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A RETROSPECTIVE EVALUATION OF NEOPLASTIC AND NON-NEOPLASTIC PATHOLOGIES IN NON-PREGNANCY ENDOMETRIAL TISSUE SAMPLES AND A LITERATURE REVIEW

GEBELİK DIŞI ENDOMETRİAL DOKU ÖRNEKLERİNDE NEOPLAZİK VE NONNEOPLAZİK PATOLOJİLERİN; LİTERATÜR EŞLİĞİNDE RETROSPEKTİF OLARAK İNCELENMESİ

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Abstract

Objective: This study retrospectively examined patients presenting with abnormal uterine bleeding. Based on the histopathological and clinical characteristics of the obtained data, we sought a statistical answer to the question "Do age, material type, clinical findings, clinical preliminary, and histopathological diagnosis parameters differ from the literature findings?"

Material and Methods: A total of 2,000 endometrial samples were reviewed and filtered according to the appropriate parameters collected within 5 years (2017-2022). The statistical significance of the data was measured using the chi-square test.

Results: The study included 1,815 patients aged 19 to 86 years. Indications for endometrial sampling were classified as menometrorrhagia/menorrhagia (49.2%), endometrial polyp (19.5%), postmenopausal bleeding (18%), endometrial hyperplasia (14.6%), and leiomyoma (2.8%). Patients were grouped by menstrual status: premenopausal (51.6%, under 45 years), perimenopausal (25.39%, aged 45-51), and postmenopausal (22.97%, aged 51 and above). Histopathological findings showed benign pathologies including endometrial polyp (61.9%), proliferative/secretory endometrium (12%), atrophic endometrium (6.6%), and chronic endometritis (0.2%). The pre-malignant findings were endometrial hyperplasia without atypia (9%) and atypical hyperplasia of the endometrium (0.6%). Malignant findings included adenocarcinoma (1.2%).

Öz

Amaç: Bu çalışmada anormal uterin kanama şikayetiyle gelen hastalar retrospektif olarak olarak incelenmiştir. Elde edilen verilerin histopatolojik ve klinik özelliklerinden yola çıkarak "yaş, materyal tipi, klinik bulgular, klinik ön tanı ve histopatolojik tanı parametreleri literatür bulguları ile farklılık gösteriyor mu?" sorusuna istatiksel olarak cevap aramak amaçlanmıştır.

Gereç ve Yöntemler: Son 5 yılda (2017-2022) gönderilen 2000 adet endometrial örnek taranmıştır ve uygun parametrelere göre filtrelenmiştir. Verilerin istatistiksel anlamlılığı Ki-Kare ile ölçülmüştür.

Bulgular: Çalışmadaki 1815 hastanın yaşları 19-86 aralığındadır. Endometrial örnekleme endikasyon sınıflandırması: menometroraji/menoraji (%49,2), endometrial polip (%19,5) postmenopozal kanama (%18), endometrial hiperplazi (%14,6) ve leiomyom (%2,8) şeklindedir. Menstrüel durumlarına göre; 45 yaş altındaki hastalar premenopoz (%51,6), 45-51 yaş arası hastalar perimenopoz (%25,39), ve 51 yaş ve üstü hastalar postmenopoz (%22,97) şeklinde üç gruba ayrılmıştır. Histopatolojik olarak, benign histopatolojik bulgular arasında endometrial polip (%61,9), proliferatif/sekretuar endometrium (%12), atrofik endometrium (%6,6) ve kronik endometrit (%0,2) bulunmuştur. Pre-malign bulgularda, atipisiz endometrial hiperplazi (%9), ve atipik endometrial hiperplazi (%0,6), malign bulgular arasında ise adenokarsinom (%1,2) saptanmıştır.

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Conclusion: An in-depth answer was challenging due to insufficient data documentation in the current practice. Nevertheless, we have presented the concordance for the four major pathologies and their distribution in the patient population. Our study has shown that endometrial polyps are the pathology most frequently diagnosed correctly. Our study detected endometrial cancer predominantly in the postmenopausal group, emphasising the importance of endometrial sampling in this group. This aligns with the existing literature.

Keywords Endometrium · histopathology · diagnosis

Sonuç: Güncel klinik ve laboratuvar pratiğinin sebep olduğu yetersiz veri dokümantasyonu nedeniyle çalışmamızda derinlemesine bir yanıt vermek zor olmuştur. Buna rağmen çalışmamız dört ana patolojinin ön tanı-histopatolojik tanı arasındaki uyumunu ve genel popülasyondaki dağılımını sunmuştur. Endometrial poliplerin en sık doğru teşhis edilen patoloji olduğunu göstermiştir. Çalışmamızda endometrial kanserin ağırlıklı olarak postmenopozal grupta görüldüğü tespit edilmiş olup bu durum, bu grupta endometrial örnekleme yapılmasının önemini vurgulamaktadır. Bu bulgu mevcut literatürle uyumludur.

Anahtar Kelimeler Endometrium · histopatoloji · tanı

INTRODUCTION

Abnormal uterine bleeding (AUB) is any bleeding other than menstrual bleeding (1). AUB aetiology depends on the patient being in a premenopausal, perimenopausal, or postmenopausal period (2). Patients who presented with AUB were reviewed retrospectively in this study. Based on the pathological and clinical features of the data, a statistical answer is sought to the question: "Are there any differences between literature results and age, preliminary diagnosis, type of the material sent, clinical findings, and histopathological diagnosis parameters?".

MATERIAL AND METHODS

For this study, 2,000 endometrial samples sent to the Private Polat Pathology Laboratory and Patomed Laboratory over the past five years (2017-2022) were screened. These samples were filtered based on specific parameters, including age, clinical diagnosis, clinical findings, type of submitted material, and histopathological diagnosis. Ultimately, 1,815 patients were determined to meet the study criteria. Samples obtained through dilation and curettage (D&C), pipelle sampling, and hysteroscopy were used. Cases involving pregnancy were excluded. The selected samples were recorded in an Excel database using Medware software, related tables were organised, and statistical analyses were subsequently conducted. Patients were divided into three groups based on menopausal status, as hormonal fluctuations associated with menopause significantly influence endometrial physiology and lead to different types of pathologies. Patients without specific menopausal information were classified by age: those under 45 were categorised as premenopausal, those aged 45 to 51 as perimenopausal, and those aged 51 and above as postmenopausal (3-7). The distribution of the preliminary and histopathological diagnoses was analysed separately and stratified by menopausal status, resulting in six distinct groups. If a preliminary diagnosis report specified only AUB or postmenopausal bleeding (PMB) without identifying specific underlying causes, this was interpreted as the absence of a specific preliminary diagnosis. Consequently, patients were categorised solely as AUB or PMB cases unless they had additional conditions, such as AUB with polyps, in which case they were classified as polyp patients. Since this situation applied to both AUB and PMB patients, it was assumed they shared similar symptomatology, with clinical naming reflecting their menopausal status. During the distribution analysis (Chi-square) of the dataset, these cases were counted as a single preliminary diagnosis. However, in the discussion and review sections of the study, they were ultimately recognised as two distinct preliminary diagnoses. The five most prevalent diagnoses were identified in both the preliminary and histopathological categories, while the remaining diagnoses were consolidated into a single category, reducing the total number of diagnoses for both groups to six. Patients were further divided into three subgroups based on their menopausal status: premenopausal, perimenopausal, and postmenopausal. Changes in frequencies for both preliminary and histopathological diagnoses were compared across these groups, and Chi-square (χ^2) and p-values were calculated. The p-value was found to be <0.001, indicating that the changes were statistically significant. The Istinye University Human Research Ethics Committee approved this study (Date: 02.02.2023 Protocol No: 23-06). The study was conducted according to the principles of the Declaration of Helsinki.

RESULTS

The study included 1,815 patients, with an average age of 45.10 years ranging from 19 to 86 years. (19 to 86 years). Among the population, 937 patients were identified as premenopausal, 461 as perimenopausal, and 417 as postmenopausal. The Chi-square (χ^2) value for the preliminary diagnosis was calculated as 137.5, while it was 418.7 for the histopathological diagnosis.

Preliminary diagnoses

Premenopausal group: AUB was the most common diagnosis (587 cases, 62.64%). Endometrial polyps (243 cases, 25.93%), endometrial hyperplasia (90 cases, 9.6%), leiomyoma (2.02%),

tamoxifen use (0.96%), findings within normal limits (0.85%), pelvic inflammatory disease (0.53%), adenomyosis (0.10%), and endometrial cancer (0.64%) were also diagnosed (Table 1).

Perimenopausal group: AUB was again the most frequently diagnosed condition (306 cases, 66.37%) followed by endometrial hyperplasia (77 cases, 16.7%) and endometrial polyps (69 cases, 14.96%). No explicit malignant tumours were reported in this group (Table 1).

Postmenopausal group: PMB was the predominant diagnosis (327 cases, 78.41%). Endometrial hyperplasia (98 cases, 23.50%), endometrial polyps (42 cases, 10.07%), leiomyoma (3.35%), tamoxifen use (1.67%), PID (0.23%), and endometrial cancer (4.07%) were the other diagnoses (Table 1).

Table 1. Distribution of preliminary diagnoses by clinical stage

Diagnosis	Pre menopausal	Peri menopausal	Post menopausal	Total
AUB	587 (62.64%)	306 (66.37%)	0	893
Endometrial polyp	243 (25.93%)	69 (14.96%)	42 (10.07%)	354
PMB	0	0	327 (78.41%)	327
Endometrial hyperplasia	90 (9.6%)	77 (16.7%)	98 (23.50%)	265
Endometrial cancer	6 (0.64%)	9 (1.3%)	30 (4.07%)	45
Leiomyoma	19 (2.02%)	18 (3.9%)	14 (3.35%)	51
Breast cancer	10 (1.06%)	3 (0.65%)	13 (3.11%)	26
Tamoxifen use	9 (0.96%)	1 (0.21%)	7 (1.67%)	17
WNL	8 (0.85%)	1 (0.21%)	0	9
PID	5 (0.53%)	1 (0.21%)	1 (0.23%)	7
Adenomyosis	1 (0.10%)	0	0	1
Total	978	485	532	1815

AUB: Abnormal uterine bleeding, PMB: Postmenopausal bleeding, WNL: Findings within normal limits, PID: Pelvic inflammatory disease

Histopathological diagnoses

Premenopausal group: In this group, endometrial polyps (651 cases, 69.47%), secretory endometrium (96 cases, 10.24%), and endometrial hyperplasia without atypia (77 cases, 8.21%), atypical hyperplasia of the endometrium (3 cases, 0.32%), and adenocarcinoma (2 cases, 0.21%) were observed (Table 2).

Perimenopausal group: In this group, endometrial polyps (265 cases, 57.48%), endometrial hyperplasia without atypia (64 cases, 13.88%), secretory endometrium (49 cases, 10.62%), WNL (4.77%), irregular proliferative endometrium (4.55%), proliferative endometrium (4.12%), insufficient material (2.81%), atrophic endometrium (1.08%), submucosal leiomyoma (0.86%), iatrogenic causes (0.65%), necrotising granulomatous endometrium (0.21%), PID (0.21%), adenocarcinoma (3 cases, 0.65%), and atypical hyperplasia of the endometrium (2 cases, 0.43%) (Table 2) were diagnosed.

Postmenopausal group: In this group, endometrial polyps (208 cases, 49.88%), atrophic endometrium (111 cases, 26.61%), insufficient material for pathological examination (33 cases, 7.91%), adenocarcinoma (17 cases, 4.07%), and atypical hyperplasia of the endometrium (7 cases, 1.67%) were found (Table 2).

Table 2. Distribution of histopathological diagnoses by clinical stage

Histopathological diagnosis	Pre menopausal	Peri menopausal	Post menopausal	Total
Endometrial polyp	651 (69.47%)	265 (57.48%)	208 (49.88%)	1124
Endometrial hyperplasia without atypia	77 (8.21%)	64 (13.88%)	23 (5.51%)	164
Secretory endometrium	96 (10.24%)	49 (10.62%)	11 (2.63%)	156
Atrophic endometrium	5 (0.53%)	5 (1.08%)	111 (26.61%)	121
Insufficient material for the pathological examination	17 (1.81%)	13 (2.81%)	33 (7.91%)	63
Irregular proliferative endometrium	27 (2.88%)	21 (4.55%)	6 (1.43%)	54
WNL	29 (3.09%)	22 (4.77%)	4 (2.92%)	55
Proliferative endometrium	37 (3.9%)	19 (4.12%)	6 (1.43%)	62
Endometrioid adenocarcinoma NOS	2 (0.21%)	3 (0.65%)	17 (4.07%)	22
Submucosal leiomyoma	9 (0.96%)	4 (0.86%)	3 (0.71%)	16
Atypical hyperplasia of the endometrium	3 (0.32%)	2 (0.43%)	7 (1.67%)	12
PID	2 (0.21%)	1 (0.21%)	4 (0.95%)	7
Chronic endometritis	3 (0.32%)	1 (0.21%)	0	4
Iatrogenic	7 (0.74%)	3 (0.65%)	0	10
Total	958	469	433	1815

WNL: Findings within normal limits, PID: Pelvic inflammatory disease

In this research, 17 of 1815 patients who presented to the clinic had a history of tamoxifen use. The histopathological outcomes of these 17 patients were evaluated; 5 patients had endometrial polyps, 4 patients had endometrial atrophy, 3 patients had findings within normal limits, 2 patients had secretory endometrium, 2 patients had insufficient

endometrial material, and 1 patient was clinically diagnosed with pelvic inflammatory disease (PID) according to the clinical data.

Among the various pathologies associated with AUB, the concordance between histopathological diagnoses and clinical preliminary diagnoses was assessed across the four most prevalent conditions in the population. For endometrial polyps, consistent preliminary and histopathological diagnoses were demonstrated in 300 patients. In the cases of both atypical hyperplasia of the endometrium and endometrial hyperplasia without atypia, "endometrial hyperplasia" from the preliminary diagnosis was designated as the matching condition, resulting in concordant diagnoses in 70 patients. Regarding submucosal leiomyoma, a consistent preliminary diagnosis of "Leiomyoma" was identified in 7 patients as the matching indication. Finally, for adenocarcinoma, 7 patients exhibited consistent preliminary diagnoses, with "Endometrial Cancer" recognised as the corresponding indication from the preliminary diagnosis (Table 3).

Table 3. Distribution of concordance

Overall diagnosis	Observed agreement	Preliminary diagnoses	Agreement percentage
Endometrial polyp	300	354	84.75%
Endometrial hyperplasia	70	265	26.42%
Submucosal leiomyoma	7	51	13.73%
Endometrial cancer	7	45	15.56%
WNL	5	9	55.56%
Premenopause diagnosis			
Endometrial polyp	216	243	88.89%
Endometrial hyperplasia	34	90	37.78%
Submucosal leiomyoma	3	19	15.79%
Endometrial cancer	1	6	16.67%
WNL	5	8	62.50%
Premenopause diagnosis			
Endometrial polyp	56	69	81.16%
Endometrial hyperplasia	23	77	29.87%
Submucosal leiomyoma	3	18	16.67%
Endometrial cancer	2	9	22.22%
Postmenopause diagnosis			
Endometrial polyp	28	42	66.67%
Endometrial hyperplasia	13	98	13.27%
Submucosal leiomyoma	1	14	7.14%
Endometrial cancer	4	30	13.33%

WNL: Findings within normal limits

DISCUSSION

AUB is a medical term to describe any bleeding that cannot be categorised within normal menstrual bleeding criteria. AUB consists of gynaecological and non-gynaecological aetiologies. The organic causes of AUB can be categorised as genital system-related disorders, systemic conditions, and iatrogenic causes (1).

Aetiologies of AUB differ according to the patients' premenopausal, perimenopausal, or postmenopausal status (2). The most common endometrial sampling indication for women aged over 45 years is AUB, whereas for women under 45 years, it is anovulatory bleeding due to exposure to unopposed oestrogen (8). Histopathologically, endometrioid adenocarcinoma is the most frequent subtype seen among endometrial cancer cases (9). The highest risk for endometrial cancer is found in the postmenopausal group. Consequently, in terms of PMB cases, endometrial sampling and evaluation should be carried out (10).

Clinicians use various endometrial sampling techniques. These techniques are divided into three main groups: D&C, aspiration technique, and hysteroscopy (11). 'Light Microscopy' is the golden standard technique for the histopathological evaluation of endometrial cancer and other endometrial pathologies. This technique has a high sensitivity for the diagnosis of endometrial hyperplasia and carcinomas (12, 13).

Endometrial polyp: Endometrial polyps are soft, fleshy, intrauterine growths that consist of the endometrial glands, stroma, and surface epithelium (3). The reported prevalence in the literature generally ranges from 4.6% to 34.5% (10, 14-19). Although reported rates vary in the literature, these findings are significantly elevated. Ozbilgec et al. and Celik et al. found that an endometrial polyp was the most frequent histopathological finding in both the premenopausal and postmenopausal groups, which aligns with our findings (9, 20). Some authors separated their results according to

menopausal state. Celik et al. and Esercan et al. subclassified their results as non-postmenopausal and postmenopausal. They found polyp incidence rates to be 74.9% and 15% in the pre-perimenopausal group and 25.1% and 1.8% in the postmenopausal group, respectively (9, 21). When our data are compared to studies that evaluate only the postmenopausal group, our results are also higher than those reported in the literature. Ates et al. found a 32% polyp rate, whereas Dogru et al. found a polyp rate of 23.7% (22, 23). In an older study by Gul et al., the result was reported as 8.6% (24).

Secretory and proliferative endometrium: During the proliferative phase, the endometrium undergoes glandular hypertrophy, stromal matrix expansion, and terminal arteriole extension into the lumen (25). In the secretory phase, mitotic activity decreases, the glands become more convoluted, and the stroma becomes oedematous and decidualize (26). In our study, proliferative and secretory endometrium were found in 3.41% and 8.59% of patients, respectively, lower than reported in the literature. Akçay Çelik et al. reported rates of 16% and 14%, Aker et al. 21% and 20%, and T. van den Bosch et al. 54% (9, 17, 27).

Atypical hyperplasia of the endometrium and endometrial hyperplasia without atypia: Endometrial hyperplasia is defined as an increased gland-to-stroma ratio and the proliferation of glands with irregular shapes and sizes compared with the normal proliferative endometrium (28). The World Health Organisation's 2020 classification system for endometrial hyperplasia has two categories: 1) Endometrial hyperplasia without atypia and 2) Atypical hyperplasia of the endometrium (29). In our study, endometrial hyperplasia was detected in 176 cases (9.69%), with atypia identified in 6.8% of these cases. Previous studies have reported hyperplasia rates of 5.35%–9.2%, with atypia present in 9.7%–12% of those (10, 17).

Irregular proliferative endometrium: Irregular proliferative endometrium displays enlarged, irregularly shaped glands within a compact stroma, which are more numerous compared to normal proliferative endometrium (26). Morphologically, it lies between normal proliferation and endometrial hyperplasia (9). In our study, it was found in 2.97% of cases, lower than reported in the literature. Previous studies reported the following rates: 7.4%-16.1% (9, 20). In our study, the majority of patients with this diagnosis were in the premenopausal group, whereas another study reported a predominance in the perimenopausal group (30).

Endometrial cancer: It is the most common gynaecological cancer and is mostly in the type of endometrioid adenocarcinoma; 80% of the cases are seen in post-menopausal period while 95% of patients present with abnormal uterine bleeding (18). According to other research, an increased incidence of premalignant/malignant lesions is shown within the postmenopausal group (9). Our study also aligns the outcome as the highest incidence of endometrial cancer in the postmenopausal group. In the literature, endometrial cancer incidence rates are between 0.4% and 1.9% (21, 23). In one study, patients diagnosed with endometrial cancer fall into the premenopausal and perimenopausal period, which is contradictory to other studies (21). With regard to the subtypes of cancer; a research demonstrated that among 14 cases, endometrioid adenocarcinoma (n=6) was the most frequently diagnosed subtype (23), which is parallel to our research.

Atrophic endometrium: Atrophy of the endometrium, which is frequently associated with postmenopausal bleeding, occurs due to the prolonged absence of endogenous or exogenous oestrogenic stimulation (30). In the literature, clinical studies report an atrophy rate of 40.1%, which surpasses the polyp percentage (27.3%) in our research (19). Furthermore, in another study, the atrophy incidence (3.77%) was significantly lower than our results (18).

Insufficient for pathological examination: Inadequate material for pathological examination is a common situation in endometrial sampling. There might be numerous reasons. Factors such as the physician's experience and the sampling method can affect the outcome. Nulliparity and increased age are also some factors that cause inadequate sampling (31). Ates et al. demonstrated in their studies that menopause status negatively affects endometrial biopsy sampling (22). In the literature, the rate changes between 0.9% and 31% (10, 11, 18, 20, 23, 24, 31-33). Our results align with the literature, reinforcing the correlation between menstrual status and the rate of "inadequate material for pathological examination."

Iatrogenic: AUB due to iatrogenic causes is a common entity. The drugs are mostly associated with bleeding as follows: Gonadal steroids, anticoagulants, and dopamine antagonists (12, 20). Bleeding due to progestins occurs when there is a high progesterone-oestrogen ratio. The endometrium becomes atrophic or ulcerated in the absence of an oestrogenic component, which makes it prone to bleeding (34). According to our study, the most common iatrogenic cause was exogenous progestin use. There is no patient found in the postmenopausal group.

Submucosal leiomyoma: The submucosal leiomyoma rate ranges from 1.6% to 3.5% in the literature (10, 21, 23, 35). Dogru et al. and Esercan et al. reported similar rates that were higher than those observed in our study (21, 23). Patrizi et al. who conducted a similar study examined both leiomyoma and endocervical polyps together, found a 2.23% rate in the premenopausal group and 3.24% in the postmenopausal

group (35). Among the 51 pre-diagnosed leiomyomas, only 16 submucosal cases met the inclusion criteria in our study, leading to a slightly lower leiomyoma rate compared with the literature.

Endometritis: Endometritis is a medical term describing an acute or chronic inflammation of the endometrium that can be attributed to infectious causes or noninfectious epithelial microerosions. Genital tuberculosis generally occurs due to the reactivation and dissemination of a primary infection (36). In this research, four patients were diagnosed with chronic endometritis, two with necrotising granulomatous endometritis due to genital tuberculosis, and two with nonspecific endometritis. Other medical studies indicate that chronic endometritis is frequently caused by infectious aetiologies, with the highest incidence observed in the premenopausal group, coinciding with this study. While one study demonstrates that 2.8% of patients were premenopausal and 0.5% were postmenopausal, another research shows that 1.3% of cases belong to the under-50-year age group and 0.5% to the over-50-year age group (9, 21).

Tamoxifen: Tamoxifen is a nonsteroidal anti-oestrogenic agent commonly used as part of the treatment regimen for breast cancer (37). According to the studies, the incidence of endometrial cancer is two to three times higher in patients using tamoxifen compared to nonusers (38-40). While other studies indicate that tamoxifen use in 21 of 799 patients, this number is nearly three times higher than the number found in our research (23).

Limitations: During the process of organising the study data, various challenges were encountered due to obtaining patient data from two different pathology laboratories. Terminological differences in patient records complicated data processing. The biggest pitfall of this study was the inadequate reporting of preliminary diagnoses by clinicians. The main cause of AUB was not elaborated in a significant portion of the study group. In addition, the preliminary reports were also insufficient for the analysis of the sampling method.

CONCLUSION

The question we addressed in our study was "Are there any differences between the literature results and parameters such as age, preliminary diagnosis, type of material sent, clinical findings, and histopathological diagnosis?" We could identify consistency in certain diseases/pathological conditions, but this was not possible for other pathologies. The analysis remained too superficial for conditions such as polyps, cancer, and leiomyomas. The reasons are multifactorial: pathologists may have diagnostic biases (e.g., favouring polyps), and there is often insufficient preliminary reporting by clinicians. We believe this is because, in the current clinical landscape in Türkiye, both economic and non-economic factors often lead clinicians to provide incomplete or informal preliminary diagnoses, which can impact the documentation of clinical findings. Unfortunately, our study could not provide a satisfactory in-depth answer. The current documentation practices in Türkiye do not yield sufficient data for such analysis. Despite this, we found an 84.7% concordance rate for endometrial polyps, which increased to 88.8% in the premenopausal group across the four diagnoses. The high concordance observed for polyps contrasts with the significantly lower concordance rate for hyperplasia (26.42%), indicating a notable diagnostic mismatch. Other pathologies showed inconclusive levels of concordance due to the low sample size and statistical limitations. Another key finding of the study was the predominant detection of endometrial cancer in the postmenopausal group, highlighting the importance of endometrial sampling in this population. This aligns with the existing literature. While we believe that the results of our study will contribute to the literature and be beneficial to gynaecologists and pathology specialists working in this field, we would like to emphasise the importance of consistent use of terminology in clinical findings, sampling methods, and preliminary diagnoses, particularly in retrospective and/or prospective studies.

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istinye University Human Research Ethics Committee (Date: 02.02.2023, No: 23-06).

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