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# Human papillomavirus as risk factor of infertility in male and female

**Noor AL-Huda Mohammad Ali Khalil**

University of Thi-Qar, College of Science, Department of Pathological Analysis, Nasiriyah– Iraq

**Ahmed Hasan Mohammed**

University of Thi-Qar, College of Science, Department of Pathological Analysis, Nasiriyah– Iraq

\*Corresponding author email: [ahmedhasan5@sci.utq.edu.iq](mailto:ahmedhasan5@sci.utq.edu.iq)

**Abstract**--Background: infertility is the inability to conceive after one year of marriage without using any contraceptives for both spouses. Its major public health problem worldwide and happens for many reasons including viral infections especially Human papillomavirus (HPV) which is sexually transmitted virus and have negative impact on male and female fertility. Aim of this study was to investigate HPV infection in infertile male and female. Subjects and methods, this case control study included 90 subjects, 50 patients with infertility (25 males and 25 females) selected from private laboratories in Al-Nasiriya city with age range 16-46 years old and they diagnosed based on the clinical and laboratory examinations under the supervision of specialist physician. Control group include 40 adults (20 males and 20 females) have children and looking healthy. Results showed mean age of patients and control in this study 30.62 with higher infertility rate 43-46 years old. The incidence of anti-HPV was 16%, presented as anti-HPV IgM (24%) and IgG (32%) higher in female more than in male which showed IgM (8%) and IgG (4%). Conclusion of the present study indicate that HPV infection have high risk to cause infertility in male and female by affecting the quality of sperm and reduced fertilization.

**Keywords**--ELISA, human papillomavirus, infertility.

## Introduction

Infertility is defined by the failure to achieved a natural pregnancy after 12 months or more of regular unprotected sexual intercourse (1). It affects about 10% of the world's population, according to the WHO, and in young people is considered the fifth most significant worldwide problem, and approximately 13%

of ever-married women of reproductive age were childless (2). Infertility has physiological as well as social consequences. It is caused by ovulatory problems in women, poor sperm quality in males and an idiopathic cause in men and it is influenced by sexually transmitted diseases (STDs), genetics, diabetes, pituitary hormones, and pollutants (3). There are two types of infertility; primary infertility and secondary infertility, which are determined by the existence or absence of previous successful pregnancies. Couples with primary infertility have been unable to become pregnant after at least one year of sexual intercourse without the use of contraceptive techniques; on the other hand, couples with secondary infertility have been able to become pregnant at least once but not again (4).

For many years, researchers have been looking for a correlation between microbial infection and infertility. Some Parasite related with infertility such as *Trichomonas vaginalis* and *Toxoplasma gondii*. Whereas many bacteria that related to cause infertility including *Helicobacter pylori* and *Chlamydia Trachomatis*. In other side viruses also effect on human and cause infertility, for example Human papilloma virus (HPV) (5). Human papilloma virus (HPV) is a sexually transmitted infection frequently found in men and women worldwide of reproductive age, HPV linked with malignancies and epithelial lesions as well as many detrimental impacts on the ability to reproductive function. Most genital HPV infections are probably going to be induced by the sexual transmission from genitalia to genitalia (6). Male fertility is impacted by HPV infection in several ways, early research has shown that HPV is capable of infecting sperm cells (7), and in female HPV infection has also been linked to changes in tubal variables. It has been identified as a cause of infertility, which can lead to cervical diseases. (8). The present study aimed to find a correlation between HPV infection and infertility through investigate serological diagnosis of HPV in infertile patients and compare the results with control group.

### **Subject and Methods**

A total number of 50 patients with infertility (25 males and 25 females) were selected from private laboratories in Al-Nasiriya city during November 2021 to February 2022. Inclusion criteria of those patients include male and female have infertility with age range 16-46 years old. The diagnosis was based on the clinical and laboratory examinations under the supervision of specialist physician. Control group include 40 adults (20 males and 20 females) have children and looking healthy. Both patients and control group received a set of questions. The present study based on Enzyme-linked immune sorbent assay (ELISA) in the detect of both IgM and IgG antibody against HPV.

### **Sample collection and ethical approval**

Five ml of venous blood was taken from patients and the control group. Blood was collected in coagulate gel tubes and left to clot at room temperature, then centrifuged at 3000 rpm for 10 minutes to separate the serum, the serum sample was separated in 2.0 ml Eppendorf tubes for serological tests. Serum samples were frozen at (-20C) until delivered to the working laboratory at Pathological Analysis Department at College of Science, Thi-Qar University. This study subjected to the qualification of ethical consideration and according to the form

prepared for this purpose by the Iraqi Ministry of Health. Also, the research got to agreement by the committee of ethical standards at the College of Science, Thi-Qar, one of the Colleges belonging to the Ministry of Higher Education and Scientific Research Iraq. In addition, informed consent was obtained from all patients and healthy persons before taking samples.

### Statistical analysis

The statistical analysis of this case control study performed with the statistical package for social sciences (SPSS) 20.0. Numerical data were tested for normality testing using Shapiro-Wilk test found that the data were abnormally distributed. The data described as median and 5-95 confidence interval and Mann-Whitney U test used for comparison between two groups. Categorical data were described as count and percentage. Chi-square test used to estimate the association between variables. The lower level of accepted statistically significant difference is bellow or equal to 0.05. Relative risk used to estimate the potential risk of pathogen associated with incidence of disease.

### Results

#### Age and sex groups

The current study included 90 persons divided into 50 patients have infertility and 40 healthy reproductive control. The age range of infertile patients was 16-46 years old, with age mean 30.62 years old. The results showed that 95% of infertility occur within age 43-46 years old while only 5% of infertility lay within age 16-20 years old. Regarding control group, those persons were selected to be within the age group of patients to exclude the effect of age to get viral infection. However, the mean of age for control group was 28.30 years old and statistically there was no significant differences between patients and control regarding the age ( $P = 0.774$ ), (Table 4-1).

Table 4-1  
Distribution of patient and control groups according to the age

Parameter	Statistical Function	Study groups	
		Patient	Control
Age (years)	Mean	30.62	28.30
	Standard Deviation	6.87	4.54
	Median	30.00	28.00
	Percentile 05	20.00	19.50
	Percentile 95	43.00	35.00
P value		0.774 <sup>NS</sup>	

NS: None significant differences

Infertile patients divided into male and female and the results showed presence of infertility in (50%) of female and (50%) of male in the present study. (Table 4 – 2).

Table 4-2  
Correlation between sex and age of patient and control groups

Parameter	Statistical function	Sex			
		Female		Male	
		Patient	Control	Patient	Control
Age (years)	Mean	27.88	28.15	33.36	28.45
	Standard Deviation	6.41	5.59	6.30	3.30
	Median	28.00	28.50	32.00	28.00
	Percentile	50%		50%	
P value		0.894 <sup>NS</sup>		0.022*	

NS: None significant differences

\*: significant differences

### Detection of anti-HPV IgM and IgG Antibodies

Detection of anti-HPV IgM antibody appear to be positive in 16.00% of patients and negative in 84.00% while, anti-HPV IgM in control groups was presence relatively lower than in patients. The results showed no significance differences between patients and control (P=0.185). On the other hand, the results of detection anti-HPV IgG antibody in patients was positive in 18.00% and negative in 82.00%, while in control group the results were negative in 92.50% and 85.00% for IgM and IgG respectively. the results also showed no significance differences (P=0.465) with high relative risk in an anti-HPV IgM (RR=1.37 (0.9-2.8), (Table 4-3). Presence of anti-HPV IgM and IgG antibodies appeared the infection percentage was in female higher (24.00%) for IgM and (32.00%) for IgG than in male. Although the result showed no significance differences between infertile male and female but the relative risk present higher in female in an anti-HPV IgM (RR=1.7 (1.1-2.7) and greater in male (RR=1.8 (1.4-2.4), (table 4-4 and table 4-5).

Table 4-3  
Detection Anti-HPV IgM and IgG antibodies in patients and control groups

		Study groups		P value	Relative risk
		Patient	Control		
HPV IgM	Positive	8	3	0.185 <sup>NS</sup>	1.37 (0.9-2.8)
		16.00%	7.50%		
	Negative	42	37		
		84.00%	92.50%		
HPV IgG	Positive	9	6	0.465 <sup>NS</sup>	1.1 (0.7-1.7)
		18.00%	15.00%		
	Negative	41	34		
		82.00%	85.00%		

NS: none significant differences

Table 4-4  
Comparison between male and female of infertile patients regarding detection of Anti-HPV IgM antibody

		Female		Male	
		Patient	Control	Patient	Control
HPV IgM	Positive	6 24.00%	1 5.00%	2 8.00%	2 10.00%
	Negative	19 76.00%	19 95.00%	23 92.00%	18 90.00%
p value		0.089 <sup>NS</sup>		0.606 <sup>NS</sup>	
relative risk		1.7 (1.1-2.7)		0.89 (0.32-2.5)	

NS: none significant differences

Table 4-5  
Comparison between male and female of infertile patients regarding detection of Anti-HPV IgG antibody

		Female		Male	
		Patient	Control	Patient	Control
HPV IgG	Positive	8 32.00%	6 30.00%	1 4.00%	0 0.00%
	Negative	17 68.00%	14 70.00%	24 96.00%	20 100.00%
p value		0.573 <sup>NS</sup>		0.556 <sup>NS</sup>	
relative risk		1.04 (0.6-1.8)		1.8 (1.4-2.4)	

NS: none significant differences

## Discussion

Infertility is a condition of the male or female reproductive system described by the inability to conceive after the period of 12 months or more of unprotected sexual activity (9). According to large-scale studies, about half of all cases of infertility are caused by female factors, 20% to 30% by male factors, and 20% to 30% by common causes of infertility in both sexes (10). Human papilloma virus is one of the most common sexually transmitted viruses that affect fertility and cause genital infections and infertility. HPV is a pathogen that causes long-term infections without causing noticeable symptoms, in some cases of infertility sexually transmitted viruses are suspected to be a factor. HPV has an effect on sperm parameters and in some cases infection with the human papillomavirus can impair sperm motility, has been linked to sperm DNA breakage and sperm pH changes. HPV infection has been to have a deleterious impact on male fertility, even leading to infertility (11).

The current study indicates to the presence of anti-HPV antibodies in both patients and control groups. The results showed detection of anti-HPV IgM in 16% and anti-HPV IgG in 18% of patients. These findings were relatively same in previous studies conducted in Thi-Qar Province in 2020, which indicated to the presence of anti-HPV IgG in 14.63% of infertile patients (12). The present study

showed that detection of anti-HPV IgM and IgG antibodies were in female (24% IgM and 32% IgG) more than male (8% IgM and 4% IgG). A study conducted in Hilla city, Iraq showed opposite findings, where the presence of anti-HPV IgG antibody was high (15.4%) of infertile male (13), and same was detected in a study performed in Italy where the percentage of anti-HPV IgG was 10.6%. (14).

HPV infection is grossly involved in human infertility, the effect is site/tissue specific on the cells of human reproduction system. Male infertility associates with HPV infection of the semen, specifically HPV infection affects the quality of sperm cells, reducing their fertilization potential. HPV-infected sperm cells can transfer the virus to oocyte. Female infertility associates with HPV infection of the placental cells, HPV causes their miss-function, including compromised attachment of the trophoblasts, and causes damage and death of the infected oocyte/zygote/blastula/blastocysts (15). HPV infection is strongly linked to increased tubal infertility, endometriosis, and PID (16). HPV infection seems to be significantly related to negative effects on both the female and male reproductive system and consequently on the normal reproductive function and related infertility. As HPV infection has a negative effect on sperm quality, if semen is infected with the HPV it is thought to affect the acrosomal reaction and lead to reduced acrosome functionality and capacity (17).

HPV infections can activate two distinct pathways: one that produces infectious virion and another that produces noninfectious malignancy, the former pathway appears to be implicated in fertility change, according to evidence (18). HPV infections in men have long been known to cause sperm contamination (19), influence of HPV on sperm parameters can alter the quality of sperm by causing orchitis, epididymitis, urethritis, or urethral stickiness, among other things (20) and can affect sperm motility in men (21). HPV seems to affect both men and women, virus can bind to the head of a spermatozoon, reduce sperm motility in men, may reduce the endometrial implantation of trophoblastic cells and cause trophoblastic apoptosis women (22).

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