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Association between high-risk human papillomavirus infection female infertility

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Abstract

From a biological perspective, HPV is a very successful pathogen; that is, it can induce chronic infections without any systemic symptoms, allowing the host to periodically shed large amounts of transmissible virus to naïve individuals. A cross-sectional study was carried out in Kirkuk city-Iraq from June 2019 to the end of November 2019, including 200 women who attended to private clinics and suffering from infertility, and 100 controls (women without infertility). Five ml of blood was collected by vein puncture from each subject enrolled in this study. Blood samples were placed into sterile test tubes, the obtained sera were then aspirated using automatic micropipette and transferred into clean test tubes for detection of HPV16 and 18 E7 proteins by using ELISA technique. The study showed that the highest rate of HPV E7 proteins (29.5%) was detected in women with infertility comparing with healthy women (12%) with highly significant relation of HPV with infertility (P. value: <0.05). The study stated that the highest rate of infertile women was infected with HPV 16 (37.29%) followed by HPV 58 (30.26%) while HPV 18 was found in 12.26% of those women and 13.56% of them was infected with both HPV 16 and HPV 58 genotypes. The highest mean of age were recorded among infertile women compared with healthy women (32.21 ± 6.68 v.s 31.80 ± 5.38 year) although the result was non-significant (P: > 0.05). The highest mean of BMI were recorded among non-infertile women compared with infertile women (23.92 ± 1.55 v.s 25.36±1.99 kg/m^2), the result was significant. There was no significant difference regarding to LH, FSH, E2, progesterone level between infertile and control group women (p: < 0.05). It was concluded that female infertility was associated with HPV infection specially with HPV 16 and 18 serotypes.

Key words: *HVP, High risk; Female infertility*

Introduction

HPV is a double-stranded nonenveloped DNA adenovirus, which belongs to a large family of more than 130 genotypes [1]. The genome of the virus can be divided into three main domains: a noncoding upstream regulatory region of 1 kb in size; an early region with six genes, namely, E6, E7, E1, E2, E4, and E5; and a late region with two genes, L1 (major capsid protein) and L2 (minor capsid protein) [2]. These viruses are generally classified as either low-risk types that cause benign warts or high-risk types that are associated with cancers [3]. While HPV 6 and 11 are the most common low-risk types that cause anogenital warts, HPV 16 and 18 are the most common oncogenic or high-risk types, which are responsible for up to 70% of all cervical cancers worldwide [4]. The different types of papilloma viruses exhibit characteristic tropism: cutaneotropic (HPV 1, 4, 5, 8, 41, 48, 60, 63, and 65) types are isolated in cutaneous and plantar warts, whereas mucosotropic (HPV 6, 11, 13, 18, 39 44, 55, 16, 31, 33, 35, 52, 58, 67, etc.) types are identified in benign and malignant lesions of the anogenital tract, oral cavity, oropharynx, and larynx. The female genital tract faces high and frequent antigenic exposures [5]. Before reproductive age, numerous antigens are recognized as "self" or "own" commensal microbiota [19]. However, once sexual activity begins, the genital tract must deal with exposure to several other exogenous antigens, including those derived from the male reproductive tract

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[6]. From a biological perspective, HPV is a very successful pathogen; that is, it can induce chronic infections without any systemic symptoms, allowing the host to periodically shed large amounts of transmissible virus to naïve individuals [7]. It is widely accepted that sexually transmitted infections such as Chlamydia trachomatis, Neisseria gonorrhoeae, and Treponema pallidum can lead to alterations in fertility or even infertility [8]. Reproductive alterations have also been associated with sexually transmitted viruses, including HIV, cytomegalovirus, and herpes simplex virus [(9,10)]. Recent data have also suggested HPV as a fertility-altering agent [1]. HPV infections can induce two different pathways: an infectious virion-producing pathway and a noninfectious cancer-producing pathway [11]. Evidence suggests that the former pathway may be involved in fertility alteration [2]. However, the role of HPV as a direct cause of infertility remains uncertain [4]. The aim of the study was to detect the prevalence of human papillomavirus (HPV) in sera of infertile women comparing with healthy ones.

Methodology

A cross-sectional study was carried out in Kirkuk city-Iraq from June 2019 to the end of November 2019, including 200 women who attended to private clinics and suffuring from infertility, and 100 controls (women without infertility). Five ml of blood was collected by vein puncture from each subject enrolled in this study. Blood samples were placed into sterile test tubes, the obtained sera were then aspirated using automatic micropipette and transferred into clean test tubes for detection of HPV16 and 18 E7 proteins by using ELISA technique..

Statistical analysis:

Computerized statistically analysis was performed using IBM SPSS V23.0.0 statistic program. Comparison was carried out using; Chi square and T-Test.

Finding

The study showed that the highest rate of HPV E7 proteins (29.5%) was detected in women with infertility comparing with healthy women (12%) with highly significant relation of HPV with infertility (P. value: <0.05), Table 1.

Table 1: Detection of HPV E7 proteins in infertile and healthy women

HPV result	infertile Women		Control group	
	No.	%	No.	%
HPV +ve	59	29.5	12	12
HPV -ve	141	70.5	88	88
Total	200	100	100	100

P. value: <0.05.

The study stated that the highest rate of infertile women was infected with HPV 16 (37.29%) followed by HPV 58 (30.26%) while HPV 18 was found in 12.26% of those women and 13.56% of them was infected with both HPV 16 and HPV 58 genotypes, Table 2.

Table 2: Coinfection between HPV genotypes (16,18 and 58) in women with infertility

HPV genotype	Infertile Women	
	No.	%
HPV16	22	37.29
HPV 18	9	12.26
HPV 58	18	30.51
HPV 16/18	1	1.69
HPV 16/58	8	13.56
HPV 16/18/58	1	1.69
Total	59	100

Table 3 show that the highest mean of age were recorded among infertile women compared with healthy women (32.21 ± 6.68 *v.s* 31.80 ± 5.38 year) although the result was non-significant (P: > 0.05). The highest mean of BMI were recorded among non-infertile women compared with infertile women (23.92 ± 1.55 *v.s* 25.36±1.99 kg/m^2), the result was significant (P<0.05).

Table 3: Distribution of infertile and non-infertile women according to age and BMI.

	Infertile	**Control group**	**P value**
Age (years)	32.21± 6.68	31.80 ±5.38	NS
BMI(kg/m^2)	23.92 ± 1.55	25.36±1.99	< 0.05

Table 4 show there was no significant difference regarding to LH, FSH, E2, progesterone level between infertile and control group women (p: < 0.05).

Table 4: Levels of LH, FSH, E2 and progesterone in infertile and control group.

Mean ± SD of	Infertile women	Control group	P value
LH(mlU/ml)	4.11±1.38	4.37±2.05	NS
FSH(mlU/ml)	5.71±2.33	4.97±2.38	NS
E2(pg/ml)	1778.5±683.28	1798.59±1296.01	NS
progesterone (ng/ml)	1.00±0.35	1.04±0.40	NS

Discussion

It is important to study HPV detection in pregnancy, which represents a special immunological state that may be a risk factor for HPV infection [1]. Some studies have shown a higher frequency of HPV cervical infection in infertile women compared to non-infertile controls, possibly because of an effect of elevated estrogens which may affect the viral replication, or due to the altered immunity [(7-9)]. HPV infection is common in the general population, including normal infertile women. In normal full-term pregnancy, prevalence of HPV was reported to vary between 2.2 and 75% in the cervical tissue, with a summary estimate of 17.5% [5]. Correspondingly, the prevalence of HPV was significantly higher in the cervix and placental and infertile tissue of women who underwent spontaneous infertility [8]. Although the prevalence of HPV was significantly different in normal pregnancies and the spontaneous infertility group, our results based on 5 cohort studies and 3 case-control studies indicated that there was no significant association between HPV infection and spontaneous infertility. When the included studies reported HR-HPV infection alone. However, the pooled OR of 4 cohort/case-control studies [(9-11)] reported that the HR/LR–HPV infection indicated that HPV infection was a risk factor for spontaneous infertility. It was reported that there are 2 different pathways in the natural history of HPV infections, namely, the infectious virion producing pathway and the clonal transforming pathway [12]. The infectious virion producing pathway can lead to subfertility or early infertility and it is infectious. Oncogenic (HR) HPV types induce more rapid cell division arrest than LR-HPV or intermediate HR-HPV types. It takes the embryo longer to die after LR-HPV infection, which makes it possible to measure the spontaneous infertility [13]. In China, a 10.2% HPV prevalence was reported, with genotypes 16 and 58 being the most frequent (29% and 19% respectively) [14]. In the United States HPV prevalence reported was 35.6%, (11.6% low risk and 29.5% high risk types) [15]. Another study in the United States reported 29% prevalence, the most frequent genotypes being HPV16 (21%), HPV31 (12.7%), HPV18 (9%) and HPV51 (9%) and HPV6/11 (6%) [16]. In Spain, HPV prevalence found was 6.5%, with HPV16 and HPV6/11 being the most frequent genotypes [13]. Coinfection with multiple HPV types has been associated with a higher risk of cervical abnormalities [15]. Longitudinal studies are needed in order to

determine the risk associated with multiple infections in obstetric patients. Of relevance are the high risk genotypes, which may clear spontaneously after the inmmunological state is restored, or persist and may cause lesions. Also of importance are genotypes 6 and 11 identified in the mothers: if they are transmitted they could represent a risk for the newborn, because of the possible of development of laryngeal and respiratory papillomatosis later in childhood. The most common causes of pregnancy loss in the first trimester are of genetic origin [16]. Amongst other important risk factors are maternal age younger than 20 or older than 35 years old, placental inflammation and infection, but the etiology is often uncertain [17] . One other study demonstrated that spontaneous infertility was associated to a previous pregnancy loss and to women's age older than 35 years old [18] . In our study, which comprises to our knowledge the largest cohort of IW, no associations between hrHPV infection and lower pregnancy rate or higher abortion rate were found in hrHPV positive women treated with IVF or in oocyte recipients from hrHPV positive oocyte donors. Similarly to our study, several other studies found no associations between positive HPV detection and lower pregnancy rate [(19,20)]. On the other hand, on other study reported significant associations between HPV infection and reduced pregnancy rate in women treated by IVF (23.5% [4/17] in HPV + *vs*. 57% [51/89] in HPV-, $P = 0.02$) [21] .

Conclusion: Female infertility was associated with HPV infection specially with HPV 16 and 18 serotypes.

Conflict of interest: non

Source of findings: self findings.

Ethical clearance: This research was carried out with the patient's verbal and analytical approval before the sample was taken

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