Association of human papillomavirus types 6,11,16,18 infections and antisperm antibody titer with infertile males in Diyala province

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Chapter one
Introduction

1. Introduction

Human papillomavirus (HPV) is a small double-stranded circular DNA virus with a genome of approximately 8000 base pairs, belong to *papillomaviridae* family of which over 170 types are known, more than 40 types are transmitted through sexual contact (Burd and Dean, 2016). The HPV genome is composed of six early (E1, E2, E4, E5, E6, and E7) open-reading frames (ORF), two late (L1 and L2) ORFs, and a non-coding long control region (LCR) (Zheng and Baker, 2006).

The viral life cycle strictly follows the differentiation of the host keratinocyte, and it is thought that the virion infects epithelial tissues through micro-abrasions, whereby the virion associates with putative receptors such as alpha integrins and laminins, leading to entry into basal epithelial cells through clathrin-mediated endocytosis and/or caveolin-mediated endocytosis depending on the type of HPV (Scheurer *et al* ., 2005; Doorbar *et al*., 2012). Viral genome integration into host DNA genome increases E6 and E7 expression. These two viral oncogenes, E6/E7 proteins inactivate two tumor suppressor proteins, p53 and pRb to promote cellular proliferation and chance malignancy. The degree to which E6 and E7 are expressed is correlated with the type of cervical lesion that can ultimately develop (Ganguly and Parihar, 2009). The phylogeny of the various strains of HPV generally have diversified along with the human population and evolved along five major branches that reflect the ethnicity of human hosts (Chen *et al*., 2011).

Human papillomaviruses are transmitted vertically and horizontally; infants, children, and adults can acquire both high-risk and low-risk infections through various non-sexual modes of transmission especially at the time of birth and by close contact even though HPV is mainly transmitted sexually (Sabeena *et al*., 2017). Most HPV infections are clinically asymptomatic and resolve spontaneously. However, in some people, the infection persists and results in warts or precancerous lesions, which consequently increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth, or throat (Heidegger *et al*., 2015). Nearly all cervical cancers are due to HPV with two types, HPV16 and HPV18, accounting for 70% of cases, beside that between 60% and 90% of the other cancers are also linked to HPV. HPV6 and HPV11 are common causes of genital warts and laryngeal papillomatosis (Ljubojevic

and Skerlev, 2014; Gao and Smith, 2016). Risk factors for persistent HPV infections include early age of first sexual intercourse, multiple partners, smoking, and poor immune function (Doorbar, 2016). Individuals with inherited immunodeficiencies, autoimmune disorders, organ or bone marrow transplantation, or infection with human immunodeficiency virus are at increased risk of infection with both low-risk and high-risk HPV types (Burd and Dean, 2016). Worldwide, HPV is estimated to infect about 12% of women at any given time. HPV infection is the most frequently sexually transmitted disease in the world. Estimates of HPV prevalence vary from 14% to more than 90%， depending on the HPV strains that were tested for and the target population (Castellsague *et al*., 2017).

The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART Terminology defines infertility as a disease of the reproductive system characterized by failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild *et al*., 2009). Estimates suggest that worldwide between 3-7% of all heterosexual couples or women have an unresolved problem of infertility. 20-30% of infertility cases are due to male infertility, 20-35% are due to female infertility, and 25-40% are due to combined problems in both partners, and 10-20% are unknown cause (Szkodziak *et al*., 2016). Primary infertility is infertility in a couple who have never had a child and secondary infertility is failure to conceive following a previous pregnancy. Infertility may be caused by infection in the man or woman. Male infertility is most common due to deficiencies in the semen, and semen quality is used as a surrogate measure of male fecundity (Cooper *et al*., 2010).

Sexually transmitted diseases are caused by several pathogens, including bacteria, viruses and protozoa, and can induce male infertility through multiple pathophysiological mechanisms. Among these is the HPV which has been detected in semen from symptomatic and asymptomatic men with testicular, accessory gland and urethral infections associated with poor sperm quality and decreased sperm concentration and motility (Gimenes *et al*., 2014). Several studies had demonstrated that HPV sperm infection can be long lasting frequently associated with ASAs that may further reduce male fertility (Garolla *et al*., 2013). Therefore, it was recommended that HPV

detection and genotyping could be of great value in infertility diagnosis at least in idiopathic infertility cases (Souho *et al*., 2015).

A systematic review of the literature included a total of 40 publications on HPV DNA detection and risk factors in men, the HPV prevalence was 1.3%-72.9% in studies in which multiple anatomic sites or specimens were evaluated; 56% of these studies reported > or =20% HPV prevalence, which varied on the basis of sampling, processing methods, and the anatomic site(s) or specimen(s) sampled (Dunne *et al*., 2006). Likewise, a systematic review and clinical management proposal at the Centers for Reproductive and Health care for treating infertile male patients with HPV infection, found that the prevalence of HPV sperm infection ranges between 2 and 31% in men from general population and between 10 and 35.7% in men affected by unexplained infertility. The presence of HPV in semen is associated with an impairment of sperm motility and the presence of anti-sperm antibodies (Foresta et al., 2015). In another meta-analyses study, HPV DNA prevalence in 4029 semen samples varied from 0 to 100%. The pooled prevalence in infertile populations was 16% and that HPV-16 was the most common type overall (Laprise et al., 2014). Moreover, HPV DNA was detected in 70% of male partners of HPV-infected women: 32% in the high-risk HPV group, 14% in the low-risk HPV group, and 24% in both. HPV detection per anatomic site includes glans, prepuce, distal urethra, scrotum, and the anus (Nicolau *et al*., 2005).

A more worthy finding comes from Garolla and co-workers who reported that a reduction in natural and assisted cumulative pregnancy rate and an increase in miscarriage rate are related to the presence of HPV at sperm level, although they were unable to explain the exact mechanism (Garolla *et al*., 2016). Of note, it was documented a very high prevalence of infection in the semen of patients with risk factors for HPV with different effects on sperm motility (Foresta *et a*l., 2010).

Aims of the study:

For the best of our knowledge this is the first study in Iraq in this field which was designed to achieve the following goals:

Firstly: Molecular detection of HPVs in seminal fluids of patients with primary and secondary infertility versus normal healthy subjects specially the HPV-16, 18, 11 and HPV-6.

Secondly: Exploration of the effect of HPVs on the quality of semen, regarding the total sperm count, sperm motility, and sperm morphology with reference to other demographic and health risk factors.

Thirdly: Detection of anti-sperm antibody titers and figure out its effect on parameters of sperm quality among infertile patients.