertility is a medical condition defined by the inability to achieve a confirmed pregnancy despite engaging in regular, unprotected sexual activity for 1 year. This condition is believed to impact approximately 8–12% of couples within the reproductive age group across the globe [2]. Findings indicate that 33–41% of infertility cases are attributed exclusively to female factors, while male factors are responsible for 25–39%. Additionally, 9–39% of cases result from a combination of both male and female factors [3]. The most frequently recognized causes of female infertility include ovulatory disorders, endometriosis, pelvic adhesions, and tubal blockages. Other factors, such as abnormalities in the tubes or uterus and hyperprolactinemia, also contribute to infertility in women [4]. As well, various factors have been identified as contributing to male infertility, such as erectile dysfunction, varicocele, congenital conditions, hormonal imbalances, immune system issues, and environmental exposures to chemicals and radiation [5]. However, there are some cases where the cause of infertility remains unknown, with a significant proportion of infertile couples being diagnosed with unexplained infertility [6]. Among these various causes of infertility, infections have been proposed as potential contributors, with growing interest in the impact of human papillomavirus (HPV) on reproductive health [7–9].

HPV ranks as one of the most prevalent sexually transmitted infections (STIs), with the majority of sexually active people likely to encounter it at least once during their lives [10]. The virus is primarily transmitted through intimate sexual activities, including vaginal, anal, or oral contact, with an infected partner [11]. HPV belongs to the *Papillomaviridae* family and encompasses a wide array of viruses. This family comprises more than 200 types, with at least 40 known to target and infect the anogenital area [12]. Some types are categorized as high-risk (HR) such as HPV-16 and HPV-18 because they significantly contribute to the development of cancers such as cervical, anal, and oropharyngeal cancers. In contrast, low-risk (LR) types such as HPV-6 and HPV-11 are primarily associated with non-cancerous conditions, like genital warts [13, 14]. HPV infections often go unnoticed in both men and women due to the absence of symptoms. However, they can result in severe long-term complications and even death. Cervical cancer claims the lives of over 340,000 women annually. In men, HPV is commonly observed through the development of anogenital warts, which not only contribute to considerable health burdens but also play a significant role in facilitating the spread of the virus [15]. Beyond these challenges posed by HPV, accumulating evidence suggests that this virus may play a role in causing infertility among both males and females.

HPV DNA has been found in various semen components, such as sperm cells, somatic cells, and seminal plasma [16]. A systematic review and meta-analysis,

involving 5194 male participants, revealed that HPV DNA was found in 11.4% of semen samples from the general population and 20.4% from individuals attending fertility clinics [17]. Additionally, the findings indicated that men with HPV-positive semen faced a notably higher likelihood of infertility [17]. This may be explained by the fact that HPV infection has the potential to compromise sperm DNA integrity and negatively impact sperm parameters including sperm count, concentration, viability, and morphology [18]. As well, it is proposed that the presence of HPV in semen may markedly impair sperm progressive motility in infertile individuals, indicating the significant contribution of HPV to infertility in men [19]. Additionally, men with HR-HPV-positive semen demonstrated reduced semen volume, sperm concentration, and overall sperm count compared to those with HR-HPV-negative samples [20]. In another way, HPV may indirectly cause infertility by inducing anti-HPV immunity and inflammation [18]. HPV infection may contribute to infertility by promoting the production of anti-sperm antibodies (ASA) [21]. Garolla et al.'s study suggests that HPV infection in the semen of infertile men is frequently correlated with elevated levels of ASAs, which are connected to decreased sperm motility and could exacerbate fertility issues [22]. Multiple mechanisms have been suggested through which ASAs can impact male fertility. These include clumping of sperm, reduced ability to penetrate cervical mucus, complement system activation causing sperm damage within the female reproductive tract, and disruption of sperm–egg interactions [22]. HPV-infected sperm cells are thought to function as carriers for HPV antigens on their surface, in addition to sperm antigens. For individuals who have been exposed to HPV, frequent encounters with HPV-infected sperm may enhance the immune response, leading to the antibody-mediated removal of both infected and uninfected sperm. This process could trigger epitope spreading, disrupting immune tolerance to sperm antigens and further reducing sperm viability [23]. However, the exact connection between ASA and anti-HPV antibodies in infertility requires further exploration.

Crucially, multiple studies have indicated that HPV is found in the equatorial region of the sperm head, a key area responsible for triggering the process of sperm egg fusion [24, 25]. Therefore, there is a possibility that infected sperm can penetrate the oocyte, introducing the HPV genome, which the fertilized oocyte is capable of transcribing actively [26]. Thus, the impact of HPV infection on female fertility has become an area of growing interest. HPV may elevate the likelihood of miscarriage by promoting apoptosis in trophoblastic cells and impairing their ability to implant within the endometrium [27]. In women, HPV may influence ovarian reserve by triggering persistent inflammation. This inflammatory response could impair granulosa cell function, which in turn might lead to a reduction in circulating anti-Müllerian hormone (AMH) levels [28].

In general, the main mechanism through which HPV can cause infertility in men and women is not clearly understood. However, one possible mechanism could be the oxidative stress (OS) induced by the virus. OS occurs when there is a disruption in the balance between the generation and removal of reactive oxygen species (ROS) within cells and tissues [29]. ROS are highly reactive molecules such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (·OH). These molecules are essential for various cellular processes, such as differentiation, proliferation, autophagy, necrosis, and programmed cell death, by acting as signaling molecules or modulating transcription factor activity [30]. However, when the body's defense systems fail to effectively neutralize them, these molecules can inflict damage on cells and tissues, contributing to various diseases [31, 32]. ROS interacts with key cellular components, leading to DNA base oxidation, lipid peroxidation, and protein carbonylation. As a result, they cause irreversible harm by modifying DNA, lipids, and proteins in the cytosol, disrupting their structure and impairing their normal functions [33]. Most importantly, OS is recognized as a contributing factor among various causes of infertility in both men and women [34–36]. Therefore, since HPV can cause OS, this could be one of the potential mechanisms leading to infertility.

There is evidence which shows that HPV can impact sperm cells by causing cellular damage and impairing sperm motility through the elevation of OS [37]. HPV is known to significantly induce OS, which may adversely affect reproductive health [38]. This OS imbalance can harm sperm cells by causing mitochondrial damage and altering essential cellular components, including lipids, nucleic acids, and proteins [39]. OS in females has been linked to various reproductive disorders, such as endometriosis, polycystic ovary syndrome (PCOS), and cases of infertility with no clear cause. Additionally, it may contribute to pregnancy-related complications, including miscarriage, recurrent pregnancy loss, preeclampsia, and intrauterine growth restriction [40]. Nonetheless, the precise mechanisms and the relationship between HPV and infertility remain uncertain and have yet to be definitively clarified. Additionally, some studies suggest no connection between the two [41, 42]. So, this review aims to explore the potential impact of HPV on infertility, focusing on its direct effects of HPV (especially OS) on the reproductive system. This comprehensive understanding may also serve as a guide for developing future

health measures aimed at addressing the impact of HPV on infertility.

Unveiling the link between OS and HPV

Overview of OS

OS is recognized as a condition in which the production of ROS exceeds the biological system's capacity to neutralize these reactive molecules or repair the damage they cause [43]. ROS, naturally generated during cellular metabolic processes, play critical physiological roles at low to moderate concentrations. However, at elevated levels, they can inflict significant damage on cellular components such as lipids, proteins, and DNA [44]. OS occurs when ROS accumulate in excessive amounts due to an imbalance between their generation and elimination. This imbalance arises when antioxidant defenses, responsible for neutralizing ROS, are insufficient to counteract their production [45]. OS plays a role in numerous diseases associated with aging, including diabetes, heart disease, cancer, and neurodegenerative disorders [46].

ROS encompasses free radicals as well as their non-radical derivatives [47]. ROS are naturally produced during cellular metabolism. Free radicals are highly reactive molecules that typically possess one or more unpaired electrons, making them unstable and prone to interacting with other biological compounds [48]. Under normal metabolic conditions, the continuous production of ROS and other free radicals plays a critical role in physiological processes such as ATP generation, catabolic and anabolic reactions, and cellular redox cycles. However, excessive production of free radicals may result from internal biological factors or external environmental factors such as exposure to chemicals, pollutants, or radiation [49]. The three main types of ROS with significant physiological relevance include superoxide anion ($O_2^{\cdot-}$), hydroxyl radical ($^{\cdot}OH$), and hydrogen peroxide (H_2O_2) [50].

Mitochondria act as the primary location for superoxide anion generation. Under normal circumstances, electrons pass through the mitochondrial electron transport chain to the reduction of oxygen to water. However, around 1–3% of these electrons escape the chain, causing the formation of superoxide [44]. Superoxide is transformed into H_2O_2 by the action of superoxide dismutases (SODs). Additionally, H_2O_2 can be produced through the two-electron reduction of oxygen, a process facilitated by enzymes like xanthine oxidase and glucose oxidase [51]. In a reaction known as the Fenton reaction, H_2O_2 can interact with transition metals such as Fe^{2+}, resulting in its decomposition into hydroxide ions (OH^-) and hydroxyl radicals ($^{\cdot}OH$) [52]. Among all ROS, the hydroxyl radical is the most reactive and can oxidize numerous organic molecules [53]. H_2O_2 and chloride ions act as substrates for the enzyme myeloperoxidase, which catalyzes the production of hypochlorous acid (HOCl). HOCl is a powerful oxidizing agent and is essential for removing pathogens [54, 55]. On the other hand, HOCl can interact with DNA, leading to the formation of DNA–protein crosslinks, the production of oxidized pyrimidine derivatives, and DNA base modification [56, 57].

Effects of ROS

Free radicals and reactive metabolites exhibit dual functions [58]. For example, they play a crucial role in forming various cellular components and are utilized by the body's immune defense to fight off harmful pathogens. In particular, phagocytes generate and store free radicals, which they release to destroy invading microbes [59, 60]. However, excessive production of these compounds can cause damage to the body. For example, superoxide or H_2O_2, at low concentrations, exerts positive effects on cell proliferation and survival by regulating signal transduction. Conversely, at high concentrations, these compounds stimulate signaling pathways leading to apoptosis or necrosis [58].

Effects on DNA

ROS can induce various types of DNA alterations, including base destruction, single- or double-strand breaks, purine-, pyrimidine-, or sugar-related modifications, mutations, deletions, translocations, and crosslinking with proteins. A significant number of these genetic changes are closely linked to the development of cancer, aging processes, as well as disorders affecting the nervous system, heart, and immune system [44]. DNA is particularly susceptible to attack by hydroxyl radicals ($^{\cdot}OH$), which can interact with DNA bases or deoxyribose sugars, leading to the formation of various products. Attacks on the sugar backbone can result in strand breaks, whereas damage to histone proteins may lead to crosslinking, disrupting chromatin structure, DNA repair, and transcription. These changes can cause mutations or abnormal gene expression [47]. Mitochondrial DNA (mtDNA) is particularly susceptible to damage from ROS because it is located close to where $O_2^{\cdot-}$ is produced in the electron transport chain, lacks protective histones, and has few repair systems to fix any damage [61, 62]. Since mtDNA is responsible for encoding various proteins, such as those involved in the electron transport chain, mutations can impair the regulation of these proteins, increase free radical production, and disrupt mitochondrial function [63]. The formation of 8-hydroxyguanosine (8-OH-G) is one of the most well-documented DNA damages induced by OS [44]. The creation of 8-OH-G in DNA at the sites where transcription factors attach can disrupt their binding, which

in turn can change the expression of related genes [44]. Moreover, while single-strand DNA breaks caused by oxidative damage are generally well-tolerated by cells, double-strand DNA breaks caused by ionizing radiation pose a serious threat to cell survival [44]. RNA is also susceptible to oxidative damage, which has implications for disease processes [64]. Recent findings indicate that ROS influences the formation of certain microRNAs, referred to as redoximiRs. Additionally, these microRNAs interact with antioxidant response elements and genes associated with ROS, thereby impacting the balance of cellular redox processes [65]. For instance, oxidative modifications of miRNA-184 allow it to bind to the mRNA of B-cell lymphoma proteins Bcl-xL and Bcl-w, inhibiting their translation and triggering cell death [66].

Effects on protein

Free radicals can cause the breakdown of peptide chains, modify the electrical charge of proteins, promote protein crosslinking, and oxidize certain amino acids. These changes make proteins more vulnerable to breakdown and degradation by specific proteases [67]. Additionally, OS can cause structural modifications in proteins, resulting in the loss or impairment of their enzymatic activity [29]. This process involves the direct oxidation of side chains, leading to the formation of carbonyl groups such as aldehydes and ketones. Proline, arginine, lysine, and threonine are especially prone to this type of damage [68]. Additionally, the oxidation of sulfhydryl groups or methionine residues can induce structural changes in proteins, causing them to unfold and degrade. Enzymes that contain metal ions in or near their active sites are particularly vulnerable to oxidation catalyzed by metals, which has been found to impair their functionality [44].

Effects on lipid

Free radicals initiate lipid peroxidation by extracting a hydrogen atom from the methylene carbon in a fatty acid side chain, setting off a chain reaction. This disruption may affect membrane fluidity and compromise its integrity [44]. Lipid peroxidation directly breaks down membrane phospholipids, leading to membrane dysfunction. Additionally, it generates lipid aldehydes like acrolein and malondialdehyde (MDA), which are highly reactive and toxic. These compounds bind to cellular proteins, disrupting their function [69]. Also, elevated levels of hydroxyl radicals and peroxynitrite ($ONOO^-$) can promote lipid peroxidation, leading to damage to cellular membranes and lipoproteins. This damage, in turn, results in the formation of MDA, which are known cytotoxic and mutagenic compounds. Lipid peroxidation, a chain reaction driven by free radicals, rapidly propagates and impacts a large number of lipid molecules [29].

How HPV triggers OS?

Viral infections can trigger an increase in ROS, leading to an imbalance in redox regulation. This disturbance contributes to inflammation, oxidative stress, and various biological reactions that play a critical role in disease advancement [70, 71]. HPVs are among the viruses that strongly induce OS. HPV not only promotes OS but also disrupts various components of the antioxidant and DNA repair systems as a response to viral replication [72].

Several HPV early proteins can modulate the redox state of the host cell (Fig. 1). For instance, HPV-18 E2 can associate with the mitochondrial membrane, where it interacts with mitochondrial membrane proteins, including components of complex III, IV, and V [73, 74]. As well, E2 can alter the structure of mitochondrial cristae, potentially triggering the release of mitochondrial ROS and contributing to OS [73]. A recent study by Gregorio et al. demonstrated that the E2 protein of HR-HPV18 enhances ROS production and leads to a reduction in cellular glutathione (GSH) levels. Furthermore, the co-expression of E1 and E2 proteins led to elevated ROS production, which was accompanied by an upregulation of the DNA damage marker phospho-histone 2 AX (γH2 AX). This was paralleled by reductions in both GSH levels and superoxide dismutase 2 (SOD2) activity and concentration. This highlights the role of E1 and E2 in fostering OS during the replication cycle of HR-HPV [75].

Also, it is indicated that E6 oncoproteins reduce levels of GSH and catalase proteins, along with their enzymatic functions, leading to an elevated production of ROS and subsequent DNA damage [75]. E6 proteins from HR-HPVs possess a unique ability to generate spliced variants known as E6*, which are shortened versions of E6 [76, 77]. The presence of E6* reduces the activity of antioxidant enzymes including SOD2 and Gpx1/2, leading to elevated levels of ROS and subsequent DNA damage [78]. Marullo et al. demonstrated that the expression of E6 and E7 proteins is enough to trigger the production of ROS in head and neck cancer cells [79]. This OS, resulting from E6/E7 activity, is mediated by nicotinamide adenine dinucleotide phosphate oxidases (NOXs) and leads to DNA damage and chromosomal abnormalities. Notably, this mechanism of genomic instability sets HPV-positive tumors apart from HPV-negative ones, as NOX-driven OS was observed solely in HPV-positive head and neck cancer cells. Through NOX2 silencing, they pinpointed it as the main contributor to HPV-induced OS, leading to a significant decrease in ROS production, DNA damage, and chromosomal irregularities in HPV-positive cells [79]. In a separate investigation by Ramesh et al. it was demonstrated that the ectopic expression of HPV-E6/E7 led to a reduction in NQO1 activity, lowered total GSH levels, and increased ROS levels. Also, they found that

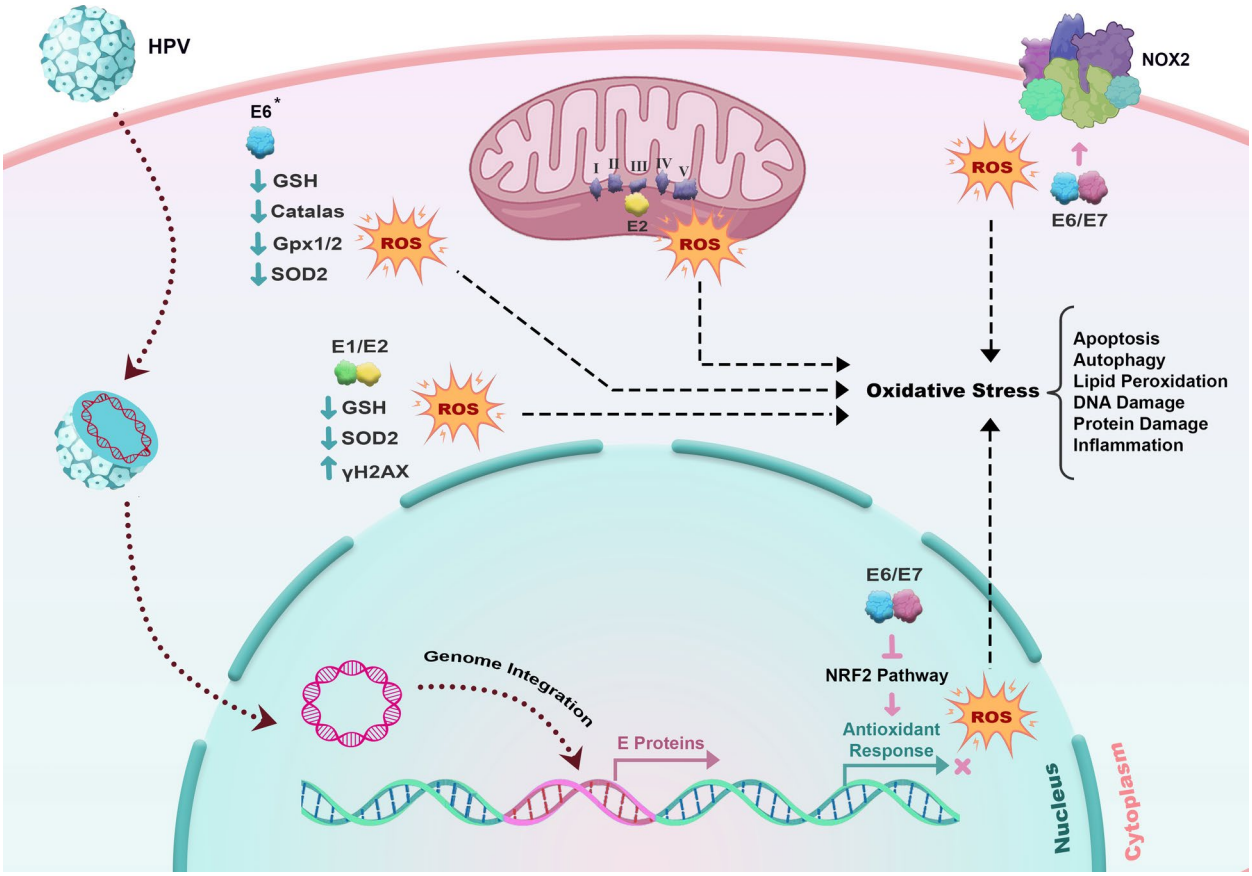


Fig. 1 The pathways associated with oxidative stress (OS) and cellular damage induced by human papillomavirus (HPV) proteins. The E2 protein interacts with mitochondrial membrane proteins (e.g., complex III), leading to the release of reactive oxygen species (ROS) from mitochondria. Co-expression of E1 and E2 proteins further elevates ROS production while reducing levels of antioxidants such as glutathione (GSH) and superoxide dismutase 2 (SOD2), resulting in increased DNA damage markers like phospho-histone 2 AX (γH2 AX). The E6 oncoprotein decreases antioxidant levels, including GSH and catalase, and a spliced variant of E6 inhibits antioxidant enzymes such as SOD2 and Gpx1/2. The E6/E7 oncoproteins activate nicotinamide adenine dinucleotide phosphate oxidases (NOXs), particularly NOX2, enhancing ROS production, which contributes to DNA damage and chromosomal instability. Additionally, E6/E7 inhibit the nuclear factor erythroid 2-related factor 2 (NRF2) pathway, reducing the activity of cytoprotective enzymes and exacerbating OS. These pathways collectively lead to apoptosis, autophagy, lipid peroxidation, DNA damage, protein damage, and inflammation, which are critical for the development and progression of HPV-associated cancers

ectopic expression of HPV-E6/E7 inhibited nuclear factor erythroid 2-related factor 2 (NRF2) activation [80]. NRF2 plays a crucial role in regulating the expression of genes that code for cytoprotective proteins, including antioxidant enzymes and GSH. Elevated NRF2 activity in cancer cells ensures a higher antioxidant defense, promoting tumor growth and contributing to resistance against chemoradiotherapy [80]. Altogether, the increased levels of ROS caused by HPV proteins result in oxidative-related DNA damage in particular double-strand breaks, which aids in the incorporation of HPV DNA into the host genome and encourages the heightened expression of E6/E7, establishing a genomic instability [81]. Moreover, recent studies have revealed that HPV infection can impair the function of aquaporin-8 (AQP8), a protein crucial for removing excess ROS in the male reproductive system. [37]. AQP8 plays a role in osmoregulation, as studies have shown that lower AQP8 levels in human sperm are associated with an increased occurrence of sperm exhibiting coiled tails, a sign of osmotic imbalance [82]. Overall, proteins linked to HR-HPVs play a significant role in initiating and sustaining oxidative and nitrosative stress within infected cells (Fig. 2).

Male infertility associated with HPV

HPV infection of male genital tract

Various viruses can infect the male genital tract (MGT) and negatively impact the reproductive system [83]. For instance, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect the MGT and also has been

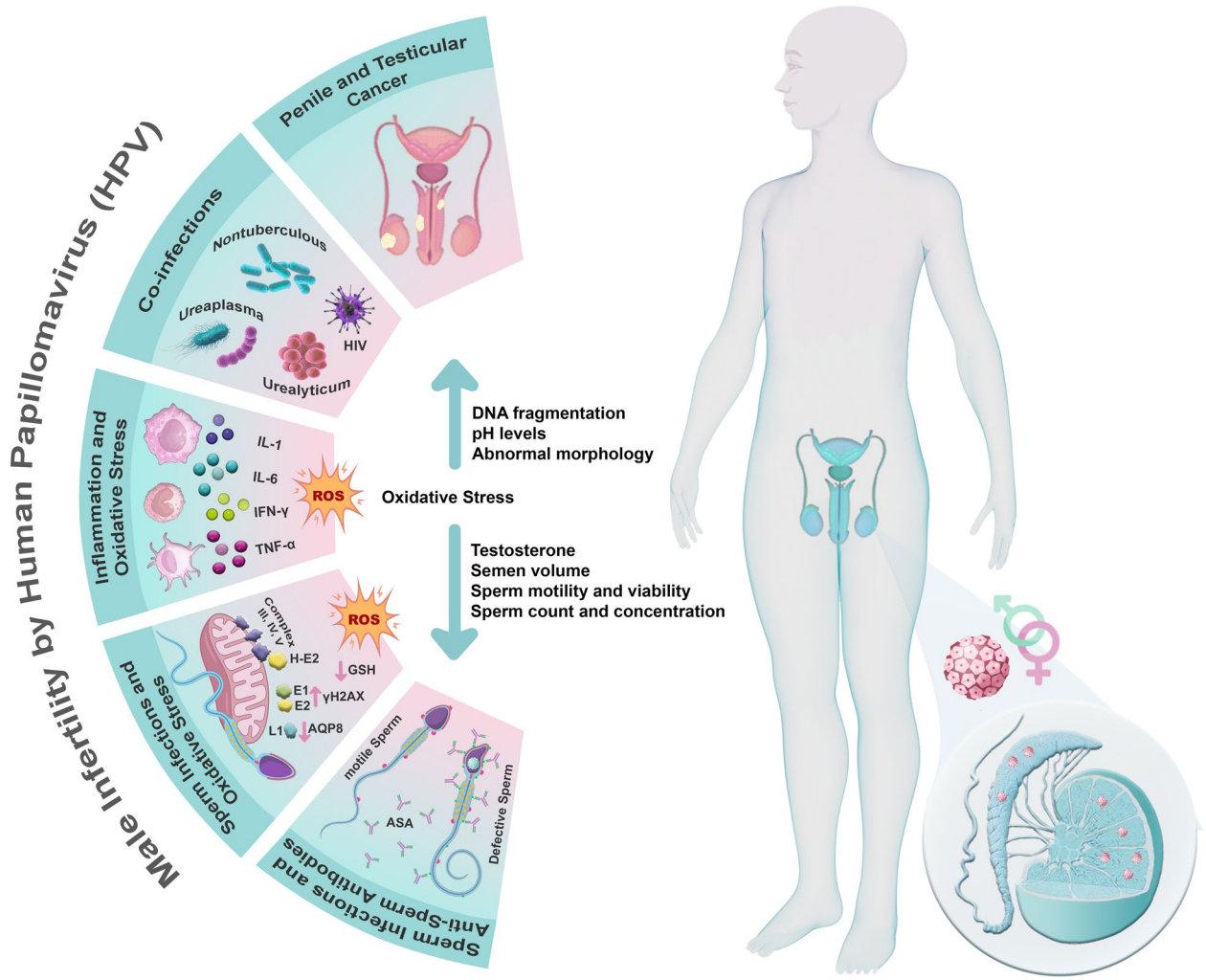


Fig. 2 The impact of human papillomavirus (HPV) infection on the male reproductive system and sperm quality. HPV infection in the male genital tract (MGT) is associated with increased viral load in the testis and epididymis, leading to an elevated risk of penile and testicular cancer, and reduced fertility. It also suggests potential co-infections with pathogens such as Ureaplasma, Urealyticum, Nontuberculous epididymitis, and HIV, which may exacerbate inflammation and oxidative stress (OS) in the reproductive tract and elevated risks of infertility. HPV DNA is detectable in all components of semen, including sperm cells, somatic cells, and seminal plasma. The infection in semen induces inflammation, recruiting immune cells and triggering the production of pro-inflammatory cytokines such as IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), which collectively contribute to reactive oxygen species (ROS) generation and OS. The resulting OS leads to increased DNA fragmentation, elevated pH levels, and abnormal sperm morphology. Furthermore, it negatively impacts hormonal and seminal parameters, including reduced testosterone levels, decreased semen volume, impaired sperm motility and viability, and lower total sperm count and concentration. In sperm cells, the interaction of HPV proteins, such as HPV-E2, with mitochondrial membrane proteins, leading to mitochondrial ROS release and OS. Co-expression of E1 and E2 proteins further exacerbates ROS production, increases DNA damage markers like γH2 AX, while decreasing glutathione (GSH) levels and superoxide dismutase 2 (SOD2) activity. Additionally, the disruption of AQP8 by the viral L1 protein impairs water and hydrogen peroxide (H_2O_2) transport and detoxification processes, contributing to sperm stress and functional impairment. HPV infection also leads to the production of ASA. HPV-infected sperm cells act as carriers for HPV antigens, initiating or boosting a humoral immune response in HPV-naïve or HPV-experienced women, respectively. This immune response can result in the antibody-mediated elimination of both HPV-infected and uninfected sperm cells, further compromising fertility. The interplay between ASA and anti-HPV antibodies, and their contribution to infertility, remains an area for further investigation

detected in sperm cells [84, 85]. The virus affects the germinal epithelium during spermatogenesis, causing a significant increase in pro-inflammatory molecules and OS, which impacts immune cells and sperm cells [86]. In response, both types of cells release extracellular traps (ETosis) to capture and neutralize the virus particles. Sperm DNA-extracellular traps like (SETs-L) trap viral particles in spermatids and spermatozoon, potentially

contributing to reduced sperm motility in some infected individuals [86].

Additionally, genital HPV infection has the potential to influence male fertility by directly impairing reproductive function. Since 2013, a notable prevalence of HPV infection in the MGT has been observed, with rates ranging from 50 to 70% [87]. HPV DNA has been identified in multiple anatomical locations, including the penile shaft, glans, coronal sulcus, semen, scrotum, perianal region, and anus [87]. Higher viral load of HPV in the testis and epididymis are linked to different pathologies of the MGT (including nontuberculous epididymitis) [23]. HPV is also associated with the development of cancers in the penis and testicles, however, its connection to testicular cancer remains uncertain and requires further investigation [88]. HR-HPV subtypes have been identified in as many as 40% of cases, with the greatest prevalence observed in the basaloid and warty variants of squamous cell carcinoma [89]. Recent findings indicate that HPV accounts for 50.8% of penile cancer cases worldwide and 79.8% of penile intraepithelial neoplasia occurrences [90]. In cases of penile cancer, HPV-16 and HPV-18 have been associated with a significant proportion of these cancers, with HPV-16 being the most common subtype [91]. An investigation conducted by Jaworek et al. on penile swabs detected HPV-51 as the predominant HR-HPV type in sperm donors, whereas HPV-16 was the most frequently detected type in infertile men [20]. The available data on the potential link between HPV and testicular cancer are inconsistent. Considering HPV's oncogenic potential and its affinity for testicular tissue, its involvement in testicular carcinogenesis remains a possibility. Further research is needed to provide clarity [92]. For example, Garolla et al. examined sperm characteristics and the presence of HPV in semen from 155 individuals with testicular cancer. Their findings revealed that these patients often exhibited abnormal sperm parameters and a greater occurrence of HPV in semen, which further deteriorated following radio and chemotherapy treatments [93]. However, several studies show no significant correlation between HPV infection and testicular cancer [94, 95].

Also, the possibility of co-infections with HPV should be considered in this regard. Research suggests that having an HPV infection can increase the risk of acquiring other STIs like HIV [96]. This can be explained by HPV's interaction with the immune system. For instance, HPV evades host immunity through various mechanisms, including disrupting pathogen recognition receptor signaling, interfering with IFN-α/β pathways, suppressing nuclear factor kappa B (NF-κB) signaling, and reducing MHC I and CD1 d expression to escape cytotoxic CD8 T cell detection [97]. These interactions with the immune system not only promote viral persistence and oncogenesis but also leave the host more vulnerable to other infections by compromising key antiviral and inflammatory defenses. In a study conducted by Fan et al. 1951 men from infertile couples were examined, revealing an overall HPV infection rate of 12.4% [98]. Coinfection rates with various STIs were also reported including *Ureaplasma urealyticum*, *Ureaplasma parvum, Chlamydia trachomatis* (CT), *Mycoplasma genitalium*, herpes simplex virus 2, *Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus agalactiae, and Staphylococcus aureus* [98]. HPV infection alone was linked to notably diminished semen volume and total sperm count. Furthermore, co-infection with HPV and *U. urealyticum* led to notable declines in sperm motility and viability [98]. Moreover, it has been observed that co-infection with CT amplified the risk of infertility in males infected with HPV through increasing levels of seminal pro-inflammatory cytokines [99]. These findings highlight the high prevalence of STI co-infections in the semen of infertile men and underscore the critical impact of such co-infections on semen quality. Figure 2 illustrates the effect of HPV infection on the male reproductive system and sperm quality.

HPV infection of semen and impacting on sperm parameters

HPV DNA is detectable in all components of semen, including sperm cells, somatic cells, and seminal plasma. Multiple HPV genotypes can coexist within a single fraction, and their relative abundance may differ between fractions [16]. Based on the findings of a systematic review and meta-analysis that encompassed 5194 male participants, it was determined that HPV DNA was detected in semen at an overall rate of 11.4% within the general population (total population = 2122) and 20.4% among individuals attending fertility clinics (n = 3072) [17]. A more recent systematic review and meta-analysis revealed that seminal HPV infection is considerably more common in infertile individuals than in the general population, with prevalence rates of 20.9% and 8.2%, respectively [100]. HPV is hypothesized to attach at the equatorial zone of the sperm head. This interaction is thought to be facilitated by glycosaminoglycans or other soluble components present on the sperm surface [24]. Emerging research indicates that HPV can infect human sperm, binding to the equatorial region of the sperm head through an interaction between the viral capsid protein L1 and syndecan-1 [24].

HPV infection (especially HR-HPVs) can affect various sperm quality parameters, including motility, DNA fragmentation index (DFI), pH levels, semen volume, sperm count, and morphology (Fig. 2) [20, 101]. Several studies have been conducted, demonstrating the correlation

between HPV infections and their potential effects on sperm quality. In research conducted by Damke et al. 229 semen samples were analyzed, revealing the presence of HPV DNA in 16.6% of cases. Among these, 10.5% had single-type HPV infections, while 6.1% exhibited multiple-type infections [102]. Single and multiple HPV-positive samples were linked to abnormal semen viscosity. Additionally, samples with multiple HPV infections showed associations with hypospermia, elevated pH levels, and increased leukocyte counts [102]. In a different study conducted by Yang et al. 1138 participants were included, with 142 testing positive for HPV (12.48%) [103]. Among the 523 males confirmed to be fertile, only 35 were HPV-positive (6.7%), and two of these had multiple infections. In contrast, 107 out of 615 infertile males were HPV-positive (17.4%), with 29 having multiple infections. The rate of HPV infection was notably higher in infertile males compared to those who were fertile. Additionally, sperm progressive motility and the percentage of sperm with normal morphology were significantly reduced in HPV-positive individuals [103]. Depuydt et al. conducted a study involving 161 infertile couples undergoing 209 intrauterine insemination (IUI) cycles. The research revealed that sperm samples testing positive for HPV exhibited a considerably higher DFI than those without HPV, with rates of 29.8% and 20.9%, respectively [104]. No clinical pregnancies occurred in instances where sperm contained HPV virions. Furthermore, over 20% of samples with normal semen characteristics (17 out of 78; 21.8%) demonstrated either increased DFI or tested positive for HPV. The research emphasized that sperm DFI serves as a strong indicator of clinical pregnancy success in women undergoing IUI, with DFI levels above 26% linked to a reduced likelihood of achieving clinical pregnancy [104].

Nevertheless, some investigations have shown no significant correlation between HPV infections and sperm quality or fertility outcomes. In the study by Faja et al. 185 men were included, with 85 in Group A (having HPV risk factors) and 100 in Group B (without HPV risk factors) [105]. The study found an HPV prevalence of 8.6%, with 11.8% in Group A and 6% in Group B. The researchers found no significant connection between sperm quality and the presence of HPV in semen. However, previous anogenital infections were linked to a higher likelihood of HPV positivity in semen. Additionally, no viral transcriptional activity was observed in the semen samples that tested positive for HPV [105]. There are also studies indicating that HPV can affect certain sperm parameters, while others remain unchanged. The impact of HPV on sperm quality appears to depend more on whether the infection is caused by an HR or LR type. In the study by Capra et al. no significant HPV-related effects were found on DFI, sperm concentration, total sperm count, or overall motility [106]. However, progressive motility and sperm morphology were notably affected by HPV positivity. Additionally, a significant difference in DFI was seen between HR-HPV and LR-HPV genotypes. A higher DFI was observed in cases involving HR-HPV types compared to those with LR-HPV types. Also, morphologically abnormal sperm in the head/neck, midpiece, and tail site were found in patients who tested positive for HPV in contrast to those who were HPV-negative. The findings suggest that while any HPV type can negatively impact certain sperm parameters, HR-HPVs specifically compromise sperm DNA integrity [106]. Also, the Cannarella et al. study demonstrates that LR-HPV infection does not significantly affect conventional sperm parameters, including sperm concentration, total sperm count, progressive motility, morphology, or leukocyte concentration. However, a higher prevalence of oligozoospermia was observed in LR-HPV-positive patients compared to controls [107].

These findings illustrate that HPV infection impacts sperm cell quality and their reproductive nature in various ways, which collectively leads to a diminished ability to fertilize the oocyte. The precise nature of these specific alterations related to HR-HPV types and the molecular mechanisms by which HR-HPV can induce them are still to be clarified. The results from other studies regarding HPV-related effects on sperm are summarized in Table 1.

Transmission of HPV from infected sperm to oocyte

As previously discussed, HPV localizes at the equatorial region of the sperm head. This region serves as the critical site for the initiation of sperm–egg fusion and acts as the organizing center for assembling the molecular complexes essential for gamete interaction and fusion processes [108]. Sperm–egg membrane fusion involves three tetraspanins: CD9, CD81, and CD151, which contribute to the formation of a tetraspanin network. The tetraspanin network, specifically CD151, plays a crucial role in sperm–egg fusion and the inoculation of HPV in keratinocytes [23]. CD151 is abundantly present in the basal layers of the cervical mucosa, where epithelial cells interact directly with the basement membrane [23]. The protein CD151 regulates the activities of associated integrins. Specifically, overexpression of α3β1 and α6β1/4 as CD151-associated integrins is predominantly observed in basal keratinocytes. Additionally, the α6β4 has been reported as a receptor for HPV-16 [23]. Mechanistically, during HPV-16 infection, viral particles travel alongside CD151 within the membrane's plane, facilitating their co-internalization into endosomes. The viral particles attach to CD151 on the cell surface and stay connected as they move laterally across the membrane, eventually

Table 1 Human papillomavirus (HPV) effects on semen parameters and reproductive outcomes

Author	Studied group	Sample type	Sample size	Rate of HPV infection	Rate of HR-HPV infection	HPV effect on semen and reproductive outcomes	Refs.
Jaworek	Potential sperm donors (SD) and male partners of infertile couples (IM)	Semen samples and penile swabs	425	41.9% (178/425)	HR-HPV genotypes were detected in 28.9% (28/97) of SD samples and 35.1% (115/328) of IM samples	High-risk (HR) HPV-positive semen samples exhibited reduced semen volume, lower sperm concentration, and decreased total sperm count However, no correlation was observed between penile HR-HPV status and semen quality parameters	[20]
Boeri	Infertile men	Semen samples	729	15.5% (113/729)	78/729 (10.7%)	Reduced sperm progressive motility and higher sperm DNA fragmentation in HPV-positive groups	[101]
Damke	Male partners of couples seeking fertility evaluation	Semen samples	229	16.6% (38/229)	5.7% (13/229)	Abnormal viscosity, hypospermia, higher pH, and increased leukocyte numbers	[102]
Niakan	Infertile male partners of couples seeking fertility assessment	Semen samples	140	12.85% (18/140)	10% (14/140)	Higher semen anti-sperm antibodies (ASAs), higher white blood cell (WBC) counts, and increased sperm DNA fragmentation	[258]
Yang	Infertile male patients comprised the case group, and confirmed fertile males comprised the control group	Semen samples	1138	17.4% of case group and 6.70% in control group	NA	Infertile males had a relatively high HPV infection rate compared with confirmed fertile males. Sperm progressive motility and the normal morphology rate were significantly decreased in HPV-positive subjects	[103]
Depuydt	Sub fertile couples	Semen samples	169	14.8%	9.6%	Increase DNA fragmentation index (DFI). When HPV virions were present in sperm, no clinical pregnancies were observed	[104]
Faja	Sexually active men	Semen samples	185	8.6% (16/185)	In samples in whom genotyping was successful 13/15 (86.7%) showed positivity to HR-HPVs	No correlation between sperm quality and seminal HPV	[105]
Capra	Patients undergoing IVF	Semen samples	117	47 (40.2%)	36	HPV positivity primarily affects progressive motility and morphology, with HR-HPV specifically compromising sperm DNA integrity, while other parameters like DFI, sperm concentration, total count, and motility remain unaffected	[106]
Kato	Infertile men	Semen samples	216	12.5% (27/216)	6.9% (15/216)	Lower sperm motility and concentration and higher superoxide dismutase (SOD) level. HPV DNA was localized to the head and midpiece of sperm	[123]

Table 1 (continued)

Author	Studied group	Sample type	Sample size	Rate of HPV infection	Rate of HR-HPV infection	HPV effect on semen and reproductive outcomes	Refs.
Olivera	Adult males attending a urology and andrology clinic	Semen samples	205	19.0% (39/205)	74.0% (20/27)	No significant alterations in routine sperm quality parameters were observed. Individuals with HR-HPV had significantly higher levels of sperm necrosis and a greater proportion of reactive oxygen species (ROS)-positive sperm compared to those with low-risk (LR) HPV or control	[127]
Moghimi	Fertile men and confirmed infertile men who referred to Infertility Centre in (case group)	Semen samples	140	11.43% (8/70)	5.7%	Men infected with HPV showed a significant reduction in the percentage of normal sperm morphology and motility rate	[259]
Garolla	Infertile couples	Semen samples	226	23.9% (54/226)	NA	A reduction in natural and assisted cumulative pregnancy rate and an increase in miscarriage rate	[175]
Foresta	Subjects with genital warts, with HPV-positive partners, infertile patients, and fertile controls	Semen samples	290	Patients with genital warts, 53.8%; infected partners, 40.9%; infertile patients, 10.2%, fertile controls, 2.2%	NA	Sperm motility was reduced in HPV-infected samples, especially when the virus was present in the sperm	[260]

disappearing after they are internalized [109]. It has been revealed that silencing of CD151 leads to a marked reduction in HPV-16 capsid-positive endosomes [109].

Therefore, there is a possibility that infected sperm can penetrate to the oocyte. Foresta et al. demonstrated that sperm carrying the HPV E6/E7 genes or exposed to the HPV L1 capsid protein can enter the oocyte, where they introduce the virus, leading to the activation and transcription of viral genes within the oocyte [24]. Cabrera et al. showed that mouse blastocysts transfected with DNA from HPV types 16 and 18, delivered via carrier sperm, exhibited HPV DNA localized in both the inner cell mass and trophoblast cells. The positive sperm control successfully produced the expected DNA fragments for HPV types 16 and 18 [25]. Moreover, there are other studies, highlighting that HPV can infect sperm and potentially be transmitted to oocytes or the placenta [110–113]. Consequently, HPV infection may enhance trophoblastic cell apoptosis and hinder the implantation of these cells in the endometrium, thereby potentially elevating the risk of miscarriage. The vertical transmission of HPV during pregnancy could contribute to the development of preterm rupture of membranes and spontaneous preterm birth. Additionally, in patients receiving IUI for unexplained infertility, HPV infection is associated with a decreased pregnancy rate [27]. A meta-analysis highlights the adverse consequences of HPV-infected sperm during the fertilization process, which is associated with an increased rate of miscarriage [114]. These events will be discussed in the following sections regarding HPV-related infertility in females.

OS as a potential mechanism of HPV-induced impairment in sperm function

The precise mechanism by which HPV affects sperm parameters has not been identified; however, one possible explanation is its influence through OS. The pathogenesis of HPV is marked by persistent infection and chronic inflammation, with OS playing a crucial role [115]. HPV-induced inflammation recruits cells that release pro-inflammatory cytokines, triggering OS. This process generates ROS that damages cell structures, promotes malignant transformation, and supports HPV's life cycle, including viral assembly [115]. Besides, HPV disrupts the redox balance in host cells, leading to OS, which may facilitate viral integration into the host genome and promote carcinogenesis [116]. These functions are attributed to the viral proteins, as previously discussed in earlier sections.

As we discussed, the HPV early proteins can interact with the mitochondria membrane. Mitochondria consist of two distinct membranes: an outer membrane and an inner membrane The inner mitochondrial membrane is further subdivided into the inner boundary membrane, which faces the outer mitochondrial membrane, and the cristae membrane [117]. The cristae membrane houses the oxidative phosphorylation respiratory chain complexes, such as complexes I, II, III, and IV [118]. Mitochondria are vital in the male reproductive system, playing key roles in spermatogenesis and oocyte fertilization. Additionally, the mitochondria in sperm cells are essential for ATP production, which is necessary to support sperm motility [119]. ROS also plays a critical role in sperm capacitation, as it regulates protein tyrosine phosphorylation. The generation of ROS activates a series of biochemical processes that augment sperm motility. However, spermatozoa are highly susceptible to ROS-induced damage, which can include harmful agents like superoxide anion, H_2O_2, hydroxyl radical, nitric oxide, and peroxynitrite. Excessive ROS production can cause OS, leading to functional impairments in sperm, such as reduced motility, mitochondrial dysfunction, and a diminished ability to fertilize oocytes [119]. Thus, it can be concluded that HPV proteins can cause OS by interacting with mitochondrial membrane [73]. As a result, HPV can affect sperm quality by disrupting mitochondrial function.

As well, several studies suggest that HPV can affect sperm quality by triggering OS. Pellavio et al. conducted research exploring the potential impact of HPV on the expression and functionality of aquaporins (AQPs) in sperm cells from patients undergoing infertility assessments as part of couple evaluations [37]. AQPs, a group of widely distributed transmembrane proteins, facilitate the movement of water and small molecules across the cell membrane. In mammalian sperm, various AQPs such as AQP3, AQP7, and AQP11 have been detected, playing crucial roles in adjusting to osmotic changes and activating sperm motility post-ejaculation [120, 121]. In humans, four types of AQPs are present in sperm, each exhibiting distinct localization: the head, midpiece, or tail. Specifically, AQP3 and AQP11 are predominantly found in the tail, AQP7 in the head, and AQP8 in the midpiece [122]. Among these, AQP8 plays a critical role in managing OS by facilitating the removal of H_2O_2, the most prevalent ROS [122]. Research has revealed that HPV infection greatly diminishes the ability of sperm cells in normospermic samples to regulate water permeability. This effect is linked to changes in both the expression and function of AQPs. The viral L1 protein appears to directly interact with AQP8, disrupting its role in facilitating water and H_2O_2 transport. Consequently, this interference impairs AQP8's detoxification processes, contributing to sperm stress and functional impairment [37].

A separate investigation involving 216 infertile men in Japan explored the presence and distribution of HPV in semen, alongside an analysis of sperm parameters and the activity of SOD in seminal plasma [123]. HPV was detected in 12.5% of semen samples, with 6.9% involving HR-HPV types. The prevalence of HPV did not significantly differ between azoospermic and non-azoospermic individuals. Among non-azoospermic men, those with HPV in their semen experienced markedly lower sperm motility and concentration than those without HPV. ISH analysis revealed the presence of HPV DNA in the sperm head and midpiece, confirming its association with sperm in young infertile men. Additionally, seminal plasma from HPV-positive patients showed elevated SOD levels compared to HPV-negative individuals [123]. SOD functions as a powerful antioxidant enzyme, rapidly neutralizing oxygen radicals via oxidation and reduction processes facilitated by transition metal ions in its active site. It converts superoxide anions into H_2O_2 while simultaneously releasing molecular oxygen [124]. As SOD is an enzyme that defends cells against OS by neutralizing superoxide radicals, it can be hypothesized that the HPV presence in semen may result in increased OS, prompting a compensatory rise in SOD activity. Olia et al.'s study revealed a notable rise in serum MDA levels among individuals infected with HPV. Additionally, urinary 8-OHDG concentrations were elevated in these patients [125]. Both MDA and 8-hydroxyguanosine are widely recognized as key indicators of oxidative stress. Notably, their levels were significantly higher in individuals with HR-HPV infections compared to those with LR-HPV infections [125]. In another finding, the HPV-infected group exhibited reduced normal morphology and diminished antioxidant levels compared to the uninfected group [126]. Similarly, they displayed elevated concentrations of lipid peroxidation, interferon-gamma (IFN-γ), IL-1β, IL-4, and IL-6, alongside the suppressed activity of catalase and SOD enzymes. Notably, motility alterations, decreased total antioxidant capacity, and heightened expression of CYP2E1, lipid peroxidation, and IL-8 were more pronounced in multiple HR-HPV infections than in single HR-HPV infection [126].

Olivera et al. investigated the impression of HR- and LR-HPV infections on male urogenital health, focusing on sperm quality, OS, and inflammation [127]. They found that HR-HPV infections led to increased ROS production in sperm, resulting in higher levels of dead sperm (ROS-positive and necrotic). HR-HPV-infected patients showed more ROS-positive sperm than those with LR-HPV, where most ROS-producing sperm remained viable. These effects were observed even without significant semen inflammation. The presence of additional uropathogens led to a modest decline in these outcomes [127]. However, they discovered that neither HR-HPV nor LR-HPV was linked to important changes in standard sperm quality parameters. Moreover, patients infected with either HR- or LR-HPV showed no significant signs of inflammation in their semen. Surprisingly, HR-HPV-positive patients exhibited lower levels of semen leukocytes and inflammatory cytokines (IL-6 and IL-1β) compared to the control group [127]. In the research conducted by Pérez-Soto et al. the impact of infections caused by HPV and CT, as well as the combined infection of HPV and CT, was evaluated in relation to sperm quality, inflammation, and OS in asymptomatic men with infertility [99]. The study revealed that 81 out of 84 samples (96.4%) tested positive for one or more pathogens. Specifically, 68% of samples were positive for HPV, 13.5% for CT, and 18.5% for both HPV and CT coinfection. Semen quality was compromised in the infected groups, with an increase in pH levels beyond the normal range across all groups. Abnormal sperm morphology was noted in both the HPV and HPV + CT groups. In the HPV group, elevated cytokine levels were observed, with the highest concentration of IL-1β seen in the HPV + CT group. No cytokines were found in the CT-only group. Additionally, all infected groups exhibited high levels of lipid peroxidation and 8-OHdG, alongside a reduction in TAC. Comparative analysis indicated that the HPV group had the highest OS [99].

Additionally, it can be suggested from another perspective that HPV may trigger an inflammatory response, leading to the subsequent recruitment of immune cells, which ultimately increases ROS production (Fig. 2). Chronic infections like HPV contribute to ongoing inflammation, which disrupts the balance between prooxidants and antioxidants. This inflammatory response triggers the secretion of pro-inflammatory cytokines, including IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), and IFN-γ [116]. These cytokines activate signaling pathways mediated by protein kinases, ultimately leading to the production of ROS [116]. Also, HPV activates the NF-κB pathway, promoting the release of cytokines and the recruitment of immune cells. This process fosters ongoing inflammation and OS [128]. The immune cells drawn to the site generate ROS, which damage essential cellular components such as lipids, proteins, and nucleic acids [116]. In general, the primary sources of ROS in the male reproductive system include sperm mitochondria, abnormally shaped spermatozoa, and activated leukocytes present in seminal fluid [129]. In a study conducted by Li et al. the primary source of ROS in seminal plasma was investigated, along with its impact on leukocytes [130]. The results showed that ROS levels in semen were closely linked to sperm function, with CD45 + leukocytes identified as the major producers of ROS. When

compared to the control group, the experimental group had elevated concentrations of IL-2, IL-4, IL-6, IFN-γ, and TNF-α. The study also suggested that leukocytes in semen may regulate ROS production via the mammalian target of the rapamycin (mTOR) pathway. Furthermore, a significant amount of ROS was found to enhance IL-6 expression in leukocytes through the NF-κB pathway [130]. Also, they found that the proportion of inactive sperm was notably higher in the leukocyte group compared to the control group. Additionally, sperm motility parameters were significantly lower in the leukocyte group, indicating that an excess of leukocytes may adversely affect sperm function [130]. Altogether, OS has a profound effect on sperm quality, adversely affecting parameters such as count, motility, morphology, and DNA integrity, which can result in male infertility [131]. Thus, since Leukocytes are the primary contributors to the generation of ROS in semen, a higher concentration of leukocytes in the semen can lead to increased production of ROS, which negatively impacts sperm functionality [132, 133].

Altogether, HPV infection contributes significantly to sperm dysfunction through the generation of OS (Fig. 2). By triggering inflammation and immune cell recruitment, HPV elevates ROS production, which disrupts mitochondrial function and sperm quality. This oxidative damage impairs sperm motility, morphology, and DNA integrity, ultimately leading to male infertility. Also, HPV can disrupt key cellular mechanisms, such as aquaporin function, exacerbating the detrimental effects on sperm. These findings underscore the importance of addressing OS in the management of HPV-related fertility issues, highlighting the need for further research into potential therapeutic interventions targeting OS to mitigate its impact on sperm function.

Detrimental effects of OS on sperm

The average level of ROS is crucial for preserving the physiological balance of the reproductive system. However, a range of internal and external factors contribute to the increased production of ROS, leading to damage to both the structure and function of sperm cells. This occurs through the activation of apoptotic processes and the oxidative degradation of essential biomolecules, including lipids, proteins, and DNA [134].

Damages to DNA

A regulated release of minimal ROS levels is essential for maintaining normal sperm function. Sperm DNA is safeguarded through two key mechanisms: its highly specialized packaging and the antioxidant defense system present in seminal plasma [135, 136]. However, excessive OS poses significant genetic risks to the sperm nucleus by inducing oxidative DNA damage [137]. Sperm cells are particularly vulnerable to oxidative damage because they contain numerous mitochondria, have an abundance of molecules sensitive to free radicals, and possess a limited capacity to defend against OS [138]. OS can modify DNA bases or lead to single-stranded and double-stranded DNA breaks [139]. Besides fragmentation of DNA, OS can lead to mutations and chromosomal abnormalities, affecting sperm potential for fertilization and decreasing fertilization rate [140, 141]. OS not only leads to the formation of oxidized DNA bases and strand breaks but can also induce de novo point mutations [142]. Unfortunately, spermatozoa possess a limited capacity for base excision repair (BER), which is a DNA repair pathway that corrects damaged or inappropriate bases in DNA, like those caused by oxidation, deamination, or alkylation [143, 144]. Although spermatozoa maintain the primary glycosylase function, like OGG1, which eliminates oxidized bases, they are missing the subsequent repair steps, including apurinic/apyrimidinic endonuclease 1 (APE1) activity [142]. Consequently, numerous oxidative DNA lesions persist unresolved until fertilization, at which point the oocyte's BER system takes on the task of correcting the damage. If the oxidized bases in sperm DNA are not corrected by the oocyte's repair mechanisms following fertilization, these mutations may persist and be inherited by all cells of the developing embryo [142]. The increased frequency of point mutations in the zygote is particularly concerning, as they can significantly affect gene regulation and will be transmitted to every cell in the offspring. Furthermore, excessive OS in the sperm nucleus presents not only genetic but also epigenetic risks [145]. When sperm are exposed to a pro-oxidant environment, especially after leaving the testes (during a period when their DNA repair capabilities are absent) various epigenetic alterations can occur. These may involve abnormal methylation or demethylation of cytosine residues, as well as modifications in the small non-coding RNA (sncRNA) profile of the sperm, which can change the embryonic development program [142]. Thus, it can be proposed that HPV can induce sperm DNA damage by causing excessive OS. Also, cells infected with HPV are more vulnerable to ionizing radiation and other chemicals that can aggravate damage to DNA [146]. Consequently, DNA damage in sperm caused by ROS during HPV infection may lead to infertility, and HPV integration can worsen the condition [23].

Oxidation of proteins

ROS alters sperm proteins by oxidizing amino acid side chains, leading to carbonyl group formation and disulfide bonds [139]. These changes cause protein aggregation and dysfunction, impairing sperm motility, structure,

and fertilization, contributing to male infertility. Oxidation primarily affects amino acids like cysteine, methionine, and tyrosine, which are highly reactive. In sperm, oxidative stress mainly impacts proteins responsible for cytoskeletal integrity, movement, and the acrosome reaction [139]. As well, OS is associated with generating carbonyl groups in peptide chains and forming carbonylated proteins. Protein carbonylation leads to decreased sperm cell quality and the protein carbonylation measurement indicates the protein oxidation damage [147].

Oxidation of lipid

The membrane of sperm cells has a large amount of polyunsaturated fatty acid. These lipids contain unconjugated double bonds which are separated by methylene group. The adjacent placement of double bonds near the methylene group makes lipids more susceptible to oxidation damage [35]. Lipid peroxidation leads to the loss of fatty acid and degrades membrane fluidity and integrity, increasing permeability to ions non-specifically, and inhibiting membrane-bound receptors and enzymes [35]. Consequently, lipid peroxidation affects the function and viability of sperm cells, impairs the fusion process, and decreases fertilization capacity [139, 148]. MDA is a common marker of lipid peroxidation but is not specific enough and quickly disintegrates into several compounds. The reactive aldehyde 4-hydroxy-2-nonenal (4-HNE) is a more specific marker of lipid oxidation [149]. 4-HNE can stimulate the production of ROS by interacting with the proteins involved in the sperm mitochondrial electron transport chain [39].

Mitochondrial dysfunction

Mitochondria play an indispensable role in producing adenosine triphosphate (ATP) which is important for the motility and function of sperm cells [150, 151]. ROS can trigger lipid peroxidation in the mitochondrial membranes, which affects their fluidity and interferes with the electron transport chain ETC. This interference leads to reduced ATP synthesis and impaired mitochondrial performance. This defect can diminish the motility and function of sperm cells [35, 152]. As mitochondrial activity is disturbed, sperm motility is decreased and sperm fertilization potential is adversely affected. Also, mitochondrial dysfunction can diminish the viability of sperm cells [141]. Mitochondria substantially regulate the apoptosis process. This regulation may be broken through its impaired function. Mitochondrial malfunction induced by ROS can stimulate apoptotic signals and release apoptotic factors. This condition leads to reduced viability and counting of sperm cells and ultimately, diminished reproductive potential [141, 153, 154]. Moreover, when mitochondria in sperm are impaired, it can lead to alterations in their structure and morphology. Furthermore, the damage caused by ROS to sperm DNA may also play a role in these structural changes [141]. Decreasing of ATP and energy following ROS-induced mitochondrial dysfunction leads to diminishing sperm motility and its fusion potential to the oocyte [155]. All of these events indicate the mutual role of ROS in the reproductive system, implying that the physiological concentration of ROS has an important impact on sperm maturation, acrosome reaction, and entirely, male reproductive potential [156]. The excessive amount of ROS can disrupt the normal activity of the reproductive system components and cause damage. DNA damage, protein and lipid oxidation, and mitochondrial dysfunction induced by OS led to reduced motility and viability of sperm cells and poor fertilization capacity. To maintain and improve male reproductive well-being, using strategies such as antioxidants can be helpful in diminishing ROS [131].

Female infertility associated with HPV

Impacts of HPV infection on the female reproductive system

HPV present in infected sperm cells has the potential to transmit the virus to both the oocyte during fertilization and the placenta. This may lead to unfavorable outcomes in pregnancy. The role of HPV infection in female infertility has garnered increasing attention, particularly regarding its effects on reproductive physiology and immune modulation. Moreover, it seems that an exaggerated immune response in reaction to HPV can cause genetic instability in reproductive cells, which may affect fertility [23]. A nationwide population-based retrospective cohort study spanning 13 years indicates that individuals with HPV face an approximately 1.4 times higher likelihood of experiencing female infertility compared to those without the infection [157]. However, the exploration of the relationship between HPV and infertility may not be forthright because of the existing confounding factors that play influential roles in reproductive outcomes. An observation study conducted by Spandorfer et al. involving 106 participants revealed that HPV-positive women experienced a significantly lower pregnancy rate compared to the HPV-negative group after undergoing IVF [158]. Based on the findings of the systematic review and meta-analysis, HR-HPV infection has been identified as a potential risk factor for female infertility; however, it is not considered an independent causative factor [159]. HPV-related infertility in women, particularly through mechanisms involving the induction of OS, requires further exploration to fully understand its impact. While the connection between HPV and infertility remains an

evolving area of research, evidence suggests that HPV may contribute to infertility through various pathways.

Effects on vaginal microbiome

HPV infection can change the vaginal microbiome, which may increase the risk of infertility [160, 161]. Lebeau et al. conducted a comprehensive study that sheds new light on the intricate relationship between HPV infection and bacterial vaginosis [160]. Mechanistically, the study highlights that in HPV-positive cells, the E7 oncoprotein plays a critical role in immune evasion by impairing pro-inflammatory-induced innate peptide expression. This is achieved through the degradation of NEMO, a key component of the NF-κB signaling pathway, which subsequently sequesters p65 in the cytoplasm, preventing effective immune responses [160]. Simultaneously, E7 reduces E-cadherin expression and disrupts the β-catenin degradation complex by interacting with both CK1 and β-TrCP. This interaction alters the regulation of β-catenin and its downstream target genes, such as c-myc, resulting in the suppression of key host defense peptides, including elafin and S100 A7 [160]. These defense peptides are essential for maintaining the vaginal microbiota, as they serve as amino acid sources for *Lactobacillus* species, the dominant bacteria responsible for maintaining a healthy vaginal environment. By downregulating these peptides, HPV persistence fosters an imbalance in the vaginal flora, ultimately leading to microbial dysbiosis [160]. Consequently, dysbiosis can lead to reduced mucus production [162]. Therefore, vaginal microecological dysbiosis and HPV infection are closely linked to infertility, highlighting the need for preventive measures. This relationship is evident in the Chinese population, where the rates of vaginal flora imbalance and HPV infection are higher in the infertile individuals [161]. Figure 3 illustrates the effect of HPV infection on the female reproductive system.

Effects on ovarian reserve

While there is limited documentation, certain research indicates that HPV might impact ovarian reserve, potentially via chronic inflammation (Fig. 3) [28, 163]. A study involving 219 women of reproductive age exhibiting different clinical symptoms revealed that HR-HPV infection is linked to a reduction in ovarian reserve, potentially affecting fertility [28]. It is suggested that the inflammation resulting from HPV infection could negatively affect the function of granulosa cells, leading to a decrease in serum anti-Mullerian hormone (AMH) levels. HPV-positive patients showed significantly lower AMH levels, with a notable difference in AMH levels between the normal and CIN III sub-groups. HPV infection in women could potentially have a considerable effect on their ovarian reserve [28].

Effects on trophoblast viability and their adhesion to endometrial cells

The process of embryo implantation begins with the attachment of trophoblast cells to the epithelial layer of the endometrium. Therefore, any complications in this process can result in infertility [164, 165]. Previous research demonstrated the capability of HPV to reproduce within trophoblast cell lines [166, 167]. Subsequently, it has been suggested that HPV may promote apoptosis in trophoblastic cells and hinder their implantation into the endometrium, potentially elevating the risk of miscarriage (Fig. 3).

In 2002, You et al. conducted an in vitro study to investigate the potential impacts of HPV's genomic components on trophoblast physiology [168]. Their findings revealed that the expression of HPV-16 oncogenes (E6 and E7) could result in trophoblast cell death, impaired recognition by endometrial cells, or the development of a malignant phenotype. These alterations could disrupt the trophoblast layer, potentially leading to dysfunction or gestational loss and contributing to spontaneous abortions [168]. In 2003, researchers discovered that infection with the HPV 31b virus led to a dose-dependent reduction in 3 A trophoblast cell numbers and weakened trophoblast-endometrial cell adhesion, both of which were prevented by neutralizing anti-HPV-31 antibodies [169]. These findings provide additional evidence that HPVs are functionally active in trophoblasts and may contribute to spontaneous abortions. Henneberg et al. observed that HPV exerted stage-specific effects on early embryonic development [170]. Their findings indicated that exposure to HPV was associated with the demise of two-cell embryos while delaying HPV exposure until later embryonic stages allowed development to proceed. Specifically, HPV-16 was found to reduce blastocyst formation, whereas HPV-18 interfered with the hatching process of the blastocyst [170]. It has also been demonstrated that HPV oncoproteins reduce trophoblast cell adhesion to endometrial cells, thereby hindering the implantation process. In the study by Hong et al. HPV-16 was found to inhibit trophoblast adhesion, a crucial process for normal implantation, while having no effect on embryo development [171]. Exposure to HPV-16 increased overall trophoblast spread, indicating that HPV-16 may disrupt trophoblast migration. These findings imply that HPV-16 could lead to abnormal placental development, potentially contributing to pregnancy loss [171].

Rocha et al. proposed that HR-HPV positivity is linked to infertility and endometriosis in the upper genital tract [9]. Okyay et al. conducted a cross-sectional study investigating the association between HPV positivity and symptoms related to endometriosis, including pain and infertility [8]. The study involved 410 patients diagnosed

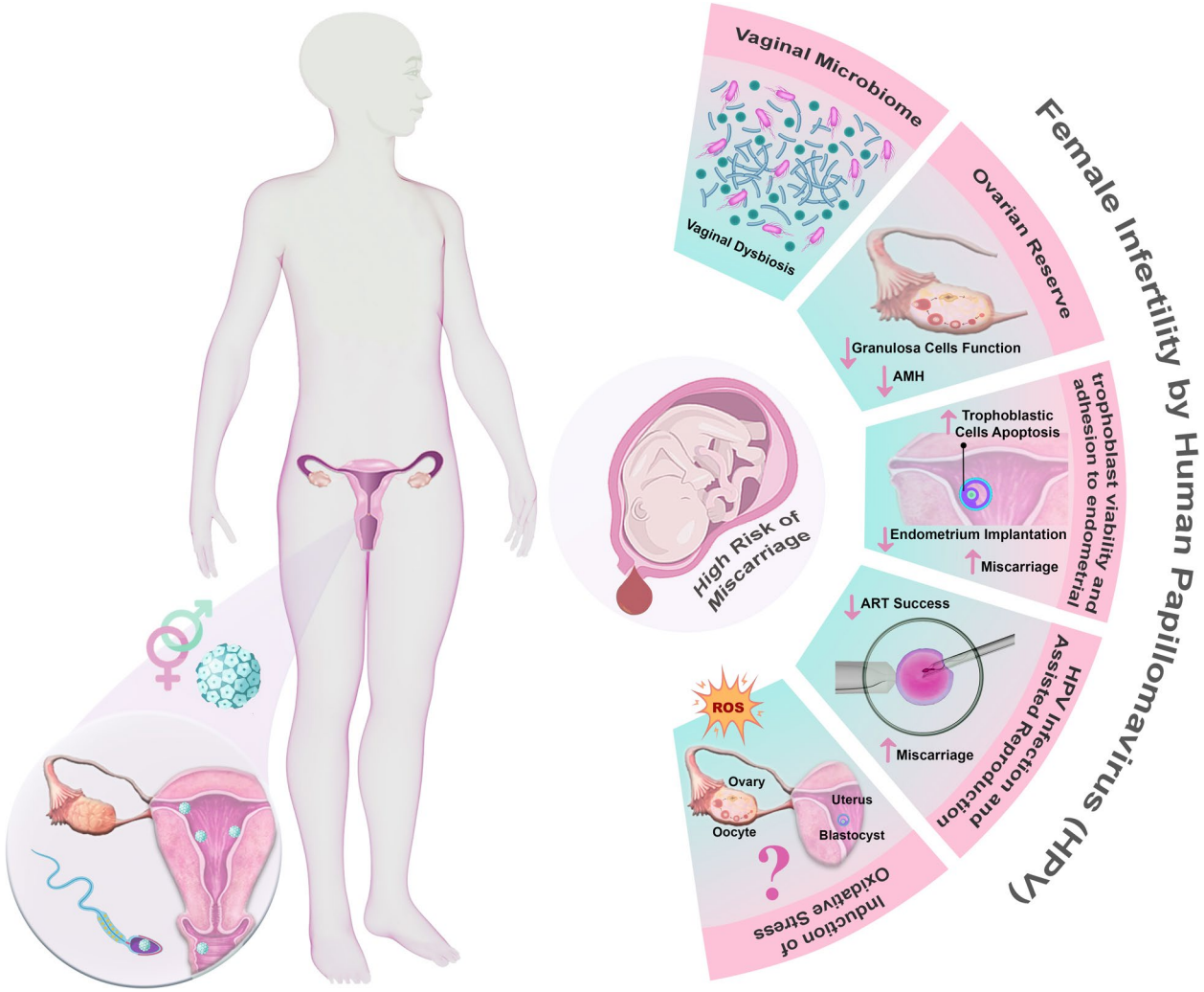


Fig. 3 The effects of HPV infection on female reproductive health. HPV infection disrupts the vaginal microbiome, leading to microbial dysbiosis and an imbalance in vaginal flora. It also negatively impacts ovarian reserve by impairing granulosa cell function, resulting in decreased serum anti-Müllerian hormone (AMH) levels, particularly in HPV-positive patients, with more pronounced effects in advanced cervical intraepithelial neoplasia (CIN III) cases. Additionally, HPV promotes apoptosis in trophoblastic cells and hinders their adhesion to endometrial cells, increasing the risk of miscarriage. Furthermore, HPV infection is associated with reduced success rates in assisted reproductive technology (ART) and a higher likelihood of adverse pregnancy outcomes. Finally, there is the potential role of OS pathways induced by HPV, which may contribute to the observed effects on fertility, including impaired oocyte quality, blastocyst development, and endometrial receptivity. However, the exact mechanisms linking OS to infertility remain unclear and require further research

with endometriosis, categorized as HPV-positive ($n=$ 202) or HPV-negative ($n=208$). Within the HPV-positive group, HPV types were further classified as either HR (HPV 16/18) or "Other HPV," encompassing all non-HPV 16/18 types. The findings revealed that dyspareunia was significantly more prevalent in the "Other HPV" group (12.8%) compared to the HPV-negative group (4.8%). Infertility rates were markedly higher among patients with HR-HPV (35.8%) compared to the HPV-negative group (7.6%) and those with "Other HPV" types (8%) [8]. Additionally, pain associated with endometriosis was reported more frequently in the HR-HPV group (49%) compared to the HPV-negative group (37%) and the "Other HPV" group (46.3%). While the rate of ovarian endometrioma was slightly elevated in the HR- HPV group (16.9%) compared to the "Other HPV" (11.4%) and HPV-negative groups (7.2%), this difference did not reach statistical significance [8].

Evidence demonstrated that HPV-16 markedly diminished trophoblastic outgrowth and led to a reduction in cell size. Exposure to HPV-16 has been correlated to a 90% reduction of trophoblast outgrowth compared

to the control group. HPV-16 may influence these processes through cAMP inhibition, activation of TNF pathways, and increased necrosis, which cumulatively lead to cell death [172]. An investigation by Freitas et al. on both decidua and chorionic villi tissues from patients with spontaneous and intentional miscarriage detected HPV DNA types 6, 11, 58, 66, and 82 [173]. The analysis of HPV DNA in products of conception obtained from first trimester spontaneous and electively terminated pregnancies revealed that HPV prevalence is higher in spontaneously aborted conception products [174]. The long-term follow-up of pregnancies exhibited a prominent miscarriage rate in HPV infected (62.5%) versus uninfected couples (16.7%), as described by Garolla et al. [175].

As well, the study conducted by Gomez et al. investigates whether HPV infection of extravillous trophoblast cells impairs cell invasion and contributes to adverse reproductive outcomes due to placental dysfunction [176]. Apoptosis and invasion tests were conducted on extravillous trophoblast cells that had been transfected with the HPV-16 plasmid. Additionally, case–control research was conducted to detect HPV DNA in placental tissue from spontaneous preterm delivery cases, severe preeclampsia cases requiring early delivery, and controls delivering at term. The results showed that HPV-transfected cells exhibited significantly higher apoptosis rates and reduced invasion capabilities compared to controls. HPV was found to be more prevalent in placentas from spontaneous preterm deliveries compared to the control group, but no significant difference was found for preeclampsia cases. The study concluded that HPV infection may induce placental dysfunction and is linked to adverse pregnancy outcomes, like spontaneous preterm delivery [176]. Another study was conducted to examine the impact of HPV DNA from the E6–E7 region on the integrity of DNA in blastocyst-stage embryonic cells [177]. The study aimed to determine whether the presence of HPV DNA disrupted blastocyst DNA and if the extent of DNA damage varied depending on the HPV type. Female mice were superovulated and mated, and their embryos were cultured to the expanded blastocyst stage, where they were infected with DNA fragments from HPV types 16, 18, 31, or 33. The results revealed that only HPV type 16 caused significant DNA fragmentation, while no correlation was found between HPV DNA fragment size and the intensity of DNA damage [177]. The study concluded that HPV type 16 induces apoptosis in embryonic cells through DNA fragmentation, with effects occurring rapidly within 24 h. The intensity of DNA damage did not correlate with the HPV type, although other HPV types might impact embryos under different conditions [177]. Also, the study by Boulenouar et al. found that HPV-16 E5 protein reduced the viability of trophoblastic and cervical cell lines, but E6 and E7 proteins, which promote cell growth, counteracted E5's cytotoxic effects [178]. Additionally, E5 decreased trophoblastic cell adhesion to both tissue culture plastic and endometrial cells, similar to the effects of E6 and E7. E5, along with E6 and E7, also enhanced cell migration and invasiveness. Cells that expressed HPV-16 early proteins driven by the long control region promoter demonstrated enhanced growth, increased mobility, and greater invasiveness compared to the control group. Notably, E-cadherin expression was reduced in trophoblastic cells expressing E5, E6, and E7. Furthermore, the activities of NF-κB and activator protein-1 were increased. Altogether, HPV-16 early proteins promote trophoblastic cell growth and contribute to a malignant phenotype by impairing cell adhesion, enhancing motility and invasiveness, and downregulating E-cadherin, a key marker of cancer progression [178].

However, some studies indicate that HPV cervical infection is not linked to spontaneous abortion, and the infection rate of HPV does not appear to be elevated in cases of spontaneous abortion [179, 180]. Furthermore, the primary limitations of these studies stem from the in vitro experiments and animal models, which often fail to reflect true human conditions in vivo. To validate these results, extensive in vivo research is necessary, but such studies are scarce in the literature, mainly due to ethical constraints on conducting reproductive experiments in humans. Altogether, the role of the placenta in the etiology of miscarriage has been a subject of investigation, yet the evidence remains ambiguous. Further exploration is necessary to clarify this potential association and its implications for pregnancy health. The results of other studies are summarized in Table 2.

Detrimental effects of OS on females' reproductive system

ROS influences multiple ovarian functions, such as hormone production, egg maturation, ovulation, blastocyst development, implantation, and the regulation of the corpus luteum during pregnancy. OS is a key factor in modulating the physiology of both ovarian germ cells and stromal cells. Additionally, ROS may significantly impact fertilization and the implantation process [181]. Although ovarian functions demand a regulated level of ROS, an excessive level of ROS interferes with several mechanisms in various organs of the female reproductive system and leads to DNA, lipid, and protein damage in oocytes. Furthermore, OS is associated with some reproductive disorders including PCOS, endometriosis, infertility, embryonic resorption, poor pregnancy outcomes, preeclampsia, intrauterine growth restriction, and fetal mortality [181, 182].

Table 2 HPV effects on trophoblast

Author	Findings	Refs.
You et al.	The activation of HPV-16 oncogenes (E6 and E7) may lead to the death of trophoblast cells, hinder their recognition by endometrial cells, or promote the emergence of a malignant phenotype. These changes can compromise the trophoblast layer and play a role in pregnancy loss	[168]
Calinisan et al.	HPV type 16 can induce apoptosis in embryonic cells by causing DNA fragmentation, with this effect occurring within 24 h. Remarkably, significant DNA fragmentation was observed solely with HPV type 16, in comparison to other HPV types tested, suggesting that HPV type 16 may exert a more potent or distinct influence on DNA integrity in blastocyst cells	[177]
You et al.	HPV-31b infection led to a dose-dependent reduction in 3 A trophoblast cell numbers and diminished adhesion between trophoblast and endometrial cells	[169]
Henneberg et al.	The study underscored the stage-specific effects of HPV on early embryonic development. It was found that HPV exposure at the two-cell stage led to embryo loss, whereas delaying exposure to later stages permitted continued development. HPV type 16 was shown to impair blastocyst formation, while HPV type 18 hindered the blastocyst hatching process	[170]
Gomez et al.	HPV infection in extravillous trophoblast cells triggers cell death and may interfere with the placental invasion of the uterine wall. As a result, this infection could lead to placental dysfunction, which is linked to negative pregnancy outcomes, such as spontaneous preterm birth	[176]
Boulenouar et al.	HPV-16 early proteins promote trophoblastic cell growth and contribute to a malignant phenotype by impairing cell adhesion, enhancing motility and invasiveness, and downregulating E-cadherin, a key marker of cancer progression	[178]
Hong et al.	HPV-16 disrupted the adhesion of trophoblasts, which is crucial for proper implantation, but did not affect embryo development. After exposure to HPV-16, there was an increased spread of trophoblasts, suggesting that HPV-16 impacted trophoblast migration. These results imply that HPV-16 may contribute to abnormal placental growth, potentially playing a role in pregnancy loss	[171]
Chen et al.	HPV-16 caused a reduction in nuclear size and trophoblast outgrowth. It also induced higher levels of cell necrosis in trophoblasts, suggesting that its pathogenic mechanism may involve the inhibition of cAMP pathways and/or the activation of TNF pathways	[172]
Ambühl et al.	HPV DNA was identified in trophoblast cells, mesenchymal cells of the placental villi, including Hofbauer cells, and parts of the surrounding endometrium. However, placental HPV infections are unlikely to be a significant risk factor for spontaneous preterm labor or spontaneous abortions	[261]

Damage to oocyte

OS can induce damage to oocytes including nucleic acid damage, lipid and protein peroxidation, and mitochondrial dysfunction [183]. DNA damage induced by the excessive level of ROS can cause DNA strand breaking and chromosomal abnormalities [144]. OS leads to the apoptosis of most germ cells in the ovary, including those that have been ovulated. While both mitochondrial and death receptor pathways contribute to oocyte apoptosis, the mitochondria-mediated mechanism predominantly drives the loss of germ cells from the ovary due to OS. Additionally, OS within the follicular fluid compromises oocyte quality, ultimately impairing reproductive success [184]. Consequently, all of this damage influence on oocyte fertility potential.

Embryonic damage

Embryo formation includes the incorporation of components of sperm and oocyte during fertilization. A certain level of ROS is essential for key embryonic processes, including pronuclear formation, initial cell division, and overall cell growth. However, excessive ROS levels can negatively impact embryo development, causing developmental arrest, heightened DNA damage, and alterations in gene expression that may lead to abnormal fetal growth and health issues [185, 186]. Additionally, elevated ROS levels in the embryo lead to mitochondrial alterations, cell cycle arrest, ATP reduction, and programmed cell death [187].

Reproductive disorders in ovaries

OS can induce damage to the ovary. OS accelerates ovarian aging by triggering apoptosis, inflammation, mitochondrial dysfunction, telomere attrition, and damage to essential biomolecules [183, 188]. As a result, elevated ROS levels and heightened sensitivity of oocytes to OS contribute to spindle disorganization, genetic irregularities, telomere attrition, and diminished developmental potential in aging oocytes [189]. These irregular conditions greatly disrupt the process of meiotic recombination, leading to mistakes in chromosome separation and eventual loss. As a result, oocytes undergo defective meiotic division, which significantly reduces egg quality [155]. Moreover, several studies have shown that increased levels of ROS play a crucial role in the development of PCOS, and its clinical manifestations result from excessive ROS generation. PCOS is a disorder characterized by the formation of multiple cysts in the ovaries and hormonal dysregulation, which can lead to infertility in females [190, 191]. The majority of PCOS patients develop insulin resistance (IR). In individuals with IR, high blood sugar levels trigger an increase in

ROS production via the NADPH oxidase p47(phox) subunit. Additionally, elevated glucose levels stimulate the secretion of TNF-α from mononuclear cells, a key factor in IR development. This process also boosts the activity of NF-κB, which further aggravates OS by activating NADPH oxidase. The result is an ongoing cycle of heightened ROS generation and sustained inflammation [190].

Reproductive disorders in the uterus

It has been suggested that HPV infection may contribute to the development of chronic inflammation, potentially leading to the progression of endometriosis [28, 192]. Endometriosis is an inflammatory disorder which is recognized by the migration of the endometrial tissue to positions other than the uterus. Endometriotic implants are typically located within the pelvic region. Common areas where these implants are found include the ovaries, fallopian tubes, and the peritoneal lining of the pelvis, all of which are in close proximity to the ovarian follicles [193, 194]. After implantation, macrophages and leukocytes recruited and elevated pro-inflammatory cytokines and ROS production [194]. Also, a high level of free iron is found in implant sites, leading to an increase in the destructive form of ROS. The excessive concentration of ROS may interfere with oocyte, embryo, or oviduct motility and induce more inflammatory responses, as observed in patients with endometriosis [194].

Furthermore, an imbalanced level of ROS may lead to recurrent pregnancy loss [195]. Recurrent pregnancy loss refers to the repeated occurrence of two or more consecutive miscarriages before reaching 20 weeks of gestation, encompassing both embryonic and fetal losses. This condition is a common reproductive health issue linked to infertility [196]. In addition to the imbalanced level of ROS, several factors such as immunological disorders, and chromosomal anomalies can cause recurrent pregnancy loss [197, 198]. OS related to insufficient antioxidant factors is considered an important pathological agent of recurrent pregnancy loss. Studies have shown that individuals experiencing recurrent pregnancy loss exhibit elevated levels of ROS alongside reduced activity of antioxidant enzymes [198].

Another complication associated with OS is preeclampsia [199]. Preeclampsia is a vascular disorder during gestation recognized through hyper-blood pressure and proteinuria. Preeclampsia arises from defective placentation, which results from insufficient trophoblast invasion and abnormal remodeling of the spiral arteries, ultimately leading to reduced oxygen supply to the placenta. This hypoxic environment promotes the release of anti-angiogenic molecules which disrupt endothelial function and trigger systemic inflammation. Additionally, OS, mitochondrial dysfunction, and immune system imbalances further contribute to disease progression [200, 201]. OS in the kidney during preeclampsia disorder can result in proteinuria [202]. Preeclampsia is also linked to fetal growth restriction FGR, preterm birth, and placental abruption, all of which stem from impaired placentation [203]. Additionally, gestational hypertension (GH) is another hypertension disorder that is similar to preeclampsia but without proteinuria. The OS in GH and preeclampsia can lead to placental hypoxia and inflammatory responses inducing several complications [204].

Besides, an imbalance condition between oxidant and antioxidant status may lead to an increase in intrauterine growth restriction (IUGR) [205]. IUGR, also known as fetal growth restriction (FGR), is a problem during gestation resulting in decreased growth rate and progression of mortality and several diseases later in adulthood, including type 2 diabetes, obesity, hypertension, and cardiovascular disease [206, 207]. Different causes have been found for FGR, including impaired function of the placenta, fetal causes, or maternal disorders such as maternal endothelial cell impairment and placental dysfunction are the most common cause of FGR [207]. Moreover, heightened OS disrupts both maternal and placental functions, which can ultimately lead to fetal loss and, IUGR [208]. Due to the increased activity of free radicals in IUGR, using antioxidant supplements may prevent or decrease IUGR [209].

Reproductive disorders in the fallopian tubes

There is evidence that proposes that ectopic pregnancies may be associated with the presence of high OS [210]. An ectopic pregnancy occurs when the egg implants outside the uterine cavity, often in fallopian tubes. The exact cause of ectopic pregnancy remains unclear; however, various risk factors are associated with its occurrence. These include smoking, prior tubal surgery, and infection with *C. trachomatis*. It is suggested that these factors may contribute to implantation within the fallopian tube by disrupting normal tubal function [211]. The high level of OS can change the tubal epithelial cells to collagen fibers and impair the transportation of the embryo. Also, OS can disrupt the cilia's motion and smooth muscle contractions and interfere with transportation. Furthermore, the imbalanced status between oxidant and antioxidant can lead to increasing the concentration of ROS and disrupt the development of embryos. Several factors, including infection, inflammation, and some abnormalities, make fallopian tubes susceptible to OS [34, 210]. Ectopic pregnancy can impact the health and fertility capacity of a mother. Hence, managing OS reduction can be an essential factor for appropriate fallopian tube function and ectopic pregnancy prevention [34].

Other reproductive disorders

Preterm birth is known as the birth before 37 weeks of pregnancy. Extremely preterm infants frequently experience complications affecting various organ systems, including the heart, brain, eyes, digestive tract, kidneys, respiratory system, and metabolism. Although numerous factors can lead to premature birth, uterine infection and inflammation are regarded as the most probable contributors [34, 212]. As well, OS is a crucial factor leading to premature infant disorders, including bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, and some other diseases [213]. However, an increased redox environment has an essential role in preterm births; more research is required to understand the relationship between OS and preterm births [214]. As well, OS may have a correlation with unexplained infertility [215]. Unexplained infertility is recognized when infertility tests reveal no obvious cause for a couple's fertility problems. OS has been identified as a key factor in the underlying causes of unexplained infertility. It may contribute to issues such as reduced endometrial receptivity, diminished oocyte quality, early ovarian failure, mild endometriosis, tubal disorders, pelvic adhesions, and disruptions in immune and hormonal function [216]. Another factor causing unexplained infertility is an insufficient level of folate or polymorphism in genes involved in folate metabolism, leading to an increasing level of homocysteine. The high amount of homocysteine may induce apoptosis and affect oocyte quality and endometrial progression [217].

Altogether, the results showed that an imbalance status between oxidant and antioxidant elements can raise OS affecting the female reproductive system and inducing some complications, including recurrent pregnancy loss, IUGR, premature birth, and ectopic pregnancy. Some other factors, such as age, lifestyle changes, or environmental agents can aggravate OS conditions and adversely impact female fertility potential [40].

Impact of HPV infection on assisted reproduction

Assisted reproductive technology (ART) encompasses medical interventions designed to aid conception by handling eggs and sperm externally. This includes methods such as IUI, in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) [218]. HPV infection is suggested to have a negative impact on pregnancy outcomes, potentially reducing ART success rates and increasing the risk of miscarriage (Fig. 3) [27]. HPV is thought to disrupt critical processes in ART, including the acrosome reaction, the interaction between sperm and the oocyte, and their subsequent fusion [18]. Several investigations show the negative impact of HPV on assisted reproductive outcomes.

Depuydt et al. conducted an study to examine the influence of cervical HPV infection on pregnancy outcomes following IUI [219]. Their findings revealed that women who tested positive for HPV had a significantly lower chance of pregnancy after IUI, with success rates of 1.87% compared to 11.36% in HPV-negative women. The presence of HPV was linked to poorer outcomes following IUI [219]. Research by Garolla et al. revealed a significantly higher miscarriage rate among couples with HPV infection (62.5% compared to 16.7%). The presence of HPV in sperm was associated with a decline in both natural and assisted cumulative pregnancy rates, as well as an increased risk of miscarriage [175]. Additionally, it has been observed that HPV-positive patients undergoing IVF treatment tend to have lower pregnancy rates compared to their HPV-negative counterparts [158, 220]. According to a systematic review and meta-analysis investigating the impact of HPV infection on sperm parameters and IVF outcomes, findings revealed a significant association between HPV infection and reduced pregnancy rates. Additionally, there was an even stronger correlation between HPV infection and increased miscarriage rates [114]. Therefore, a significant statistical correlation exists between pregnancy loss rates and positive HPV DNA test results in the male partners of infertile couples. As a result, in ART procedures, HPV infection in male partners appears to be a predictor of unsuccessful pregnancy outcomes [221]. Similarly, a recent study found that sperm samples infected with HPV had a notably higher DFI compared to those without HPV (29.8% vs. 20.9%) [104]. Furthermore, no clinical pregnancies were observed when HPV virions were seen in sperm. Sperm DFI was identified as a strong predictor of clinical pregnancy outcomes in women undergoing IUI with these sperm. When DFI exceeded 26%, the likelihood of clinical pregnancies decreased, suggesting that IVF may be a more appropriate option [104]. Nevertheless, some studies suggest that there is no connection between HPV infection and ART outcomes. For example, research by Zullo et al. found that HPV infection does not seem to negatively impact ART success, as measured by live birth rates, though it may slightly affect embryonic development kinetics [222]. While there were some kinetic differences in embryonic development (e.g., quicker development in the early stages and slower development at the early blastocyst stage in HPV-positive women), these differences did not affect embryo morphology or final outcomes [222].

However, there are several ways to counteract the HPV effect on ART outcomes. One approach involves HPV vaccination, which can enhance sperm motility in HPV-positive male partners and significantly boost pregnancy rates [223]. Another approach is the use of

sperm-washing techniques, which may enhance pregnancy rates in ART procedures [224, 225]. For instance, the enzyme hyaluronidase, approved for use in IVF laboratories, can disrupt the bond between HPV and syndecan-like glycosaminoglycan components on sperm surfaces [87].

OS induced by other oncogenic viral infections and its association with infertility

In addition to the HPV, other oncogenic viruses, including Epstein–Barr virus (EBV), hepatitis B virus (HBV), and hepatitis C virus (HCV), have been shown to induce OS, contributing to their pathogenesis and cancer development [226, 227]. EBV is a member of the *γ-herpesvirus* subfamily. Research indicates that EBV infection triggers OS, which contributes to viral reactivation, the transformation of B cells, and possibly the onset of EBV-associated malignancies [228–230]. The EBV nuclear antigen 1 (EBNA1) promotes the buildup of ROS by enhancing the expression of NOX2 [231]. Evidence suggests that EBV can present in both the female and male genital tracts [232–234]. As well, multiple studies have documented the detection of EBV in semen, with varying prevalence rates [235, 236]. According to the study by Huerta et al. EBV appears to influence sperm quality [237]. Their findings indicate that all sperm samples exhibiting impaired fertility parameters contained EBNA and showed downregulation of endothelin-1 and vimentin. The researchers also suggested that EBV may induce alterations at the miRNA level, potentially contributing to reduced sperm quality [237]. However, the precise mechanism and the connection between EBV and infertility, as well as the role of EBV-induced OS in infertility, remain unclear. Further research is required to clarify these relationships.

HBV, a member of the *Hepadnaviridae* family, has the ability to induce OS, which plays a key role in the progression of chronic infection, liver inflammation, and cancer. Those suffering from chronic hepatitis B show heightened sulfhydryl concentrations, enhanced lipid peroxidation, and DNA damage caused by oxidative stress in liver tissues [227]. During liver infections, HBV triggers OS, primarily due to the activity of the HBx protein [238]. HBx contributes to the generation of ROS through two separate pathways. One pathway operates independently of p53, likely by disrupting mitochondrial function. The other pathway is p53-dependent, where HBx triggers p53 activation, which in turn escalates ROS production through a self-reinforcing cycle between ROS and p53 [238]. Investigations have found HBV in the semen samples [236, 239]. Similar to observations in HPV cases, HBV has also been reported to affect semen parameters [240]. Semen samples that tested positive for HBV showed a significant reduction in sperm viability and progressive motility, along with a notable decrease in sperm DFI. Additionally, the number of HBV DNA copies in semen demonstrated a strong positive correlation with sperm DFI [240]. However, conflicting results have been reported, indicating no significant differences in semen volume, sperm concentration, or motility between seminal plasma HBV DNA-positive and HBV DNA-negative groups [241]. It has been suggested that when human sperm cells come into contact with hepatitis B surface protein (HBs), it speeds up the initial phases of apoptosis and reduces their ability to fertilize an egg in a laboratory setting [242]. HBs can initiate the Bax/Bcl2 pathway, leading to apoptosis through AIF/Endo G activation. This process causes damage to sperm DNA, harming the sperm and ultimately reducing its ability to fertilize an egg [243]. The HBV genome can integrate into sperm chromosomes and induce mutagenic effects, leading to changes in their structure [244]. The integration of HBV DNA into sperm chromosomes could contribute to greater instability in these chromosomes. HBV infection could lead to significant hereditary consequences by modifying genetic material and causing chromosomal abnormalities, potentially enabling the transmission of HBV to the next generation through the germ line [244, 245]. Much like HPV, OS plays a key role in the development of sperm damage caused by HBV [246]. The presence of HBs can trigger harmful processes in sperm cells, including the production of ROS, lipid peroxidation, a decrease in antioxidant levels, activation of caspases, and DNA fragmentation. These events collectively lead to higher rates of sperm cell apoptosis, compromised membrane integrity, and impaired sperm function [246]. Moreover, in infertile men with HBV infection, semen quality indicators such as volume, pH, sperm density, forward motility, activation rate, survival rate, and normal sperm morphology were significantly reduced. In contrast, levels of IL-17, IL-18, and MDA were significantly elevated in those with HBV infection [247]. Similar to HPV, HBV can reduce the success rates of ART. Couples with a male partner infected with HBV have a higher risk of low fertilization rates following IVF [248]. Sperm washing techniques can significantly lower the chances of transmitting the virus vertically and prevent HBV from reaching the egg during ART [249].

HCV, a member of the *Flaviviridae* family, is another oncogenic virus that can cause OS [250]. HCV induces oxidative stress through the activation of multiple pathways and enzymes that generate ROS. These include mitochondrial dysfunction driven by calcium ions ($Ca2^{+}$), activation of NOX1, 2, and 4, as well as cytochrome P450 2E1 (CYP2E1) and ER oxidoreductin 1α (Ero1α) [227]. As well, HCV interferes with the activation of Nrf2/ARE-dependent genes, leading to a rise in ROS levels [251].

HCV proteins play a key role in regulating OS. The core, NS5 A, and NS3 proteins contribute to increased calcium absorption by mitochondria [252]. They also induce the oxidation of mitochondrial glutathione, which boosts the production of ROS within mitochondria. This, in turn, triggers the movement of NF-κB and STAT-3 transcription factors into the nucleus, further promoting OS [252]. Similar to HBV, multiple studies have shown that HCV can also be found in semen [253, 254]. Like HBV and HPV, HCV can impact on the sperm quality. HCV infection results in lower sperm concentration, reduced motility, diminished viability, and a decline in the proportion of normally shaped sperm [255]. The study found an inverse relationship between the length of HCV infection and both semen volume and sperm motility. Additionally, higher HCV RNA viral load was associated with a decrease in sperm count and motility [256]. Moreover, studies have indicated that HCV can lower levels of circulating testosterone and inhibin B, which is a key marker of healthy spermatogenesis [257].

Altogether, in addition to HPV, other oncogenic viruses such as HBV and HCV can be detected in semen and may affect sperm quality. However, due to conflicting reports showing no correlation, more in-depth studies are needed to strengthen these associations and uncover the underlying mechanisms in the future.

Conclusion

In conclusion, the evidence suggests that HPV can play a significant role in causing infertility in both men and women. HPV DNA has been detected in all components of semen, including sperm cells, contributing to poor sperm quality. Infection in semen negatively affects sperm parameters, including increased DNA fragmentation, elevated pH levels, abnormal morphology, decreased semen volume, reduced motility and viability, and lower total sperm count and concentration. These factors collectively impair the sperm's ability to fertilize the oocyte. Notably, HPV localizes at the equatorial region of the sperm head, a critical site for fertilization. This raises concerns about the potential transmission of HPV from infected sperm to the oocyte or placenta. Consequently, infected sperm can penetrate the oocyte, introducing the virus and possibly triggering the activation and transcription of viral genes within the oocyte. In women, HPV infection disrupts the vaginal microbiome, causing microbial dysbiosis and an imbalance in vaginal flora. Additionally, HPV induces apoptosis in trophoblastic cells and impairs their adhesion to endometrial cells, increasing the risk of miscarriage. HPV infection has also been linked to reduced success rates in ART and a higher likelihood of adverse pregnancy outcomes. It is believed that HPV can interfere with key ART processes, including the acrosome reaction, sperm–oocyte interaction, and their eventual fusion. However, several strategies can help counteract HPV's impact on ART outcomes. HPV vaccination is one preventive measure, while sperm-washing techniques may also enhance pregnancy rates in ART procedures. According to the studies, OS is proposed as a potential mechanism underlying HPV-induced reproductive dysfunction, negatively impacting both male and female fertility. By inducing OS, triggering inflammation, and recruiting more immune cells, HPV can contribute to infertility. HPV-induced OS can harm sperm quality and damage the female reproductive system, ultimately leading to fertility issues. Additionally, HPV-related immune responses promote the production of ASAs, which cause sperm clumping, reduce motility in cervical mucus, activate the complement system (damaging sperm in the female reproductive tract), and disrupt sperm–egg interactions. Furthermore, HPV may impact ovarian reserve by inducing chronic inflammation, which can impair granulosa cell function and decrease serum AMH levels. By inducing inflammation and recruiting immune cells, HPV also increases ROS production, which disrupts mitochondrial function and further deteriorates sperm quality.

Looking ahead, HPV vaccination could not only prevent HPV-related cancers but also reduce the risk of infertility linked to the virus. It is yet to be determined whether HPV detection and genotyping should be integrated into the diagnostic process for couples undergoing ART procedures. Given the limited number of studies and inconsistent findings, further research is necessary. Moreover, the primary effects of HPV on the reproductive system vary by HPV type, with HR types like HPV-16 and HPV-18 being most commonly involved, suggesting that vaccination could effectively prevent these reproductive issues. However, it is important to acknowledge several limitations in the current understanding of HPV-related infertility. The exact causal mechanisms through which HPV contributes to infertility are still not fully understood, and further research is needed to clarify these relationships. Variations in study methodologies, HPV types, and populations studied could limit the generalizability of the findings, highlighting the need for more comprehensive and controlled studies to confirm these observations.

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Using of language models
In this study, we utilized language models primarily for paraphrasing and restructuring text to avoid plagiarism, ensuring the integrity of the research process.

Author contributions
O.SA and A.L: Investigating, review and editing, writing original draft. S.ED and A.VF and M.B and: review and editing and writing original draft. B.M: review and editing, visualization. N.A, M.T, and M.K: review and editing. A.AP: review and editing. SM.J and L.S: supervision, review and editing.

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