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Original Article

The association between cervical HPV and female fertility

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ABSTRACT

Objective: Genital human papillomavirus (HPV) infection is the most common sexually transmitted viral infection worldwide with a prevalence of 10-12% in the female population in the reproductive age; few studies addressed the effect of HPV infection on fertility. It is aimed to investigate the presence of HPV infection in infertile women in the present study.

Materials and methods: In this retrospective cross-sectional study; the outpatient infertility clinic records between July 2020 and January 2023, were evaluated. Infertility examination and evaluation were performed following the guidelines. Infertile female individuals and control group's HPV results were analyzed.

Results: 234 infertile and 340 non-infertile females were included in the study, HPV positivity was found %11.5 for all infertile women. No significant relationship was found between and HPV (p=0.850).

Conclusion: No significant association was found between female infertility and HPV. Still HPV may play a role in infertility with different genotypes. Further studies should include HPV genotypes.

Keywords: HPV; infertility; women

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Introduction

Infertility is a common condition which is experienced by 15% of all couples and defined as failure to achieve pregnancy within twelve months of unprotected intercourse or therapeutic donor insemination in women younger than thirty five years or within six months in women older than thirty five years[1]. While the cause of infertility can be male or female, and sometimes both, the cause cannot be determined in 25-30% of couples[2]. Couple infertility who tried to conceive for at least one year and who could not achieve pregnancy despite the presence of patent fallopian tube, normal uterine cavity, adulatory menstrual cycle in women and normal semen analysis in men; should be evaluated in the unexplained infertility group[1, 3]. Sexually transmitted diseases (STDs) are responsible for 20% to 60% of female infertility by causing pelvic inflammation and tubal injury[4, 5],. Pathological changes in the fallopian tubes may affect fertilization and embryo transfer, and endometrial lesions may impair sperm capacitation and embryo implantation. Some viruses are considered as one of the most common sexually transmitted pathogens, in addition to mycoplasma, chlamydia trachomatis and neisseria gonorrhoeae[4, 5].

Human papillomavirus (HPV) is a DNA virus from the papillomaviridae family, containing more than 170 identified types[6]. HPV represents a well-established and most common infectious cause for different types of cancer in females as well as males[7, 8].

Recently association between spontaneous abortion and HPV has been studied[9].Although genital HPV infection is the most common sexually transmitted viral infection worldwide with a prevalence of 10-12% in the female population in the reproductive age, few studies addressed the effect of HPV infection on fertility[6, 10]. While it is suggested that HPV has a role in male infertility by impairing the quality and progressive motility of sperm, its effects on female fertility are not clearly known[11-12]. However,in the Population-Based Cohort Study conducted in 2020, women with HPV infection had an increased risk of infertility compared to the non-HPV cohort [13]. The aim of this study is to evaluate HPV infection in infertile women.

Material and methods

In this retrospective cross-sectional study; the outpatient infertility clinic records between July 2020 and January 2023, were evaluated. In the clinic, the diagnosis and evaluation of infertility were performed in accordance with the American College of Obstetricians and Gynecologists (ACOG) guidelines. Detailed anamnesis and routine gynecological examination of women were performed; furthermore ovarian reserve of the patients by serum

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antimullerian hormone (AMH) and/or basal hormone tests and antral follicle count on transvaginal ultrasound, and hysterosalpingography was performed. Male individuals with detailed anamnesis and semen analysis were evaluated and infertility categorized by the clinic. Infertile individuals were classified in advance. Female individuals' age, body mass index (BMI) and duration of infertility were noted. Control group included random healthy women without any missing data, referred to the gynecology clinic for routine HPV screening and no registration for any other diagnosis in the last year of the study.
As a part of the community cervical cancer screening program, all women aged 30 and over are examined free of charge for HPV in the country by the ministry of health. Patients screened for HPV were included. Results were noted as given by ministry of health HPV 16, HPV18 or HPV others. HPV others includes HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 genotypes. Results with two or more genotype concomitantly were excluded. Also women under the age of thirty which screening is not covered by government insurance policy, women with secondary infertility and mullerian anomalies were excluded from the study.

Statistical Analysis and Ethical Approval

Data analysis was performed with SPSS (version 24.0; IBM Corp). All data were presented as the mean (±SD) or rate (%). A 1-sample Kolmogorov–Smirnov test was performed to analyze the distribution of clinical variables. The Mann–Whitney U test and the $\chi 2$ test were used for the comparison of the non-parametric variables. A P value of less than .05 was considered statistically significant. The study was approved by the local ethics committee (2023/03-43).

Results

234 infertile and 340 non-infertile women were included in the study. Mean age of the patients was 32.25 ± 1.63 (30-38). Overall HPV, HPV 16, HPV 18 and HPV others prevalence were 11.8% (n=68), 2.4% (n=14), 3.5% (n=20), 5.9% (n=34) respectively.
Infertile HPV positive females'; mean age (years), mean BMI and duration of infertility (months) were 32.23±1.65 (30-38), 23±1.56 (21-28) kg/m2 and 23.34±1.67 (12-28) respectively. Control patients mean age and BMI were 32.29±1.61 (30-36) years and 23±1.44 (20-28) kg/m2.
The characteristics and HPV positivity between control and infertility group were summarized in table (Table 1).

Table 1. HPV and characteristics of the patient

	Control (n=340)	Infertility (n=234)	*p*
Age (years)	32 (31-33)	32 (32-33)	*0.567**
BMI(kg/m^2)	23(22-24)	23(22-24)	*0.094**
HPV (+)	%12.1 (n=41)	%11.5 (n=27)	*0.850#*

**Mann-Whitney U test, #Pearson's Chi-square*

There was no significant difference between the groups in terms of age (p=0.567) and BMI (p=0.094). HPV positive patients were detected at a rate of 11.5% (n=27) in the infertile group and 12.1% (n=41) in the control group. There was no significant difference in the measure of patient with positive HPV test, between the groups (p=0.850). In control group HPV 16, 18, and others prevalence were 2.6% (n=9), 3.8% (n=13), and 5.6% (n=19) respectively. In infertile group HPV 16, 18, and others prevalence were 2.1% (n=5), 3% (n=7), and 6.4% (n=15) respectively. There were no significant differences in the comparing the HPV genotypes (Table 2).

Table 2. HPV genotypes vs Infertility

	Control (n=340)	Infertility (n=234)	*p*
HPV (+)	%12.1 (n=41)	%11.5 (n=27)	*0.850*
HPV 16	%2.6 (n=9)	%2.1 (n=5)	*0.909*
HPV 18	%3.8 (n=13)	%3 (n=7)	*0.762*
HPV others	%5.6 (n=19)	%6.4 (n=15)	*0.818*

Chi-square test

Discussion

Sexually transmitted diseases are one of the main causes of primary infertility. It is known that other microorganisms in the vaginal microbiome, especially Chlamydia trachomatis and Neisseria gonorrhea, play a role in infertility by causing salpingitis [9]. While comprehensive studies were carried out in the oncogenic effect of HPV on female genital tract recently, very limited information about infertility due to HPV has emerged. This study provides considerable insight into relation between HPV and female infertility.

As reported Spandorfer et al. HPV positivity was 16% in the patients who underwent in vitro fertilization (IVF) [14]. Lundqvist et al. extended current information of incidence of HR-HPV in infertile women undergoing IVF, was found similar in fertile women [15]. Also another study found that HPV was detected in 15% of infertile women planned for IVF and reported almost all (92%) the test results were HR-HPV type [16]. Present results slightly differ from previous findings reported in the literatüre [17].
There are studies in the literature showing that HPV may have negative effects on fertility. A significant association between HR-HPV infection and infertility has been reported by Rocha et al [18]. A systematic review underlined the association between HPV and poor fertility outcomes are caused by triggering apoptosis in embryonic cells as well as its negative effects on semen[9,19]. Also it is demonstrated that HR-HPV infection is not an independent cause for female infertility, but is a potential risk factor[4]. Interestingly Duan et al. reported that infected sperm play a role in HPV transfection into the oocyte during fertilization, and this situation causes low fertility success [20]. A lower pregnancy rates were reported in HPV positive women, and suggested that HPV infection reduces success of IUI pregnancy by six-fold [14-17].
Even though present results differ some earlier studies, they are consistent with those of Lundqvist et al. and Strehler et al.'s [15,21]. In those studies neither IVF nor artificial reproductive technologies (ART) were appeared to be effected by HPV. Likewise persistent or non-persistent infection could not be linked to female infertility [22]. These values corroborate with others' suggesting no association between HPV and ART success [23-25]. The evidence we also found, supports those assumptions, and added no significant relation between HPV positive women with infertility.
It is plausible that a number of limitations could have influenced the results obtained. The first is the non-categorization for the patients and male exclusion for testing HPV. The second is not pointing out the pregnancy outcomes. These limitations reveal the difficulty of collecting data on infertile couples. However the considerable size of the patients should be noted.
The present findings have some implications for solving the relation between HPV and infertility. Future studies should target on the cellular inflammation responses and different viral genotype.

Conclusion

No significant association was found between female infertility and HPV. The incidence of HPV in women with infertility is not different from the population. Different types of HPV may play a role in infertility. Epidemiological studies including HPV types are needed.

Disclosure

Authors have no potential conflicts of interest to disclose.

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