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Original Research

The Human Papillomavirus and Its Relationship to Infertility and Endometriosis

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Abstract

Background: The pathogenesis of endometriosis is still debatable, and many studies reported a predisposition to infectious and immunological factors. In this study, we aimed to evaluate the human papillomavirus (HPV) positivity in endometriosis pain-related symptoms and infertility. **Methods**: In this cross-sectional study, 410 endometriosis patients were enrolled in this study. HPV-positive (n = 202) and HPV-negative (n = 208) patients compared with pain-related symptoms, infertility, and endometrioma presence. The term "Other HPV" was utilized to encompass all HPV types with the exception of HPV 16 and 18, which were specifically identified as HPV 16/18. **Results**: Dyspareunia in the "Other HPV"-positive group (12.8 %) was statistically higher than in the HPV-negative group (4.8%; p = 0.007). The infertility rate was significantly higher in the HPV 16/18 positive group (high-risk HPV) 35.8% than in the HPV-negative (7.6%), and "Other HPV" positive group (8%; $p < 0.001$). Endometriosis-related pain symptoms were significantly higher in high-risk HPV (49%) than in the HPV-negative (37%), and "Other HPV" positive group (46.3%; p = 0.046). The ovarian endometrioma rate was slightly higher in group HPV 16/18 positive population (16.9%) than in "Other HPV" types positive (11.4%), and HPV-negative groups (7.2%; p = 0.08). **Conclusions**: Our results could provide a potential predisposing role of HPV infection in pain in endometriosis clinics and infertility. Moreover, HPV subtypes may have a different impact on clinical conditions.

Keywords: HPV; dysmenorrhea; pelvic pain; endometriosis; infertility

1. Introduction

Endometriosis is an estrogen-dependent and chronic inflammatory gynecological disease, described as the implantation of endometrial-like tissue outside the uterus [1]. There are many theories about the pathogenesis of the disease. However, the exact pathogenesis of endometriosis remains unclear. The strongest theory is based on the retrograde flow of endometrial tissue from the fallopian tubes into the peritoneal cavity, and ectopic implantation of the endometrial tissue [2].

The true prevalence is unknown due to the diagnosis being challenging. It is estimated that almost 10% of the asymptomatic, and 25–40% of the infertile population are affected by endometriosis [3]. Moreover, women who suffer from chronic pelvic pain are affected by approximately 70% of endometriosis [4]. Dyspareunia, dysmenorrhea, abnormal uterine bleeding, chronic pelvic pain, and infertility are the most common features of endometriosis [5].

Endocrine, infectious, immunologic, proinflammatory, and proangiogenic processes have a role in the severity of disease [6]. Intrauterine infections can break the immune barriers and cause proinflammatory responses with innate immune system cells in genetically predisposed patients [7]. Intracellular inflammatory mechanisms like nuclear factor kappa light chain enhancer of activated B cells (NF-kB) change intranuclear gene expression levels and modulate cell signaling pathways [8]. This condition also causes increased vascularity, adhesions, and infertility in endometriosis.

The patient's history, physical examination, and ultrasound findings help the gynecologist diagnose endometriosis. Endometrioma is a severe form of endometriosis in the ovary. It is usually diagnosed with unilocular, and ground-glass cystic formation detected by ultrasonography (US). However, histopathological confirmation is the gold standard for the diagnosis of endometriosis [9]. Human papillomavirus (HPV) is one of the most common sexually transmitted diseases worldwide. HPV infects host cells in the basal layer of epithelium and implants their genomes as nuclear episomes. The clinical pathologies caused by HPV infection vary according to the subtype of the virus. Low-risk types of HPV (Types 6/11) may cause genital tract lesions like genital warts, while persistent infection with high-risk types of HPV (Types 16/18) is associated with the cervix and other malignancies [10]. Studies have noted that these were especially triggered carcinogenesis through oxidative stress. This pathway is reported to create dysregulation in proinflammatory cytokine levels via E6 and E7 proteins [11].

Moreover, these conditions can also cause cell damage and chronic infection of the infected tissue. Some recent studies have investigated the relationship between sex-

ually transmitted diseases and endometriosis. They have reported a significantly higher rate of high-risk HPV positivity among patients with endometriosis by ascending from the lower genital tract to the pelvis and upper genital tract [12,13]. In another study, it has been also reported that HPV virus spreading was higher in endometriotic tissue than in other pelvic tissues [14]. These studies support the theory of migration of HPV-infected cells out of the uterine cavity with the retrograde menstrual flow. In this study, we aim to evaluate whether the presence of HPV in the endometriosis clinic has an impact. Infertility and pain-related symptoms are aimed to be compared with HPV positivity.

2. Materials and Methods

This cross-sectional study was performed at Dokuz Eylul University School of Medicine, Department of Gynecology and Obstetrics, between January 2019 and December 2021. All subjects gave informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Dokuz Eylul University (Approval Number: 7344-GOA).

The patients with endometriosis and/or endometrioma who were diagnosed with surgery (laparotomy or laparoscopy) and/or imaging methods (magnetic resonance imaging (MRI) or ultrasound (US) findings), and clinical examination findings (uterine immobility, pelvic tenderness) were included in this study. Endometriosis-related pain symptoms including dysmenorrhea, chronic pelvic pain, and dyspareunia were evaluated according to visual analog scores. The 6 or more values scores have used the threshold for each parameter. Patients who had not been able to get pregnant (conceive) after one year (or longer) and women aged 35 years or older after 6 months of unprotected sex were defined as infertile.

According to the 2021 World Health Organization (WHO) cervical cancer and precancerous lesions screening guideline, women between the ages of 30 and 65 years are also screened for the presence of HPV-DNA from vaginal swab samples [15]. Cobas 4800 HPV Test (Roche Molecular Systems, Pleasanton, CA, USA) was used according to manufacturer's instructions. The software program evaluated the results qualitatively, and 14 HPV genotypes (hrHPV) including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were investigated. While expressing the HPV results, the term "Other HPV" was used except for HPV 16 and 18, which was referred to as HPV 16/18.

The patients with any of the following criteria were excluded: history of cervical lesion or cancer, history of pelvic inflammatory disease, history of sexually transmitted infectious disease, patients who have been vaccinated against HPV, and immunosuppressive conditions.

A total of 410 endometriosis patients; HPV-positive patients (n = 202) and HPV-negative patients (n = 208) were included in our study. Endometriosis symptoms were compared according to the HPV presence. HPV 16 or 18 positive cases [Group 1 (n = 53)], "Other HPV"-positive cases [Group 2 (n = 149)], and HPV-negative cases [Group 3 (n = 208)] were defined. Age, HPV status, presence of endometrioma, and all clinical findings of endometriosis were evaluated among groups. The patients were also evaluated according to the presence of endometrioma and HPV test analysis because it is known to be a factor associated with other clinical presentations. According to this, they were divided into four groups: HPV (+)/Endometrioma (+), HPV (+)/Endometrioma (–), HPV (–)/Endometrioma (+), and HPV (–)/Endometrioma (–).

Table 1. Endometriosis-related gynecological complaints, HPV Positivity, and HPV subtypes.

	n = 410 (%)
Age (mean ± SD, years)	37.1 ± 6.3
Endometriosis related pain symptoms, n (%)	172 (41.9 %)
Dysmenorrhea	77 (44.8)
Chronic pelvic pain	65 (37.8)
Dyspareunia	30 (17.4)
Infertility rate, n (%)	47 (11.5 %)
Primary	42 (89.3)
Secondary	5 (10.7)
Infertile patients	
Age (mean ± SD, years)	36.4 ± 4.1
Infertility duration (mean ± SD, years)	2.3 ± 1.3
Endometrioma presence, n (%)	37 (9%)
HPV-positive, n (%)	202 (49.3%)
High risk (HPV 16/18 subtypes)	53 (26.2)
Others	149 (73.8)

SD, Standard deviation; HPV, Human papillomavirus.

The data was analyzed on the statistical package program IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as a number of units (n), percent (%), mean ± standard deviation (mean ± SD), median (M), minimum (min), maximum (max), and interquartile range (IQR). Descriptive values between HPV-positive and -negative groups were analyzed with the Chi-square test. The normal distribution of the frequentist statistics was evaluated with the Shapiro-Wilk test. Categorical data of Groups I, II, and III were compared with the Fisher exact test. If there is a contingency between the groups, sub-group analysis was made with the Bonferroni Correction test. A value of $p < 0.05$ was considered statistically significant. Also, infertility duration is compared with Kruskal-Wallis Analysis.

3. Results

Endometriosis-related gynecological complaints, HPV Positivity, and subtypes of a total of 410 patients who supply all inclusion criteria are shown in Table 1. The mean ages of the patients were 37.1 ± 6.3 years. Ranging

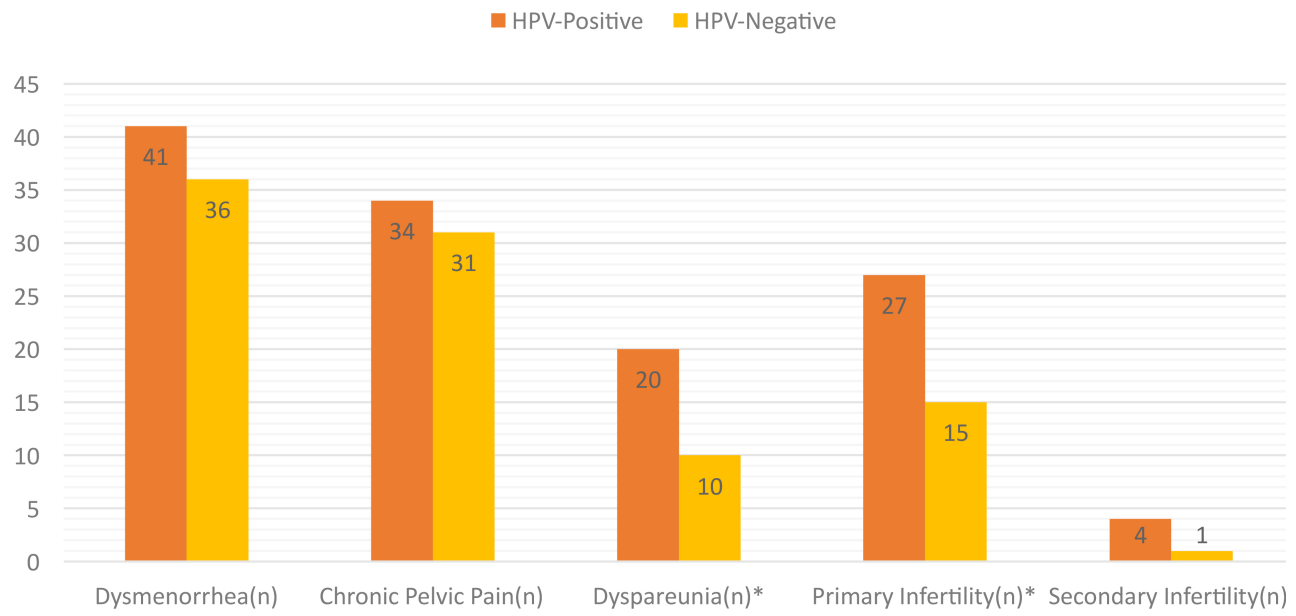

Fig. 1. HPV presence rates and endometriosis-related clinical symptoms, *$p = 0.04$.

from 30 to 53 years. The most common gynecological symptom of endometriosis in participants was dysmenorrhea (18.7%; 77 patients). It is followed by chronic pelvic pain (15.8%), infertility (11.2%), and dyspareunia (7.3%). Infertility rates were 11.5% (47 patients). The mean infertility duration was 2.3 $\pm$ 1.3 years, ranging from 0.7 to 6 years. The mean ages of the infertile patients were 36.4 $\pm$ 4.1 years, ranging from 30 to 49 years.

Regarding asymptomatic endometriosis, which was detected in surgery but with noclinical findings, was observed in 37.5% of the population (154 patients). HPV-negative population rate was 50.8% (208 patients), and 49.2% of the population was HPV-positive (202 patients). 12.9% of the population observed HPV 16/18 positive. HPV status of the patients and endometriosis-related clinical symptoms are compared in Fig. 1. While dysmenorrhea and chronic pelvic pain were not significantly different among HPV-positive (20.3%) and -negative (17.3%) groups, the rate of dyspareunia in the HPV-positive group (9.9%) was statistically higher than in the HPV-negative group (4.8%) ($p = 0.04$). Likewise, the infertility rate was significantly higher in the HPV-positive group 13.4% than in the HPV-negative group 7.2% ($p = 0.04$).

HPV subtypes and endometriosis-related gynecological complaints are shown in Table 2. Endometriosis-related pain symptoms were significantly higher in Group I (49%) with 26 patients than in Group II (46.3%) and Group III (37%) ($p = 0.046$). Dyspareunia was the least often pain symptom when compared with dysmenorrhea and chronic pelvic pain. Also, dyspareunia was significantly higher in Group II at 12.8% than in Group III patients at 4.8% ($p = 0.007$). Group I (35.8%) was significantly higher than Group II (8%) and Group III (7.6%) in infertility rates ($p < 0.001$).

A total of 9% of all patients had ovarian endometrioma. Gynecological complaints according to HPV and endometrioma positivity are compared in Table 3. All the clinical complaints about pain and infertility were higher in endometrioma-positive patients. HPV positivity was not different among endometrioma positive (7.3%) and endometrioma absence (43.6%) ($p = 0.1$). HPV presence did not cause any difference between endometrioma-positive and absent groups. Although overall infertility rates were not significantly different between HPV-positive (1.5%) and HPV-negative (0.8%) patients ($p = 0.74$), in the endometrioma-absent group, the infertility rate was significantly higher in the HPV-positive population (6%) compared to HPV-negative patients (3.1%) ($p = 0.02$). When the endometrioma presence compared with HPV subtypes, the endometrioma rate was slightly higher in Group HPV 16/18 positive population (16.9%) than in "Other HPV" types positive (11.4%), and HPV-negative (7.2%) groups ($p = 0.08$).

4. Discussion

The primary aim of this study was to identify whether HPV is a triggering factor for endometriosis-related gynecologic disorders. While in an overall study group, the HPV-positive population rate was detected at 49.2%. Oppelt *et al.* [14] reported 25% of the endometriosis population had positive HPV screening, 26.8% were negative for HPV, and 48% represented patients in whom no HPV testing was performed, owing to no clinical relevance. When the HPV unstudied group was excluded, the HPV positivity rate in endometriosis patients correlates with our study.

Vestergaard *et al.* [16] investigated the possible involvement of a pathogenic virus in ectopic endometriosis tissues and endometrial tissues. The virus prevalence var-

Table 2. HPV subtypes and endometriosis-related gynecological complaints.

	Group I	Group II	Group III	
	(HPV 16/18)	("Other HPV" types)	HPV-negative	*p*-value
	n = 53 (100%)	n = 149 (100%)	n = 208 (100%)	
Endometriosis-related pain symptoms, n (%)	26[a] (49%)	69[b] (46.3%)	77[b] (37%)	0.046
Dysmenorrhea	12 (22.6%)	29 (19.4%)	36 (17.3%)	0.63
Chronic pelvic pain	13 (24.6%)	21 (14.1%)	31 (14.9%)	0.19
Dyspareunia	1[ab] (1.8%)	19[a] (12.8%)	10[b] (4.8%)	0.007
Infertility presence	19[a] (35.8%)	12[ab] (8%)	16[b] (7.6%)	<0.001

[a] and [b] show the difference between the groups. The groups that had different letters are statistically significant.

Table 3. Gynecological complaints according to HPV and endometrioma positivity together.

	Endometrioma present			Endometrioma absent		
	n = 37 (9%)			n = 373 (91%)		
	HPV (+)	HPV (–)	*p*	HPV (+)	HPV (–)	*p*-value
	n = 23 (%)	n = 14 (%)	0.74	n = 179 (%)	n = 194 (%)	0.1
Endometriosis related pain symptoms, n (%)	40 (100%)	22 (100%)		55 (100%)	55 (100%)	
Dysmenorrhea[1]	19[b] (47.5%)	12[b] (54.5%)	0.8	22[a] (40%)	24[a] (43.6%)	0.98
Chronic pelvic pain[1]	15[b] (37.5%)	8[b] (36.3%)	0.6	19[a] (34.5%)	23[a] (41.8%)	0.7
Dyspareunia[2]	6[b] (15%)	2[ab] (9.2%)	0.39	14[a] (25.5%)	8[a] (14.6%)	0.13
Infertility presence	6 (100%)	3 (100%)	0.74	25 (100%)	13 (100%)	0.02

[a] and [b] show the difference between the groups. The groups that had different letters are statistically significant. [1], $p < 0.001$; [2], $p = 0.003$; +, positive; –, negative.

ied slightly but was not significant when comparing the endometrium of healthy women and women with endometriosis (10% *vs*. 3%, $p = 0.33$). As explained, there is a conflict about the presence of HPV viral genomic components in the tissues. Moreover, a meta-analysis was designed to analyze HPV and endometriosis relations. According to this study, HPV infection and endometriosis indicate that HPV could be an etiologic viral agent for the pathogenesis of disease with a retrograde menstrual flow theory [17]. In the literature, studies report that HPV activity increases with increased estrogen levels. HPV is an established etiology of cervical carcinomas, and oral contraceptive usage increases the risk of HPV infection 2.9 times more than the negative population [18]. 17β-estradiol intake increases HPV 18 E6/7 mRNA expression levels in HeLa cells and the activity of cervical cancer cells [19]. In another study, during the pregnancy period, high-risk HPV positivity detection rates significantly increased (24.9% *vs*. 13.3%, $p < 0.001$) [20]. Activation of these viruses by hormonal factors may be associated with endometriosis and endometriosis-related estrogen-dominant microenvironment.

Herein, endometriosis-related gynecologic disorders were analyzed according to HPV presence. Although the ovarian endometrioma rate was higher in Group I, the result was not statistically significant in our population (16.9% *vs*. 11.4% *vs*. 7.2%, respectively; $p = 0.08$). Heidarpour *et al*. [12] investigated the presence of high-risk HPV in ovarian endometriosis and reported a significantly higher rate of high-risk HPV infection among patients with endometriosis (26% *vs*. 10.2%, $p = 0.02$). When we compare our results with this study, there may be relevance between ovarian endometrioma and the high-risk-HPV positivity.

"Other HPV" types of positivity are statistically related to dyspareunia in our study (12.8% *vs*. 4.8%, $p = 0.007$). Dyspareunia is a pain in the lower genital tract and cervical tissue during sexual intercourse. Castle *et al*. [20] reported that HPV viruses have more adherence to the vaginal epithelium than potent oncogenic subtypes (42.5% *vs*. 33.7%, $p < 0.001$). However, other benign vulvar conditions and cervical dysplasia treatment may also cause dyspareunia and cause a conflict in analysis. Dyspareunia and decreased sexual desire were reported in cervical intraepithelial neoplasia (CIN) treated groups in prior studies [21]. A recent study, which investigates sexual function in HPV-positive population in Turkey reported that non-significant change in the Arizona Sexual Experience Scale (ASEX) when compared to HPV-negative infection ($p = 0$ .49) [22]. The ASEX scale evaluates sexual desire, arousal, genital response (lubrication for women), and orgasmic satisfaction. These criteria are related and can be associated with dyspareunia.

The high-risk HPV (HPV16/18) positivity (35.8%) is significantly related to infertility when compared with "Other HPV"-positive patients (8%) and HPV-negative patients (7.6%) ($p = 0.01$). In a recent study from Brazil, Rocha *et al*. [13] reported an association between high-risk HPV infection in the upper genital tract infection, with infertility and endometriosis (44% *vs*. 17.1%, $p = 0.027$).

Also in this study, HPV detection in the endometrial cavity and intraabdominal space was 5.4 times greater when compared with the non-endometriosis control group (95% confidence interval (CI) 1.07–97.25) [13]. Some studies report an association between assisted reproductive technique (ART) success, HPV infection in sperm, and the female genital tract [23]. Spandorfer *et al*. [24] reported that pregnancies obtained by *in vitro* fertilization (IVF) treatment were two times higher than in HPV-negative women (23.5% *vs*. 57, $p < 0.2$). They reported that oocyte and embryo quality were not different among HPV-positive and -negative groups. However, a meta-analysis showed that there is insufficient data about the negative impact of HPV infection and ART outcomes [25]. When we compare our results with these studies, there may be relevance between infertility and high-risk HPV types (16 and 18).

Endometrioma has the same clinical symptoms as endometriosis. Dyspareunia, chronic pelvic pain, and infertility are also symptoms of endometrioma [26]. When endometrioma and HPV positivity were compared together, there was no strong correlation between HPV status and other gynecological symptoms. If HPV subtypes are included in the analysis, results may be different since the inflammatory pattern of HPV is more related to high-risk HPV subtypes. As explained before, endometrioma presence is reported slightly higher with HPV 16 and 18 positive population. HPV positivity might be a worsening risk factor for endometrioma symptoms. Moreover, the risk of neoplastic transformation of endometriosis has been estimated to be 0.5% to 1.0% [27]. HPV itself has an oncogenic virulence ability on lower genital tract malignancies. These oncogenic properties may suggest the neoplastic transformation of endometriosis lesions. However, further studies are needed for this relation.

Our study presented some strong evidence, as we included a large study population, as well as and there had not been yet a study between endometrioma and endometriosis clinic symptoms and HPV presence. On the other hand, there were some limitations to our study. Indeed, endometriosis clinical stages are not included in the study, and HPV study on the endometriosis tissue may improve the clinical correlation. Clinical complaints might be worse at the higher stages in patients.

5. Conclusions

HPV 16 and 18 have a significant relation with dyspareunia and infertility. Moreover, ovarian endometrioma has a weak correlation with the high-risk HPV group. When comparing gynecological symptoms with ovarian endometrioma and HPV positivity together, there is no correlation in favor of HPV positivity.

However, if this comparison is made with a larger population with the inclusion of high-risk and "Other HPV" subtypes, the high-risk HPV population may contribute significant results. Our findings serve as the basis for future larger studies that fully investigate the role that HPV might be a worsening factor for endometriosis and ovarian endometrioma. Further studies are needed to demonstrate the exact pathogenesis and relation between endometriosis and HPV.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

EO, HK, and OY designed the research study. AA and EC performed the research. HK and OY analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All subjects gave informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Dokuz Eylul University (Approval Number: 7344-GOA). .

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Conflict of Interest

The authors declare no conflict of interest.

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