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HPV infection and endometrial polyps: insights from a case-control study

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Abstract

Background Endometrial polyps are common benign lesions characterized by localized overgrowths of endometrial tissue within the uterine cavity. The etiology and pathogenesis of these polyps remain unclear. Human papillomavirus (HPV) infection, known for its association with various genital tract conditions, has been investigated concerning endometrial polyps, although research in this area is limited.

Methods A case-control study involving 62 premenopausal women was conducted, with endometrial polyp cases and control groups matched for age and BMI. Biopsy samples were collected for HPV testing using polymerase chain reaction (PCR). Clinical and demographic data were collected and analyzed for associations between HPV presence and endometrial polyps.

Results Results showed a higher prevalence of HPV (all types) in cases (4, 12.9%) compared to controls (1, 3.2%), with low-risk HPV being the most prevalent genotype detected and HPV 16 tested positive in one case diagnosed with polyp. While no significant association was found between HPV infection and the presence of endometrial polyps, the study suggests a potential role for HPV in their development. Interestingly, HPV presence in endometrial polyps was unrelated to histopathological features, patients' age, or BMI.

Conclusion This study provides insights into the potential involvement of HPV infection in the development of endometrial polyps. Despite no significant association found, the prevalence of HPV in these polyps suggests a possible contributory role. Further research with larger sample sizes and more robust methodologies is warranted to clarify this association and its clinical implications.

Keywords Endometrial polyp, Human papilloma virus, HPV infection

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Introduction

Endometrial polyps are benign localized overgrowths of endometrial tissue within the uterine cavity, composed of glands, stroma, and blood vessels covered with epithelium [1]. In perimenopausal women, the prevalence of endometrial polyps is reported to be between 20% and 25%. As a common type of endometrial disease, with easy relapse, most endometrial polyps remain asymptomatic, and abnormal uterine bleeding is the common clinical manifestation in those who experience symptoms [2]. The etiology and pathogenesis of endometrial polyps remain unclear. Some investigators suggested that the endometrial polyp form as a consequence of abnormal expression of estrogen and progesterone receptors. The development of endometrial polyps is also correlated with hypertension, obesity, and a delayed onset of menopause [3, 4]. In some cases, endometrial polyps are associatedwith infertility, and despite their benign nature, a minority may undergo hyperplasia and malignant changes [1, 5].

Human papillomavirus (HPV) is recognized as the most prevalent sexually transmitted pathogen worldwide, and its prevalence is on the rise globally. Sexual intercourse is the main route of transmission leading to potential complications in the female genital tract like anogenital warts, cervical intraepithelial neoplasia, and cervical cancer [6–8]. The infection is more reliably detected by polymerase chain reaction (PCR) and is recognized by distinct histological changes in epithelial cells including multinucleation and koilocytosis [9].

Despite the wealth of evidence establishing the connection between HPV and warts across different areas of the human body, research on the link between HPV and endometrial polyps has been limited to just one study thus far [10]. Several studies have indicated the detection of HPV in endometrial adenocarcinoma, which is a tissue adjacent to, but lacking, the stratified squamous epithelium of the exocervix [11, 12].

It remains unclear whether tumors characterized by glandular-type epithelium show morphological signs of HPV infection. This uncertainty persists because koilocytotic-like changes have been observed only in the squamous component of certain endometrial adenocarcinomas and HPV's role in the development of endometrial cancer appears to be minimal or insignificant [13–15].

Given the limited available data, our study is designed to investigate the presence of HPV in the endometrium through PCR and evaluate its correlation with endometrial polyps in premenopausal women, in an attempt to help develop effective molecular biological methods to predict prognosis and treatment for endometrial polyps.

Materials and methods

We conducted a case-control study involving 62 premenopausal women, who were referred to us between January 2016 and January 2017. This study was approved by the local Ethics Committee of the Iran University of Medical Science (IR.IUMS.REC.1396.29944). Written informed consent was obtained from all participants.

Inclusion Criteria was women aged 18 to 52 years with a normal Pap smear result. Participants were those referred to the Endoscopy Unit at Rasool-e-Akram Hospital for hysteroscopy in order to investigate abnormal uterine bleeding (AUB) or infertility. None of the patients had a history of vulvar, vaginal, or cervical HPV-related lesions, intraepithelial neoplasia, or carcinoma. In the control group, patients with infertility or AUB were included, and a sample of normal endometrium without any polypoid lesions was obtained via hysteroscopy. Patients who refused to consent to enrollment in the study were excluded. Additionally, patients with any atypia or malignancy in their pathology reports were also excluded from the study.

After preparing all patients for hysteroscopy, endometrial or polyp samples were sent for pathology examination [16]. Diagnosis of polyps was based on typical histological criteria. The survey was conducted in 62 women 31 with endometrial polyp and 31 with normal endometrial tissue. Control women were matched to cases by age and body mass index (BMI). Age, BMI, gravidity, endometrial thickness, and HPV types detected in endometrial tissues were studied. HPV was detected usingimmunocytochemistry and in situ hybridization, identifying the virus type and measuring HPV-DNA content.

Study samples for DNA extraction included endometrial polyps or endometrial samples in paraffin-embedded endometrial tissue sections by =PCR. A specific DNA extraction protocol was implemented for these samples. HPV testing was performed in the Department of Pathology at the Iran University of Medical Sciences, Tehran.

HPV positivity was assessed by hybridization of PCR products in an enzyme immunoassay, nested PCR with common and specific primers of HPV16 and HPV 18, and detection with gel electrophoresis. First run with common HPV-primer set: HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 66, 68, 70 and then with HPV16 and 18 type primer done. Sensitivity was no less than 1000 genome equivalents in 1 ml of sample (GE/ml). HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 were considered HR types in the present report.

Clinical and demographic data were collected before the procedure. Data was collected and entered into a standard data entry sheet, subsequently, cleaned

Table 1 Characteristics of the study population

	Polyp Positive (Mean ± SD)/(No.(%))	Polyp Negative (Mean ± SD)/(No.(%))	*P*-value
Age	40.03 ± 9.6	37.8 ± 8.1	0.3
Gravid	2.7 ± 2.2	1.8 ± 1.2	0.06
Live birth	2.22 ± 1.7	1.4 ± 1.02	0.03
BMI	28.67 ± 4.1	27.41 ± 4.2	0.2
EL	11.61 ± 3.1	9.83 ± 2.1	0.01
HPV			0.3
Yes	4 (12.9%)	1 (3.2%)	
No	27 (87.1%)	30(96.8)	

and prepared for analysis. Descriptive statistics were expressed as mean ± SD for continuous variables and as proportions for categorical variables. For comparison of the study and control groups, a *t*-test, and regression analysis was conducted. A *P* value of <0.05 was considered statistically significant. We estimated odds ratios (OR) and 95% confidence intervals (CI) for the associations between HPV and endometrial polyps using binary logistic regression. In the multivariable logistic regression model, the ORs were adjusted for age, endometrial thickness, and BMI. The statistical analysis was performed with SPSS (version 21; IBM Inc., Armonk, NY, US).

Results

Table 1 presents the baseline characteristics of the participants. Both groups were similar in terms of age, BMI, gravidity, live birth, endometrial thickness (EL), and HPV presence. However, there was a significant difference in the mean number of live births between the groups ($p<0.05$). While the prevalence of HPV (all types) was higher in cases compared to controls (12.9% vs. 3.2%), no significant association was found between HPV presence in the endometrium and the presence of polyps.

The primary focus of this study was to identify HPV in both normal endometrium and polyps. Although cases of HPV16 were more prevalent in the polyp group compared to controls (3.2% vs. 0%), the statistical analysis did not reveal a significant difference. Low-risk HPV was the most common genotype observed, with HPV16 detected in only one polyp sample. Despite the lack of significant difference in the frequency of HPV-positive cases between polyps and normal samples, the presence of four positive samples among polyp tissues may still suggest an association between HPV and endometrial polyps. Furthermore, there was only one case of endometrial polyp that tested positive for HPV 16, with no positive result for HPV 18. Overall no statistically significant association was found between HPV and endometrial polyps .

Regarding other factors, the odds ratio for age <30 versus age ≥ 30 was 1.12 (95% CI: 0.29–4.28), which was not statistically significant. A BMI <30 was associated with a decreased risk of endometrial polyps compared to a BMI ≥ 30 (OR, 0.8; 95% CI: 0.3–1.5). Elevated endometrial thickness was linked with endometrial polyps, with an odds ratio of 5.8 (95% CI: 1.57–21.6). Although the odds ratio for HPV in endometrial polyps compared to normal endometrial tissue was 7.4 (95% CI: 0.7–73.6), it was not statistically significant (Table 2).

Table 2 Association between HPV and endometrial polyp, age, BMI, EL

	Cases No.(%)	Controls No.(%)	Adjusted OR	CI (95%)
Age				
<30	6(19.4%)	7 (22.6%)	1	
≥30	25 (80.6%)	24 (77.4%)	1.12	(0.29 – 4.28)
BMI				
<30	27 (87.1%)	25 (80.6%)	1	
≥30	4 (12.9%)	6 (19.4%)	0.8	(0.1 – 3.5)
EL				
>12	18 (58.1%)	27 (87.1%)	1	
≤12	13 (41.9%)	4 (12.9%)	5.8	(1.57 – 21.6)
HPV				
Negative	27 (87.1%)	30 (96.8%)	1	
Positive	4 (12.9%)	1 (3.2%)	7.4	(0.7 – 73.6)

Discussion

Endometrial polyps are common benign lesions of the endometrium, characterized by localized overgrowths of glands and stroma that protrude from the endometrial lining. despite the high prevalence, the precise origin and causative factors remain unclear. Several factors have been linked to the development of endometrial polyps, including hormonal imbalances, genetic predisposition, inflammation, and iatrogenic interventions [5, 17]. While endometrial polyps are typically benign, they carry an increased risk of malignancy. Case series have shown that the risk of malignancy in endometrial polyps can vary widely, ranging from 0 to 15%, and ameta-analysis has determined that the prevalence of malignancy in endometrial polyps is approximately 2.7% [18, 19].

The presence of human papillomavirus in both normal and abnormal endometrial tissues raises many questions and necessitates further investigation. HPV was originally thought to infect only specific sites and tissues, particularly the stratified squamous epithelium of the lower female genital tract, such as the vulva, vagina, and exocervix. This infection is frequently linked to conditions like condylomata acuminata, intraepithelial neoplasia, and invasive carcinomas, with affected tissues showing cytopathic effects, including multinucleation and koilocytotic atypia [20, 21]. Since HPV infection is, site- and tissue-specific, the endometrium may not be a suitable host for HPV replication and maturation. While the connection between HPV and warts in different parts of the human body is well-established. As far as we know, its association with endometrial polyps has been examined

in only one study, which found one sample that tested positive for HPV type 18, among 50 endometrial polyp samples [10]. Such a correlation could have significant clinical implications. If HPV, especially oncogenic subtypes, is linked to endometrial polyps, there might be an increased risk of these polyps developing into endometrial cancer. Additionally, vaccination against HPV could potentially prevent the formation of some endometrial polyps and thus reduce the incidence of endometrial cancer [10].

In the present study, we found four positive samples of HPV in patients with endometrial polyps, in contrast to the control group, which had only one positive case. Among these, only one sample was positive for HPV 16, and none tested positive for HPV 18. The HPV detection method we employed in our study is likely more accurate compared to other methods, as our biopsy-based approach is more reliable for detecting HPV than brush sampling. Interestingly, the presence of HPV in endometrial polyps was found to be unrelated to histopathological features, patients' age, or BMI. Although the differences in HPV-positive case frequencies between our study and control subjects were not statistically significant, the presence of 4 positive samples in polyp tissues may suggests a potential role for HPV in endometrial polyps. This study collectively indicates that some endometrial tissues may be infected with HPV, warranting further investigation. Nonetheless, the presence of HPV in the endometrium is not uncommon in benign and malignant lesions of the endometrium. Fujita et al. found HPV DNA in endometrial tissues, especially in carcinomas, suggesting that HPV infection could contribute to the development of these cancers [22]. In another study, it was found that high-risk HPVs, particularly HPV-16, are present in a subset of endometrial and ovarian carcinomas, with an overall prevalence of approximately 10% and the prevalence of HPV in women with endometriosis has been reported to be 24%,. This indicates that HPV infection likely plays a minor role in the development of endometrial and ovarian carcinomas compared to its significant involvement in cervical cancer [23, 24].

Our study presents several strengths and limitations. The case-control design allows for effective comparative analysis, and the utilization of biopsy-based methods with paraffin-embedded tissue samples ensures enhanced accuracy. However, being hospital-based, there's a risk of selection bias, potentially affecting the applicability of our findings to the broader population. Moreover, the stratified analysis was conducted on a relatively small sample size, requiring cautious interpretation. However, in our study, there were no tumors that did not have either integrated or mixed integrated/episomal DNA. In future studies, we will use more robust methods to measure HPV integration for more reliable determination. The difference in results could be partly explained by differences in the sensitivity of the HPV detection techniques used. This is further supported by the absence of relevant epithelial changes, lack of correlation with histological features or prognosis, and the low incidence rates with precancerous endometrial lesions [25].

In our study, we observed that HPV infection was more prevalent among premenopausal patients with endometrial polyps. However, we were unable to statistically validate this finding, potentially due to the small sample size. Nevertheless, similar to Kucukyıldız' s study, none of the young patients with endocervical polyps exhibited signs of malignancy, reinforcing the notion that these patients do not require more aggressive treatment [26].

The association between HPV infection and endometrial polyps remains elusive. Some argue that HPV, originating from the lower genital tract, is merely present in the endometrium without playing a significant pathogenic role in endometrial polyp development [13]. Despite the limitations of our study, including its small sample size and case-control design, the detection of several HPV-positive cases prompts the need for further investigation to better understand this relationship.

Conclusion

This study contributes to understanding the association between HPV infection and the development of endometrial polyps. We acknowledge that if there is any relationship, the mechanisms underlying this relationship remain unclear, as we did not find a direct correlation between HPV infection and the formation of endometrial polyps. While HPV is present in some endometrial polyps, it is still uncertain whether HPV infection precedes polyp formation or if polyps provide a favorable environment for HPV persistence in the uterus. More extensive studies with larger sample sizes and stronger methodologies are necessary to clarify any potential association and its clinical significance because endometrial polyps are known to have a higher risk of progressing to endometrial cancer, and certain HPV types are highly oncogenic. Understanding any link between HPV and endometrial polyps could have important clinical implications, particularly in risk assessment and prevention strategies for endometrial cancer.

Abbreviations

HPV	Human papillomavirus
PCR	Polymerase Chain Reaction
AUB	Abnormal Uterine Bleeding
BMI	Body Mass Index
EL	Endometrial Thickness

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Data availability
All data from this study are included in this published article.

Declarations

Ethics approval and consent to participate
The study is approved by the ethical committee of Iran University of Medical Sciences (Approval Number: IR.IUMS.REC.1396.29944). Informed consent was obtained from all participants upon enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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