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# Do myometrial lesions affect the discrepancy of pathological findings in women with endometrial hyperplasia?

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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## Abstract

**Background/Aim:** Benign myometrial lesions are frequently found in pathologic specimens of hysterectomies. High rates of coexistence of these lesions with endometrial cancer have also been reported. Our aim was to evaluate the effect of myometrial lesions on the consistency of diagnoses between endometrial sampling results and final hysterectomy findings in patients with endometrial hyperplasia (EH) before hysterectomy.

**Methods:** Two hundred seventeen patients who were diagnosed as having EH via endometrial sampling and underwent hysterectomy within three months were included in this retrospective cohort study. The patients' preoperative and postoperative pathologic findings were compared, and discordant results were defined to be either overdiagnosed or underdiagnosed.

**Results:** The overall diagnostic concordance between the endometrial sampling results and the final hysterectomy pathologic findings was 32.2%. The rate of concurrent endometrial carcinoma (EC) among all EH was 22.1%. The discordance between preoperative endometrial sampling and final hysterectomy specimen results was evaluated, and patients with underdiagnosis were older (60.5 years, $P < 0.001$), had a higher BMI (30.84 kg/m$^2$, $P < 0.001$), were mostly postmenopausal ($P < 0.001$), had lower parity numbers (median = 2, $P = 0.002$), and had a lower rate of co-existing adenomyosis ($P = 0.009$). The rates of co-existing leiomyoma between the groups were not different. No effect of other demographic characteristics was observed in the multivariate regression analysis; however, the presence of adenomyosis was a significant independent risk factor affecting a 5.8-fold increase in overdiagnosis (-1.50; OR: 0.17 (0.05-0.50) $P = 0.002$) and 4.5-fold increase in underdiagnosis (-1.50; $P = 0.005$).

**Conclusion:** Co-existing adenomyosis could lead to discordance of the pathologic findings in women with EH diagnoses before hysterectomy.

**Keywords:** Adenomyosis, Endometrial hyperplasia, Leiomyoma, Diagnosis

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## Introduction

Endometrial hyperplasia (EH) is an abnormal proliferation of the endometrial glands and stroma [1]. In 1994, the World Health Organization (WHO) divided EH into four groups according to cytologic nuclear atypia and glandular complexity: simple hyperplasia without atypia, complex hyperplasia without atypia, simple hyperplasia with atypia, and complex hyperplasia with atypia [2]. In 2014, the WHO revised the EH classification into two groups based on only nuclear atypia: non-atypical EHs (NAEH) are defined as benign, and atypical EHs (AEH), which are similar to endometrial intraepithelial neoplasia (EIN), and considered as precursors of endometrial carcinoma (EC) [3]. The clinical significance of atypical hyperplasia, in particular, is that these patients have an up to 40% probability of having concomitant EC detected in the final pathologic examination of hysterectomy specimens [4, 5].

It may not be easy to distinguish EC precursor AEH from well-differentiated EC [6]. Therefore, studies have focused on identifying patients with concurrent EC and evaluating factors that contribute to the discrepancy between endometrial sampling results and final pathologic findings of hysterectomy specimens. The most studied subject has been the effect of different endometrial sampling methods. The effect of patient-related factors, such as age, body mass index (BMI), chronic diseases, and nulliparity on the coexistence of EC with AEH was also evaluated [7-9].

Adenomyosis and leiomyoma, which are benign myometrial lesions, are frequently found in pathologic specimens of hysterectomies performed with benign indications at rates of 20-30% and 40-60%, respectively [10, 11]. High rates of coexistence of these benign myometrial lesions with EC have also been reported (adenomyosis 18.9-22.6%; leiomyoma 27%) [12-14].

Therefore, in this study, we aimed to evaluate the effect of myometrial lesions, such as adenomyosis and leiomyoma, on the discordance of pathologic findings in patients who were diagnosed as having any type of EH before undergoing hysterectomy.

## Materials and methods

This retrospective observational study was performed in a university-affiliated hospital. Institutional review board approval was obtained (2011 KAEK 25 2021/04-09). The study complied with the principles of the Declaration of Helsinki. All patients signed informed consent forms before undergoing surgery, allowing their medical records to be used for research purposes.

Patients who were diagnosed as having EH through endometrial sampling and had undergone hysterectomy within three months following the diagnosis between May 2016 and May 2021 were reviewed. The medical records of 288 patients were evaluated. Women, whose endometrial sampling results classified according to the WHO 2014 EH classification and who underwent hysterectomy as first-line therapy were included [3]. Additionally, patients with full medical records were included to avoid recall and diagnostic suspicion biases. In order to avoid observer bias, patients whose pathology specimens were evaluated in another center were excluded (n = 9). In addition, patients who received progestin treatment before hysterectomy, using tamoxifen or hormone replacement therapy, whose duration between EH diagnosis and hysterectomy was longer than three months, and those with missing medical records were excluded (n = 62) . A total of 217 patients remained in the study. Endometrial sampling was performed under local anesthesia using an Endosampler® device. Endometrial sampling and hysterectomy specimens of patients were reviewed by gynecologic pathologists in our institution.

The presence of myometrial lesion was concluded according to preoperative ultrasonography reports and pathologic examination results after hysterectomy. Final hysterectomy histopathology results for endometrium, which were reported as ‘secretory’ or ‘proliferative’ were considered normal.

The patients were evaluated in three groups according to the consistency of endometrial sampling and final hysterectomy pathology results: overdiagnosis, underdiagnosis, and concordance. Among patients with preoperative diagnosis of NAEH (n = 105), those diagnosed as normal according to hysterectomy were defined as overdiagnosed. Those with AEH and EC in final pathologic examinations were defined as underdiagnosed, and patients with NAEH in the hysterectomy examination were defined as concordant. Among patients with preoperative diagnoses of AEH (n = 112), those who were normal and had NAEH in the final pathologic examination were defined as overdiagnosed; those with EC in the final pathological examination were defined as underdiagnosed, and patients with AEH in the final examination were defined as concordant. Patients with EC were staged according to the revised *2009 International Federation of Gynecology and Obstetrics* (FIGO) staging system [15].

**Statistical analysis**

The SPSS version 20.0 software package (SPSS Inc., Chicago, IL, USA) was used for data storage and statistical analysis. The descriptive statistics of the data were presented as mean (standard deviation). The Shapiro-Wilk test was used for detecting the distribution pattern of variables. The Mann-Whitney U test, Kruskal-Wallis and Chi-squared tests were used for comparing continuous and categorical variables among groups. Multivariate logistic regression was performed to detect the independent effects of variables on discordant results. *P*-values of $< 0.05$ were considered statistically significant.

## Results

A total of 217 patients who were diagnosed as having EH before undergoing hysterectomy and met the inclusion criteria were retrospectively evaluated regarding their hysterectomy histopathology results.

The histopathologic results of endometrial samples and final hysterectomy specimens are shown in Table 1. The overall diagnostic concordance between the endometrial sampling results and the final hysterectomy pathologic findings was 32.2%; 26.7% of patients were underdiagnosed and 41.0% were overdiagnosed. Concurrent EC was observed in 22.1% of all patients.

According to the endometrial sampling results among the EH groups, the patients in the AEH group had a higher BMI

than NAEH (29.6 kg/m$^2$ vs 27.5 kg/m$^2$, $P$ = 0.005). There was no difference between the groups in terms of other demographic data (Table 2).

Table 1: Endometrial sampling and final hysterectomy histopathology results

| Endometrial sampling results | Final Hysterectomy findings | | | | |
|---|---|---|---|---|---|
| | Normal | NAEH | AEH | EC | Total |
| NAEH | 60 (57.1) | 28 (26.7) | 10 (9.5) | 7(6.7) | 105 (48.3) |
| AEH | 21(18.8) | 8(7.1) | 42(37.5) | 41 (36.6) | 112 (51.7) |
| Total | 81 (37.3) | 36 (16.6) | 52 (24.0) | 48 (22.1) | 217 (100) |

NAEH: Non-atypical endometrial hyperplasia, AEH: atypical endometrial hyperplasia, EC: endometrial carcinoma. Values are given in percentages.

Table 2: Demographic characteristics of the groups according to the endometrial sampling results

| | NAEH n = 105 | AEH n = 112 | *P*-value |
|---|---|---|---|
| Age (years) | 52 (40-79) | 53.5 (36-84) | 0.664 |
| BMI (kg/m$^2$) | 27.5 (21.8-35.1) | 29.6 (21.5- 39.1) | 0.005 |
| Parity | 3 (0-10) | 3 (0-7) | 0.112 |
| Menopause status, n (%) | | | |
| Premenopausal (n = 88) | 48 (45.7) | 40 (35.7) | 0.167* |
| Postmenopausal (n = 129) | 57 (54.3) | 72 (64.3) | |
| Myometrial lesions, n (%) | | | |
| Adenomyosis (n = 64) | 32 (29.5) | 34 (30.4) | 0.459* |
| Leiomyoma (n = 98) | 60(57.1) | 38 (33.9) | 0.001* |

BMI: Body Mass Index, NAEH: Non-atypical endometrial hyperplasia, AEH: atypical endometrial hyperplasia. Values are given as median (range) unless stated. The Mann-Whitney U test was performed. *Chi-squared test was used.

Those with underdiagnosis had significantly higher BMI (30.4 kg/m$^2$, $P$ = 0.001) and were older (60 years, $P$ < 0.001) than the other groups. The rate of patients in the postmenopausal period was also high in the underdiagnosis group (75.9%, $P$ < 0.001). Co-existing adenomyosis was lowest in the underdiagnosis group and significantly different from the others ($P$ = 0.004) (Table 3). There was no difference between groups in terms of co-existing leiomyoma rates (Table 3).

Table 3: Comparison of groups according to endometrial sampling and final hysterectomy pathological results compatibility

| | Overdiagnosis (n = 89) | Underdiagnosis (n = 58) | Concordance (n = 70) | *P*-value |
|---|---|---|---|---|
| Age (years) | 51 (38-72) | 60 (37-79)[b] | 52 (36-84) | < 0.001 |
| BMI (kg/m$^2$) | 27.5 (21.8-35.1) | 30.4 (21.5-38.0)[b] | 27.5 (21.9-39.1) | 0.001 |
| Parity | 3 (0-10) | 3 (0-6)[b] | 3 (1-7) | 0.04 |
| Menopause status[a] | | | | |
| Pre- (n = 88) | 46 (51.7) | 14 (24.1)[b] | 28(40.0) | 0.004 |
| Post- (n = 129) | 43 (48.3) | 44(75.9)[b] | 42 (60.0) | |
| EH diagnosis to surgery interval (days) | 45 (16-82) | 39 (18-88) | 42 (20-81) | 0.301 |
| Adenomyosis[a] | | | | |
| Yes (n = 65) | 34 (38.2) | 8 (13.8)[b] | 23 (32.9) | 0.004 |
| No (n = 152) | 55 (61.8) | 50 (86.2)[b] | 47 (67.1) | |
| Leiomyoma[a] | | | | |
| Yes (n = 98) | 46 (51.7) | 25 (43.1) | 27 (38.6) | 0.245 |
| No (n = 119) | 43 (48.3) | 33 (56.9) | 43 (61.4) | |

BMI: Body mass index, EH: endometrial hyperplasia. Values are given as median (range); The Kruskal-Wallis test was used unless stated otherwise. [a] Chi-squared test was used. Values are given n (%). [b] The group that differs from others.

The rate of co-existing adenomyosis was 29.9% among all EH cases, and the rate of co-existing adenomyosis was 13% in patients with a preoperative diagnosis of AEH and a final pathologic diagnosis of EC. In a multivariate logistic regression model, in which factors identified as potential risk factors ($P$ < 0.05) in univariate analyses were included, no significant independent effects of age, BMI, parity, menopausal status, or presence of fibroids on discordant results were observed. The presence of adenomyosis was found to be a significant independent risk factor in obtaining discordant pathologic results. Overdiagnosis was found to be 5.8 times more likely in the presence of adenomyosis, regardless of age (B = -1.76; OR: 0.17 (0.05-0.50) $P$ = 0.002). The presence of adenomyosis was also found to increase the probability of underdiagnosis by 4.5 times (B = -1.50; OR: 0.22 (0.07-0.63), $P$ = 0.005).

## Discussion

To the best of our knowledge, the current study is the first to report the effect of myometrial lesions, such as adenomyosis and leiomyoma, on the discordance of pathologic findings in patients who were diagnosed as having EH before undergoing hysterectomy. We retrospectively evaluated patients who underwent hysterectomy and their endometrial pathology results. We calculated the discordance rate of these results as 67.7%; 26.75% of patients were underdiagnosed and 41.0% were overdiagnosed. Patients who were classified as underdiagnosed were found to be older and had higher BMI than the others. It was also concluded that discordance rates were higher in patients with adenomyosis.

Adenomyosis is described as the presence of the endometrial glands and stroma within the myometrium. Microscopically, adenomyosis consists of non-neoplastic ectopic endometrial stroma and glands surrounded by hypertophic and hyperplastic myometrium [16]. Although traditionally the diagnosis is made through histopathologic examination, preoperative diagnosis can be made using transvaginal ultrasonography (TVUSG) or magnetic resonance imaging (MRI) due to the developments in imaging techniques [17]. Adenomyosis is found incidentally in 20-25% of benign hysterectomy specimens [18]. The relation between the diagnosis of EH and adenomyosis cannot be demonstrated with the available data. Existing literature has focused on EC developing in the presence of adenomyosis. Although the results of studies related to the co-existence of adenomyosis with EC are contradictory, a 22.6% pooled prevalence of adenomyosis in EC has been reported in recent studies, and it has been shown that this rate is not different from co-existence in benign conditions [13]. In our data, the co-existence rate of adenomyosis and EC was 12.5% (6 of 48). Although the underlying disorder is hyperestrogenism, the known etiologic factors of EC and adenomyosis are incompatible. While multiparity and use of oral contraceptives increase the risk of adenomyosis, they also reduce the risk of EC [14]. The reason for the coexistence of these two pathologies may be a coincidental association rather than a common etiology due to the high incidence of adenomyosis in peri/postmenopausal patients.

In the current study, none of the concurrent ECs originated from adenomyotic foci. Thirty-nine of the ECs were stage 1, and nine were stage 2. None of the stage 2 ECs had co-existing adenomyosis. Although the adenomyosis co-existence rate did not differ between EH subtypes, it was observed that adenomyosis accompanied fewer cases in those who were underdiagnosed in the final pathologic evaluation.

When the presence of myometrial lesions is not taken into account, several studies identify patients with EH who are likely to be underdiagnosed to avoid possible suboptimal surgery, especially in AEH cases in which concurrent EC rates are reported up to 40% [4]. Vetter et al. [19] evaluated 169 patients with complex AEH and reported that the concurrent EC rate was 48.5% and that the risk of concurrent EC increased in patients with a preoperative endometrial thickness of more than 2 cm and those aged over 65 years. Erdem et al. [9] reported that over the age of 50, diabetes mellitus, hypertension, and nulliparity were independent risk factors for concurrent EC in

AEH. In our study, we found that underdiagnosed patients were significantly older and postmenopausal. In the underdiagnosis group, patients had higher BMI and lower parity. Consistent with our results, Hui et al. [20] examined occult AEH and EC risk factors in NAEH cases and stated that patients with higher grades in the final pathology had significantly lower median parity and higher BMI. A recent study that evaluated risk factors for occult AEH and EC in women diagnosed as having NAEH in an endometrial biopsy found that patients over 51 years with complex NAEH subtype had a high risk for underdiagnosis [21]. According to the results of the mentioned studies [20, 21] and our research, it could be concluded that although NAEH was considered as benign by the WHO and the first-line treatment option was conservative, hysterectomy may be an option in the presence of risk factors for underdiagnosis in patients with NAEH.

In addition to the aforementioned risk factors regarding concurrent EC risk, the preferred endometrial sampling method is also relevant. Endometrial aspiration biopsy using a pipelle or Endosampler is the most preferred sampling method because it can be performed easily in an outpatient setting, does not require general anesthesia, and is as accurate as a D&C in the diagnosis of endometrial pathologies [8, 22]. In the current study, the Endosampler was preferred for preoperative diagnosis.

Studies of overdiagnosis in EH are limited. In one study, no characteristic features could be identified that distinguished the overestimated group from the other groups among the clinical parameters and imaging findings [23]. In our research, although the preoperative characteristics of patients with overdiagnosis did not differ from those of concordant patients, we found that the presence of leiomyoma did not affect the results, but the presence of adenomyosis increased the rates of overdiagnosis.

This novel study investigating the relationship between endometrial pathology discordance and myometrial lesions has a large sample size. Other strengths of this study include the use of the same endometrial sampling method in all patients and the evaluation of both pre- and postoperative pathology results by the same gynecologic pathologists in the same center. On the other hand, the retrospective design and conducting the study in a referral center might increase the incidence of occult EC, and this could be considered as a limitation of the study. Other limitations include the fact that the size of the preoperative lesion is not clear in the overdiagnosis group, and the possibility that the entire lesion was removed by biopsy before hysterectomy.

**Conclusion**

In conclusion, adenomyosis, which is an incidental and common benign pathology, can cause both overdiagnosis and underdiagnosis in patients with EH. For appropriate diagnostic and therapeutic management of EH, it should be highlighted that the possibility of discordant results in the presence of adenomyosis should be considered, and those patients should be carefully evaluated together with their clinical features for treatment options.

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