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Role of Human Papillomavirus Vaccination for Prevention of Male Infertility

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The human papillomavirus (HPV) is a common sexually transmitted infection that can cause various diseases, including genital warts and malignant diseases, such as cervical, head and neck, and anal cancer. Emerging evidence suggests that a HPV infection can also adversely affect male fertility. The HPV has been detected in the semen and testicular tissues of infected individuals, indicating that the virus can directly impact the male reproductive system. Indeed, many studies showed that the HPV infection could cause sperm DNA damage, decreased sperm motility, and reduced sperm concentration, contributing to male infertility. The HPV vaccination is currently only being administered to females in Korea. On the other hand, the vaccine could help mitigate these negative impacts on male fertility by protecting males against HPV infection. This paper reviews the effects of the HPV on male fertility and the potential benefits of HPV vaccination in protecting male fertility.

Keywords: Human papillomavirus; Male infertility; Vaccination; Semen analysis

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INTRODUCTION

According to the data from Statistics Korea, the total fertility rate in Korea was 0.78 in 2022, with the number of births totaling 249,000. This indicates a decrease of 11,500 births, or 4.4%, compared to the previous year, marking it the lowest fertility rate ever recorded among OECD countries. In contrast, Korea's aging rate is one of the fastest, with the elderly population aged 65 and above accounting for 17.5% of the population, totaling 9.08 million people. This figure is expected to increase, surpassing 20.6% by 2025 [1,2].

The average maternal age at childbirth in Korea was 33.01 years in 2022, showing a persistent increasing trend of more than 0.2 years compared to the previous year. Despite the lack of exact statistical data on the average paternal age, given the low rate of extramarital births in Korea (2.2%) and the continuous increase in the average age of first-time marriage (33.72 years) in 2022, it can be inferred that pregnancy and childbirth are occurring at advanced ages [3]. Numerous studies have shown that delayed pregnancy and childbirth negatively impact fertility for both male and female [4,5].

Indeed, referring to the statistical data on infertility submitted by the National Health Insurance Service during the 2020 national audit, it has been reported that 1,097,000 people were treated for infertility over the 5 years from 2015 to 2019, and the health insurance treatment expense was approximately 371.4 billion won. During this period, the number of male patients receiving treatment for infertility increased by approximately 46.8%, from 54,000 to 79,000 [6].

Hence, there is an urgent need to focus on preserving fertility to address the decline in birth rate resulting from late marriage and pregnancy and the rapid societal changes associated with low birth rates.

According to the World Health Organization (WHO), infertility is defined as the inability of a couple to spontaneously

conceive despite regular, continuous sexual intercourse without using contraception for 1 year [7]. Approximately 80% of healthy couples who try to conceive become pregnant within the first 6 months, and approximately 85% within 12 months [8]. Although there are no precise statistics on the prevalence of infertility, it affects approximately 8 to 12% of couples of reproductive age [9]. Moreover, it is estimated that more than 186 million people worldwide suffer from infertility [10].

Male factors influence 50% of cases of infertility, and approximately 20 to 30% of infertility cases are caused only by male factors. These risk factors for male infertility include sexual dysfunction, varicose veins, congenital dysplasia of the genital tract, endocrine disorders, immunogenic factors, and sexually transmitted infections [11]. Chronic viral infections, such as the hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), have been identified as risk factors for infertility affecting sperm quality, such as sperm count, motility, and morphology [12-14]. Recently, it was reported that the HPV may also be an important infectious cause of male infertility.

MAIN BODY

1. Human Papillomavirus

The human papillomavirus (HPV) belongs to papillomavirdiae and is a non-enveloped double-stranded DNA virus. More than 200 species exist, with approximately 40 species known to cause diseases around the genitals and anus [15]. The HPV is one of the most common sexually transmitted infections worldwide, with an estimated 6.2 million new cases yearly [16]. The most common transmission routes of HPV are genital-to-genital contact and hand-to-genital contact. Although rare, transmission through breastfeeding and vertical transmission through the placenta in pregnant female have also been reported [17-19].

In addition to causing the onset of a benign disease called warts, the HPV is a major risk factor for cancer development. Since Dr. Zur Hausen first published the hypothesis linking HPV infection to the development of cervical cancer, HPV has been revealed as the main etiology of malignancies, such as oropharyngeal, anal, vulvar, and penile cancer [20].

The main route of HPV penetration into the male reproductive system is through the penile preputial mucosa. The practice of circumcision has been associated with a decrease in male HPV prevalence and can reduce the risk of HPV virus infections while improving the virus clearance rates. The HPV in infected male can be located in the perianal mucosa, glans penis, foreskin of the penis, urethra and seminiferous tubules, testes, and epididymis [21].

2. Human Papillomavirus and Infertility

Referring to a meta-analysis study on the HPV prevalence in 16 countries, the rate of HPV semen infection in male in the general population was 11.4%. The HPV semen infection rate of male visiting infertility clinics was 20.4%, suggesting that HPV-positive semen is highly correlated with infertility [22]. Studies examining the effect of HPV semen infection on pregnancy success in infertile couples show that HPV infection in semen is closely related to the pregnancy success rate. In a study examining the success rates of intrauterine insemination and intracytoplasmic sperm injection in 226 infertile couples, the success rate was 38% when HPV-uninfected semen was used. In contrast, the rate dropped significantly to 14% for HPV-infected semen [23]. Depuydt et al. [24] reported the results of successful insemination using HPV-infected and non-infected semen using the data from 3 Belgian sperm banks in 2018. This study found that HPV semen infection in male had a significant impact on the success rate of natural pregnancy and assisted reproductive technology, as no pregnancy occurred when HPV-positive semen was used. Based on this study, they suggested that HPV testing should be performed regularly for sperm donation [24].

Male HPV infection induces infertility through various mechanisms. First, the prevalence of HPV infections in the testicles and epididymis is very closely related to the occurrence of inflammatory diseases, such as nontuberculous epididymitis. Repeated occurrences of these inflammatory conditions appear to cause infertility by affecting sperm production and transport [25]. A HPV infection of sperm cells appeared to reduce the ability to penetrate the oocyte because of the HPV located on the sperm head [26]. Furthermore, HPV-infected sperm act as a vehicle for virus transmission, as the HPV can be transmitted from infected sperm to the oocyte and placenta of a pregnancy. In a HPV infection of sperm, unlike in the case of epithelial cell infection, the virus does not penetrate the sperm cells but binds to the equatorial segment located in the sperm head. The equatorial segment of the sperm head is the place where mammalian sperm starts to bind to the egg, and the sperm-egg interaction and fusion control

process occur. The HPV translocates into the oocyte through interactions with the membrane protein tetraspanin, CD151, and integrin a6, and transfers the HPV gene. Using the division process of the host zygote cell, it replicates its gene, transcribes and produces necessary viral proteins, and repeats the process of self-replication [27]. As a result of such transmission, normal embryonic development and implantation are disrupted, increasing the likelihood of spontaneous abortion and premature birth [28].

The HPV decreases the quality of infected sperm and increases DNA fragmentation. Numerous studies have reported that sperm concentration and total sperm counts decrease significantly [29,30]. HPV sperm infection increased the rate of asthenospermia significantly, a condition in which sperm mobility is reduced. Sperm mobility is an important factor of fertilization because the sperm needs to travel a considerable distance to penetrate the oocytes. HPV infection increases the occurrence of DNA fragmentation [23,31,32]. This decrease in sperm quality and DNA fragmentation appears more significant in high-risk HPV types. The effect appears to differ depending on the HPV type [33]. While further research will be needed to understand the specific effects of particular HPV types on sperm, a HPV infection deteriorates sperm quality, leading to increased infertility rates.

The anti-sperm antibody (ASA) is a major risk factor for infertility. ASA is detected in a significant proportion of infertile couples (16.5% male, 21.5% female) [34]. Infertile couples in whom ASA is detected in serum and genital secretions have a significantly reduced pregnancy success rate [35]. Several studies have shown that a HPV infection in semen significantly increases the positive rate of ASA [36,37]. HPV acts as a stimulating antigen for ASA production, and the resultant ASA causes infertility by interfering with the migration and fertilization process of HPV-infected sperm and normal sperm [38,39].

3. Efficacy of Human Papillomavirus Vaccine on Infertility

In 2016, a 9-valent vaccine (Gardasil 9) was developed for 7 high-risk HPV types (16, 18, 31, 33, 45, 52, and 58) and 2 low-risk types (6, 11). The vaccine effectively showed almost 100% seroconversion against the 9 species, and the immunity was maintained for more than 6 years, proving the long-term effect of the vaccine [40]. A HPV vaccination program has dramatically reduced the incidence of HPV-related malignancies, such as cervical cancer [41]. As can be inferred from the effect of HPV on male infertility, studies are reporting the positive effect HPV vaccination can have on male infertility. Garolla et al. [42] published a randomized controlled study of the effect of the HPV vaccine on the success rate of pregnancy in infertile couples. When 151 infertile couples were divided into 2 groups of 79 vaccinated subjects and 72 non-vaccinated subjects, the HPV-vaccinated group had a significantly higher pregnancy success rate than the non-vaccinated group (15% vs. 38.9%) and a significantly lower miscarriage rate (63.6% vs. 3.3%). In addition, sperm motility of the semen of the HPV-vaccinated group was significantly higher than that of the non-vaccinated group. The detection rate of HPV DNA in sperm was reduced eightfold and ASA by more than twofold in the vaccination group, suggesting a reparative effect by the HPV vaccine in removing the HPV from semen [42]. Another study has also confirmed the positive effect of HPV vaccines. When 379 HPV semen-infected male were vaccinated with the HPV, the HPV was eradicated from the semen in 86% of male after 6 months, and the anti-sperm antibodies that had formed in approximately 38.6% disappeared [39]. These findings show that the HPV vaccine can restore fertility by improving sperm quality and removing anti-sperm antibodies. This suggests that the HPV vaccine is not limited to preventive purposes but can be used for therapeutic purposes, even in infertility patients who are already infected.

CONCLUSIONS

HPV infection is a major risk factor for infertility. HPV infections in male decrease the pregnancy success rate significantly and increase the possibility of miscarriage and premature birth by various mechanisms. HPV vaccinations of male remove the risk factors of infertility by keeping males from being infected, and they may have a therapeutic effect on infertility who are already infected with HPV. Domestic HPV vaccination projects are underway only for female, with the primary goal of preventing malignancy. On the other hand, given the impact of HPV infections and the role of its vaccination on male infertility, it will be necessary to expand the scope of vaccination targets to include male.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article

was reported.

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