



# Immunohistochemical Assessment of YAP1 Expression in Endometrial Hyperplasia with and without Atypia

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## Abstract

**Aim:** Endometrial hyperplasia, particularly when accompanied by atypia, is considered a well-established precursor of endometrial carcinoma. Yes-associated protein 1 (YAP1), a key effector of the Hippo signaling pathway, plays a crucial role in the regulation of cell proliferation, apoptosis, and tissue homeostasis and has been implicated in tumorigenesis. The present study aimed to investigate whether YAP1 protein expression in endometrial hyperplasia with and without atypia differs from that in normal endometrial tissue.

**Methods:** This retrospective observational case-control study included 122 patients: 41 cases of endometrial hyperplasia with atypia, 41 cases of endometrial hyperplasia without atypia, and 40 controls with normal endometrial histology. Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue sections using a YAP1 polyclonal antibody. Staining localization (nuclear and/or cytoplasmic), intensity, and distribution were evaluated semi-quantitatively. Statistical comparisons among the three groups were performed using parametric or nonparametric tests according to the distribution characteristics of the variables.

**Results:** No statistically significant differences were observed among the study groups in terms of YAP1 staining localization, intensity, or distribution. Both nuclear and cytoplasmic expression patterns were comparable in endometrial hyperplasia with and without atypia and in control tissues.

**Conclusion:** Yes-associated protein 1 protein expression did not differ significantly between precancerous endometrial lesions and normal endometrium. These findings suggest that YAP1 activation may represent a later molecular event in endometrial carcinogenesis rather than an early alteration during precursor stages. Further prospective studies integrating molecular and functional analyses are warranted to clarify the precise role of YAP1 in the progression from benign to malignant endometrial pathology.

**Keywords:** Endometrial hyperplasia, endometrial neoplasms, immunohistochemistry, hippo signaling pathway

## Introduction

Endometrial hyperplasia (EH) comprises a heterogeneous spectrum of pathologic lesions ranging from mild glandular proliferation to direct precursors of

endometrial carcinoma, with atypical forms conferring the highest risk of progression to endometrioid adenocarcinoma (1). EH is driven primarily by chronic exposure to unopposed estrogen, resulting in abnormal

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proliferation of endometrial glands relative to the stroma; risk factors include obesity, anovulation, estrogen-producing tumors, and exogenous estrogen exposure (2). The Hippo signaling pathway, a conserved regulator of tissue growth and organ size, controls cellular proliferation and apoptosis and has been increasingly recognized for its role in tumorigenesis across multiple organ systems (3). Yes-associated protein 1 (YAP1), a core downstream effector of the Hippo pathway, acts as a transcriptional co-activator that promotes proliferation and inhibits apoptosis when it is translocated to the nucleus; aberrant YAP1 activity has been implicated in various cancers, including endometrial carcinoma (3). In endometrial cancer, dysregulated Hippo signaling and increased nuclear YAP/TAZ activity correlate with tumor progression, poor prognosis, and resistance to therapy, suggesting a functional role in malignant transformation (3). Nevertheless, existing evidence concerning YAP1 expression in precancerous endometrial lesions is scarce, with the majority of studies predominantly concentrating on endometrial carcinoma rather than hyperplasia subtypes (4).

We hypothesized that YAP1 expression patterns differ between normal endometrium and subtypes of endometrial hyperplasia, particularly in the presence of atypia, reflecting its potential involvement in early endometrial carcinogenesis. Therefore, the present study aimed to evaluate the immunohistochemical expression of YAP1 in endometrial hyperplasia with atypia, endometrial hyperplasia without atypia, and normal endometrial tissue. By elucidating whether YAP1 expression changes at the precancerous stage, this study seeks to clarify the temporal role of Hippo-YAP signaling in the continuum from benign proliferation to malignancy, potentially identifying a biomarker for early detection or risk stratification. The findings may help determine whether YAP1 represents an early biomarker of malignant transformation or a molecular event occurring later in the progression toward endometrial cancer, thereby providing clinically relevant insight for future diagnostic or therapeutic strategies.

## Materials and Methods

### Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Pamukkale University Local Ethics Committee (approval number: 12, date: 19.10.2017). Written informed consent was obtained from all participants prior to enrollment. All clinical data were anonymized to ensure patient confidentiality.

### Study Design

This study was designed as a retrospective, observational, case-control study conducted at a tertiary gynecologic

oncology center. The study population consisted of three distinct groups: patients with endometrial hyperplasia with atypia, patients with endometrial hyperplasia without atypia, and a control group of individuals with normal endometrial histology. The study included 122 patients: 41 with endometrial hyperplasia with atypia, 41 with endometrial hyperplasia without atypia, and 40 control subjects. Clinical records, ultrasonographic findings, and histopathological reports were retrospectively reviewed. All pathological diagnoses were re-evaluated and confirmed prior to immunohistochemical analysis.

Patients histopathologically diagnosed with endometrial hyperplasia, with or without atypia, following endometrial biopsy or hysterectomy were eligible for inclusion. The control group consisted of patients who underwent endometrial sampling for abnormal uterine bleeding and who demonstrated normal endometrial histology. Patients with a current or previous diagnosis of malignancy, systemic inflammatory or metabolic disorders (including hypertension, diabetes mellitus, and thyroid disease), active infections, or prior hormonal or systemic drug use were excluded. Cases with inadequate tissue samples or suboptimal fixation were also excluded. Formalin-fixed, paraffin-embedded tissue blocks were sectioned at a thickness of 3  $\mu$ m and mounted on electrostatically charged slides. All staining procedures, including deparaffinization, antigen retrieval, and immunostaining, were performed using a fully automated immunohistochemistry system (Ventana BenchMark LT, Roche Diagnostics, Tucson, AZ, USA).

Immunohistochemical staining was carried out using a polyclonal anti-YAP1 antibody according to the manufacturer's protocol. Positive staining was defined as brown granular staining observed in the cytoplasm and/or nucleus of endometrial epithelial cells. Staining distribution and intensity were evaluated independently by a single experienced pathologist who was blinded to clinical data. Staining intensity was semiquantitatively graded as weak (+), moderate (++), or strong (+++) (Figures 1a, 1b, and 1c). The percentage of positively stained cells was categorized as <50%, 50-79%, or 80-100% (Figures 2a, 2b, and 2c).

### Statistical Analysis

Statistical analyses were performed using SPSS software version 20.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated using the Shapiro-Wilk test and visual inspection of histograms. Continuous variables were presented as mean  $\pm$  standard deviation for normally distributed data or as median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The Kruskal-Wallis test was used for non-normally distributed continuous variables, while one-way analysis

of variance (ANOVA) was applied for normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All tests were two-tailed, and a p-value <0.05 was considered statistically significant.

## Results

A total of 122 patients were included in the study: 41 with endometrial hyperplasia without atypia, 41 with endometrial hyperplasia with atypia, and 40 control subjects.

Baseline demographic and clinical characteristics of the study groups were comparable, with no significant differences in age or clinical indications for endometrial sampling. The distributions of nuclear and cytoplasmic YAP1 staining patterns were comparable across the three groups, with no statistically significant differences observed. Immunohistochemical evaluation demonstrated that both cytoplasmic and combined nuclear-cytoplasmic staining patterns were similarly distributed across endometrial hyperplasia with atypia, endometrial hyperplasia without atypia, and control tissues. Comparative analysis revealed no significant differences in staining localization among the groups.

Similarly, semi-quantitative assessment of staining intensity showed comparable proportions of weak, moderate, and strong YAP1 expression across all study cohorts, with no statistically significant differences

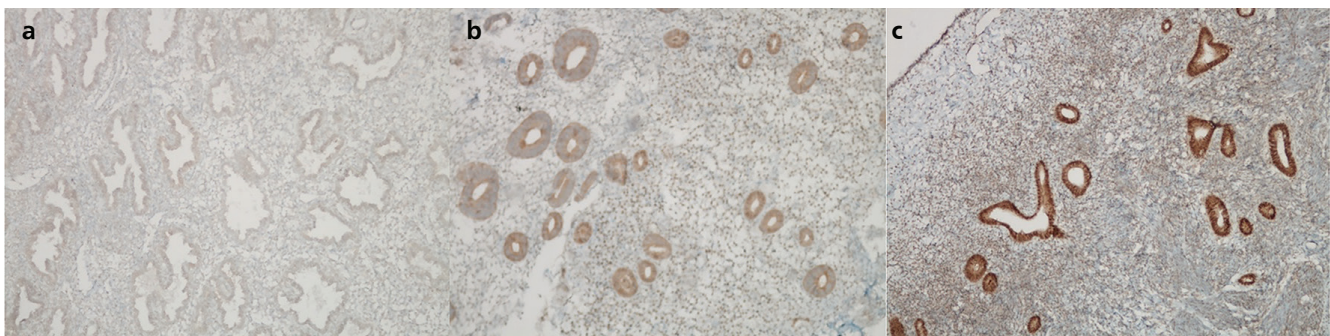
between groups. The distribution of staining percentages (<50%, 50-79%, and 80-100%) also did not differ significantly between groups.

Overall, YAP1 expression patterns did not differ significantly between precancerous endometrial lesions and normal endometrial tissue. Detailed quantitative results are presented in Table 1.

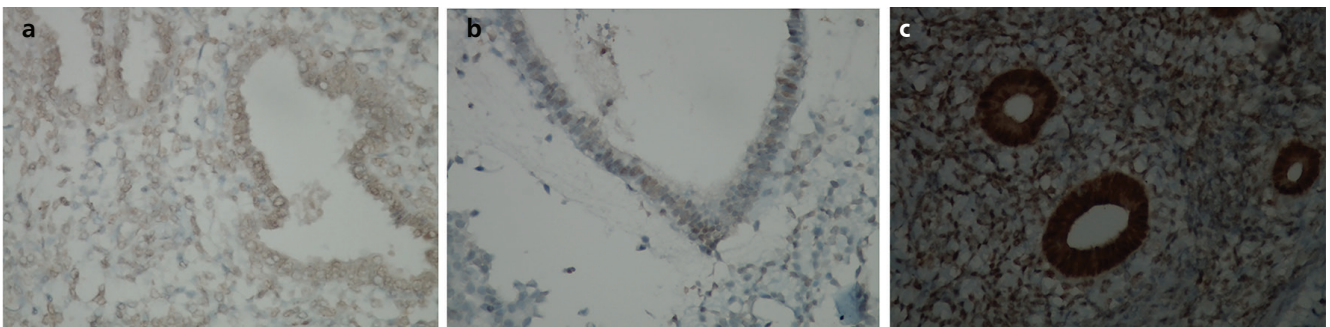
## Discussion

We investigated the immunohistochemical expression patterns of YAP1 in endometrial hyperplasia with and without atypia and in normal endometrial tissue. Our results demonstrated that YAP1 expression, evaluated in terms of localization, staining intensity, and distribution, did not differ significantly among the three groups. These findings suggest that YAP1 protein expression is not altered at the stage of endometrial hyperplasia, regardless of the presence of atypia.

Recent evidence increasingly supports the involvement of YAP1 signaling in endometrial pathophysiology. Yu et al. (4) conducted a prospective immunohistochemical study in China, including 35 patients with endometrial polyps and 35 healthy controls, and demonstrated significantly increased nuclear YAP1 expression in hyperproliferative endometrial tissue compared with normal endometrium. Their study highlighted that YAP1 activation is associated with progesterone resistance and excessive cellular proliferation, consistent with our observation of elevated



**Figure 1.** a. Weak staining intensity, b. Moderate staining intensity, c. Strong staining intensity



**Figure 2.** a. Cytoplasmic staining, b. Nuclear staining, c. Nuclear and cytoplasmic staining

YAP1 expression in endometrial hyperplasia. Importantly, while Yu et al. (4) focused on endometrial polyps, our study extends these findings to endometrial hyperplasia, a recognized precursor lesion of endometrial carcinoma, thereby expanding the clinical relevance of YAP1 dysregulation (4).

Similarly, Lin et al. (5) investigated the molecular mechanisms underlying progesterone resistance in endometriosis by analyzing human tissue samples (n=42) and an in vivo mouse model. Their work revealed that YAP1 overexpression suppresses progesterone receptor expression through upregulation of miR-21-5p, leading to impaired decidualization and sustained cellular proliferation. Although the study was conducted in the context of endometriosis, these findings strongly support our results, suggesting that YAP1-mediated progesterone resistance may represent a common pathogenic mechanism across various endometrial proliferative disorders, including endometrial hyperplasia (5).

Using a mechanistic animal model, Zhou et al. (6) investigated the role of YAP1 in bovine endometrial epithelial cells and demonstrated that upregulation of YAP1 significantly enhanced epithelial proliferation, migration, and invasion, whereas its knockdown reversed these effects. Their experimental findings provide strong biological plausibility for our clinical observations, reinforcing the role of YAP1 as a central regulator of endometrial epithelial growth. Unlike our human-based retrospective design, their controlled in vitro and in vivo approach provides mechanistic insight, complementing our translational findings (6).

Further supporting evidence comes from transcriptomic analyses by Chen et al. (7), who, using a rat model of intrauterine adhesions, demonstrated that YAP-Smad7 signaling modulates fibrotic remodeling in endometrial

tissue. Their findings underscore the regulatory capacity of YAP1 across a broad spectrum of endometrial pathologies, including fibrosis, hyperplasia, and neoplastic transformation. While their focus was on fibrosis rather than hyperplasia, both studies highlight YAP1 as a critical molecular hub governing abnormal endometrial tissue remodeling (7).

From an oncologic perspective, multiple large-scale studies have demonstrated that YAP1 overexpression correlates with tumor aggressiveness, increased proliferative index, and unfavorable prognosis across diverse malignancies. Marx et al. (8) analyzed over 17,000 prostate cancer specimens and identified high YAP1 expression as an independent predictor of early biochemical recurrence and poor clinical outcome. Although these studies were performed in prostate cancer, their results emphasize the universal oncogenic potential of YAP1-driven signaling pathways, supporting the concept that sustained YAP1 activation in endometrial hyperplasia may represent an early oncogenic event (8).

Collectively, these studies highlight YAP1 as a critical molecular determinant of abnormal endometrial proliferation and tumorigenesis. However, in contrast to reports demonstrating increased YAP1 activity in hyperproliferative or malignant endometrial conditions, our findings did not reveal a significant difference in YAP1 expression between endometrial hyperplasia (with or without atypia) and normal endometrium. This discrepancy may suggest that YAP1 activation represents a later molecular event in the progression toward endometrial carcinoma rather than an early alteration occurring at the hyperplasia stage. Our study, therefore, contributes important clinical data indicating that YAP1 overexpression may not be a distinguishing feature of precancerous endometrial lesions.

**Table 1. Comparison of groups in terms of staining status, staining density, and percentage of staining**

	Endometrial hyperplasia without atypia (n=41)	EIN (n=41)	Normal endometrium (n=40)	p
Staining status				
Nuclear	0 (0%)	1 (2.4%)	0 (0%)	0.87
Cytoplasmic	21 (51.2%)	21 (51.2%)	20 (50%)	
Nuclear and cytoplasmic	20 (48.8%)	19 (46.3%)	20 (50%)	
Staining density				
Weak	12 (29.3%)	14 (34.1%)	9 (22.5%)	0.61
Moderate	24 (58.5%)	19 (46.3%)	26 (65%)	
Strong	5 (12.2%)	8 (19.5%)	5 (12.5%)	
Percentage of staining				
<50%	7 (17.1%)	3 (7.3%)	3 (7.5%)	0.53
50-79%	2 (4.9%)	3 (7.3%)	2 (5.0%)	
80-100%	32 (78.0%)	35 (85.4%)	35 (87.5%)	

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant  
EIN: Endometrial intraepithelial neoplasia

### Study Limitations

This study has several limitations. First, it was conducted retrospectively at a single center, which may limit the generalizability of the findings. Second, the sample size, although calculated to achieve sufficient statistical power, may still be insufficient to detect subtle differences in YAP1 expression among subgroups. Third, a single pathologist performed the immunohistochemical evaluation, which may have introduced observer bias. Lastly, molecular analyses, such as mRNA or protein quantification, were not performed, which could have provided additional insight into YAP1 expression dynamics. In addition to these factors, technical issues inherent to immunohistochemical analysis may have influenced the results. Variations in antibody specificity, antigen retrieval procedures, or fixation time can alter staining intensity and sensitivity. Although a standardized automated staining protocol was used, pre-analytical variability cannot be entirely excluded. An additional limitation of this study is the absence of comprehensive data on hormonal status, menopausal condition, and exogenous hormone exposure, preventing analysis of their potential impact on YAP1 expression patterns. All these factors might have contributed to the absence of statistically significant differences in YAP1 expression between study groups.

Despite these limitations, our study benefits from strict histopathological confirmation, standardized immunohistochemical evaluation, and well-defined patient selection criteria, thereby strengthening the reliability of our findings. Moreover, the relatively homogeneous patient population minimizes confounding and enhances internal validity.

### Conclusion

Overexpression of the YAP1 protein, which has been recognized as an important factor in cancer pathogenesis, was not observed in endometrial hyperplasia, with or without atypia, compared with normal endometrial tissue. This suggests that YAP1 activation may occur later in malignant transformation than in precursor lesions. Despite the lack of differential expression, the present study provides valuable preliminary data on early molecular events in endometrial carcinogenesis. The results emphasize the potential role of YAP1 and the Hippo signaling pathway as promising molecular targets for future diagnostic and therapeutic research. Further prospective, multicenter studies integrating hormonal and molecular analyses are warranted to clarify the role of YAP1 in the transition from benign to malignant endometrial pathology.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from the Pamukkale University Local Ethics Committee (approval number: 12, date: 19.10.2017).

**Informed Consent:** Written informed consent was obtained from all participants prior to enrollment.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: A.K.K., N.Y., Concept: A.K.K., O.O., Design: A.K.K., O.O., Data Collection or Processing: A.K.K., R.S., A.K., Analysis or Interpretation: A.K.K., S.O., A.K., Literature Search: A.K.K., G.T., Writing: A.K.K., G.T.

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