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The Effect of Intrauterine Device on the Quality of Sampling Material in Patients Undergoing Endometrial Biopsy

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Abstract: Objective: This study aims to evaluate the effect of intrauterine device (IUD) use on the quality and adequacy of sampling material obtained during endometrial biopsy. The study compares the histopathological adequacy of endometrial samples between IUD users and non-users, identifying potential diagnostic challenges and implications for clinical practice. **Methods:** The study was conducted on 409 women aged 25–55 who presented with abnormal uterine bleeding (AUB) to the Gynecology and Obstetrics Outpatient Clinic at Kayseri City Hospital between April 1, 2021 and April 1, 2023. The patients were divided into two groups: **IUD users (n=215)** and **non-IUD (n=194).** Endometrial biopsies were obtained using the Pipelle curette technique without anesthesia, preserved in a 10% formalin solution, and analyzed for pathological categories and diagnostic adequacy. Pathological categories, endometrial thickness, and other parameters were statistically compared between the groups. **Results:** The proportion of unclassifiable pathological categories was significantly higher in IUD users (63.93%) compared to non-IUD (36.05%) ($p=0.013$). Additionally, a negative correlation was observed between pathological category and endometrial thickness ($r=-0.3147, p<0.001$), suggesting that thinner endometrium was associated with more advanced pathological changes. However, no significant association was found between IUD use and endometrial thickness ($p=0.073$). **Conclusion:** The findings indicate that IUD use may affect the diagnostic adequacy of endometrial biopsy specimens, likely due to inflammatory or structural changes in the endometrium. These results underlines the importance of considering IUD-related alterations when interpreting biopsy findings. Further research is needed to refine diagnostic approaches and better understand the clinical implications of these effects.

Keywords: intrauterine device; endometrial biopsy; abnormal uterine bleeding; inflammation; pathology

1. Introduction

Abnormal uterine bleeding (AUB) is a common clinical issue encountered in women of reproductive age and significantly affects their quality of life. AUB encompasses menstrual irregularities, increased bleeding volume, or bleeding occurring outside the menstrual cycle, and is often associated with hormonal imbalances, structural anomalies, infections, or endometrial pathologies [1]. In 2011, the International Federation of Gynecology and Obstetrics (FIGO) developed the PALM-COEIN system (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia – Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not yet classified) to

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systematically classify the etiological causes of AUB. This system has improved the diagnostic and therapeutic approaches to AUB [2,3].

Endometrial biopsy is a frequently used minimally invasive diagnostic method in gynecological practice to assess pathological changes in the endometrium. It is particularly valuable for diagnosing endometrial hyperplasia, polyps, infections, dysfunctional uterine bleeding, and malignancies [3]. Histopathological analysis of biopsy specimens enables accurate and precise diagnosis. However, the amount and quality of the obtained samples are critical for diagnostic reliability. Inadequate or poor-quality samples can hinder the identification of pathologies and lead to unnecessary interventions [4].

IUDs are a widely used, effective, and reliable method of contraception for millions of women worldwide. Despite their efficacy and widespread use, the biological and structural changes they induce in the uterine environment remain a subject of investigation. Limited but important findings in the literature suggest that IUDs may influence the quality of endometrial biopsy specimens [5]. Some studies have proposed that IUDs may enhance inflammatory responses and cause structural changes in the endometrium, potentially altering the diagnostic properties of biopsy samples [6,7]. However, the clinical implications and extent of these effects on biopsy quality remain limited and controversial.

The effects of IUDs on the uterus are associated with mechanical irritation, mucosal changes, localized inflammation, and cytological alterations. For instance, some studies have shown that IUD use can trigger significant inflammatory responses and tissue changes in the endometrium, which may affect the diagnostic accuracy of biopsy specimens [8,9]. Furthermore, IUDs may mask the histological diagnosis of conditions such as endometrial hyperplasia or malignancies, leading to false-positive or false-negative results [10]. However, these findings lack consistency across different types of IUDs (hormonal or copper-based) and patient populations.

Another critical aspect is the adequacy of endometrial biopsies in the presence of IUDs. The method and tools used during biopsy play a decisive role in obtaining sufficient and high-quality samples despite the presence of an IUD. Modern biopsy tools, such as Pipelle cannulas and vacuum aspiration devices, demonstrate varying levels of efficiency in patients with IUDs [11]. Therefore, systematically examining the impact of IUDs and biopsy techniques on sample adequacy is crucial for improving clinical practice.

This study aims to evaluate the effect of intrauterine device (IUD) use on the quality and adequacy of sampling material obtained during endometrial biopsy. The study compares the histopathological adequacy of endometrial samples between IUD users and non-users, identifying potential diagnostic challenges and implications for clinical practice.

2. Materials and Methods

2.1. Study Design

This study was designed as a retrospective observational study conducted at the Gynecology and Obstetrics Outpatient Clinic of Kayseri City Hospital between April 1, 2021, and April 1, 2023. The research aimed to evaluate the effect of intrauterine device (IUD) use on the adequacy and quality of endometrial biopsy specimens.

Ethics committee permission was granted by Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee with decision number 862, dated 11.07.2023. All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional research committee, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards.

2.2. Participants

The study included women with AUB who underwent endometrial biopsy, categorized into IUD users (n=215) and non-IUD (n=194). Inclusion criteria were as follows: being between 25 and 55

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years old, presenting with AUB, and providing biopsy specimens suitable for pathological evaluation. Exclusion criteria included patients whose IUDs were removed during the procedure, those with a history of endometrial hyperplasia or malignancy treatment, positive pregnancy tests, or cases with insufficient biopsy material that required re-biopsy outside the study protocol.

This study was conducted retrospectively using medical data obtained from the clinical records of women who presented to the hospital. Since the study relied solely on pre-existing patient records without any direct patient intervention or contact, obtaining additional informed consent from the individuals whose records were accessed was deemed unnecessary by the ethics committee. The data files were evaluated for research purposes between 1st and 31st August 2023.

2.3. Procedures

A total of 409 patients' data were retrospectively analyzed. Endometrial biopsies were obtained using Pipelle curettes without the use of any anesthetic agents in outpatient settings. The specimens were preserved in 10% formalin solution and submitted to the Pathology Department of Kayseri City Hospital for evaluation. Biopsy specimens were analyzed for diagnostic adequacy and compared between IUD users and non-IUD.

Biopsies deemed inadequate for diagnosis were excluded from the study protocol, and treatment plans for these patients were arranged separately. Prophylactic antibiotic therapy was prescribed to all patients' post-procedure.

2.4. Measures

Histopathological evaluation of endometrial biopsy specimens categorized into three main categories based on hormonal effects and pathological findings. This classification ensured consistent diagnostic analysis of the specimens. The first category included endometrial conditions under estrogen dominance, such as proliferative endometrium, disordered proliferation, non-atypical endometrial hyperplasia, polyps, and estrogen-influenced endometrium. These findings typically indicated hormonal stimulation during the estrogen phase. The second category represented progesterone dominance, including endometrium under gestagen influence, glandular-stromal breakdown, and secretory endometrium. These findings were characterized by stromal and glandular changes typical of the luteal phase. The third category consisted of unclassifiable cases, where specific hormonal influences were indeterminate, or insufficient biopsy material was obtained. This group included findings such as endometritis, inadequate samples, and signs of atrophy, often associated with inflammation, atrophy, or diagnostic challenges.

2.5. Data analysis

A post hoc power analysis was performed using the G*Power software for the chi-square test evaluating the impact of IUD use on pathological categories. With a total of 409 individuals distributed between IUD users and non-IUD, the effect size (w) was calculated based on the observed significant differences ($p=0.013$). The statistical power ($1-\beta$) was determined to be 88.4% at a significance level ($\alpha=0.05$), indicating that the sample size was sufficient to detect the effects of IUD use on pathological categories.

Data were analyzed using SPSS (Statistical Package for the Social Sciences) software, version 25.0. Continuous variables were compared between groups using the Student's t-test or the Mann-Whitney U test, depending on the data distribution. Normality was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk tests. Normally distributed data were reported as mean ± standard deviation ($\bar{x}\pm SD$), while non-normally distributed data were expressed as median (min–max).

Categorical variables were compared using the chi-square test to evaluate the significance of differences between observed and expected frequencies. Relationships between variables were analyzed using Pearson correlation analysis, with the correlation coefficient (r) indicating the direction and strength of the relationship, and p-values assessing statistical significance.

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Additionally, the Student's t-test was used to evaluate the relationship between IUD use and pathological categories. A significance level of $p<0.05$ was considered statistically significant.

3. Results

This study was conducted retrospectively on 409 women who presented with AUB to the Gynecology and Obstetrics Outpatient Clinic at Kayseri City Hospital between April 1, 2021 and April 1, 2023. Demographic characteristics, the pathological adequacy of endometrial biopsy specimens, and relevant variables were statistically analyzed.

No statistically significant differences were found between IUD users and non-IUD in terms of demographic characteristics such as age, parity, vaginal delivery, cesarean delivery, or endometrial thickness ($p>0.05$) (Table 1).

Table 1. Demographic Data of Individuals Using and Not Using IUDs.

Variables	IUD	Non-IUD	p
Age	42 (40.36-42.14)	40 (39.45-41.47)	0.166
• 25-34	52 (24.2%)	51 (26.3%)	0.678
• 35-44	96 (44.7%)	75 (38.7%)	0.214
• 45-55	67 (31.1%)	68 (35.0%)	0.476
Parity	3 (1-9)	3 (1-9)	0.660
Vaginal Delivery	2 (0-9)	2 (0-9)	0.440
Cesarean Delivery	0 (0-4)	0 (0-5)	0.169
Endometrial Thickness	9.7 (4-25)	10 (2-25)	0.226

* Student's t-test or Mann-Whitney U test (continuous variables), percentage comparisons.

A significant difference was observed between IUD users and non-IUD in terms of pathological categories ($p=0.013$). The proportion of individuals in the third group was higher among IUD users (63.93%) compared to non-IUD (36.05%). However, no significant differences were found between IUD users and non-IUD proportions ($p>0.05$) (Table 2).

Table 2. Pathology Evaluation in Individuals Using and Not Using IUDs.

Pathology Category	IUD	Non-IUD	p
Category 1 (Estrogen Dominance)	91 (%48.14)	98 (%51.85)	0.76
Category 2 (Progesterone Dominance)	46 (%46.93)	52 (%53.06)	0.65
Category 3 (Unclassifiable)	78 (%63.93)	44 (%36.05)	**0.013****

* Chi-square test.

No statistically significant differences between IUD and Non-IUD users in the distribution of Category 1 (Estrogen Dominance) and Category 2 (Progesterone Dominance) across all age groups ($p > 0.05$). However, in the 45-55 age group, the proportion of individuals classified under Category 3 (Unclassifiable) was significantly higher among IUD users ($p = 0.048$). This finding suggests that IUD use may be associated with a greater prevalence of atrophic or insufficient endometrial samples in postmenopausal individuals (Table 3).

Table 3. Pathological Findings by Age Group and IUD Usage.

Age Group	IUD Users (n, %)			Non-IUD Users (n, %)			p
	Category1	Category2	Category3	Category1	Category2	Category3	
25-34	22 (%37.9)	16 (%27.6)	15 (%25.8)	20 (%36.4)	14 (%25.4)	13 (%23.6)	0.72
35-44	26 (%38.8)	20 (%29.9)	19 (%28.4)	24 (%37.5)	18 (%28.1)	17 (%26.6)	0.68
45-55	19 (%36.5)	14 (%26.9)	22 (%42.3)	21 (%38.2)	16 (%29.1)	20 (%36.3)	**0.048**

* Chi-square test.

A weak, negative, and statistically significant correlation was found between pathology category and endometrial thickness ($r=-0.31$, $p<0.001$). Patients with thinner endometrial structures tended to

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exhibit more advanced pathological findings. A positive and statistically significant relationship was identified between IUD use and pathology category (r=0.21, p=0.01). The use of IUDs was observed to influence the diagnostic categories in the pathological evaluation of endometrial biopsy material. Specifically, a higher proportion of unclassifiable pathology categories was detected among individuals using IUDs.

A negative correlation was identified between IUD use and endometrial thickness (r=−0.62). However, this relationship was not statistically significant (p=0.073). This finding suggests that IUD use doesn't have a significant effect on endometrial thickness. Furthermore, no significant correlation was found between endometrial thickness and vaginal delivery, cesarean delivery, or parity (p>0.05) (Table 4).

Table 4. Correlation Between Variables.

Variables (n=409)	Correlation Coefficient (r)	p
Pathology Category - Endometrial Thickness	-0.31	**<0.001****
Pathology Category - Parity	0.04	0.357
Pathology Category - IUD	0.21	**0.01***
IUD - Endometrial Thickness	-0.62	0.073
Endometrial Thickness - Vaginal Delivery	-0.02	0.632
Endometrial Thickness - Cesarean Delivery	0.021	0.661
Endometrial Thickness - Parity	-0.01	0.783

* Pearson Correlation Analysis, Student t-test.

In summary, the results of this study indicate that both IUD use and age have a significant impact on endometrial pathology. The stratified analysis demonstrated that while estrogen- and progesterone-dominant pathologies were distributed similarly between IUD users and non-users, unclassifiable pathologies—including chronic endometritis, atrophic changes, and inadequate biopsy samples—were more frequently observed in IUD users, particularly in older age groups. The influence of age was evident, with a higher prevalence of unclassifiable findings among women over 45, suggesting the role of age-related hormonal changes in endometrial alterations. These findings emphasize the importance of considering both age and IUD status in the pathological evaluation of endometrial biopsies, which may enhance the accuracy of diagnosis and improve clinical management strategies.

4. Discussion

This study retrospectively evaluated the impact of IUD use on the diagnostic adequacy and pathological assessment of endometrial biopsy samples. Our findings suggest that IUD users exhibit distinct histopathological patterns, with a higher prevalence of advanced pathology categories compared to non-users. Additionally, IUD use appears to influence the adequacy of biopsy materials, potentially complicating diagnostic interpretation. These results are consistent with existing literature and contribute valuable insights into the histological and biological changes induced by IUDs in endometrial tissue, emphasizing the need for refined biopsy evaluation criteria in this patient population.

IUDs are widely used as an effective contraceptive method in women's health. However, the physical and biochemical changes they induce in the intrauterine environment can have significant effects on endometrial tissue. Studies in the literature have reported that IUD use triggers inflammatory responses, increases cytokine release, and leads to mucosal changes [11]. For example, Thiruvalluvan et al. (2018) stated that IUDs cause local inflammation in the intrauterine environment, leading to cellular modifications in the endometrium [12]. Similarly, in our study, more advanced changes in the distribution of pathology categories were observed among individuals using IUDs. Specifically, the significantly higher proportion of unclassifiable pathology categories in individuals using IUDs suggests that inflammatory processes may contribute to these pathological changes.

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The adequacy of samples obtained during endometrial biopsy and their pathological analysis are critical factors directly influencing the success of the diagnostic process. Rowlands et al. (2019) reported that IUD use induces changes in endometrial tissue, such as edema, stromal alterations, and inflammatory cell infiltration, which can impact the diagnostic accuracy of biopsy materials [13]. Our findings align with these observations and further reinforce the role of IUD use in the diagnostic evaluation of biopsy materials.

In our study, a negative and statistically significant correlation was found between endometrial thickness and pathology category. This result indicates that thinner endometrial structures are associated with more advanced pathology categories. The literature underlines that endometrial thickness is a critical biological marker for identifying malignant or pre-malignant conditions [14]. For example, Critchley et al. (2020) reported that thinner endometrial structures are often associated with atrophy and malignancy [3]. Our findings support this hypothesis and indicate the need for careful histopathological evaluation in patients with thinner endometrial structures.

Although the literature evaluating the effects of IUD use on endometrial biopsy results is limited, existing studies support our findings. Başol et al. (2017) compared cervical cytology and vaginal maturation indices in women using copper and levonorgestrel-releasing IUDs, noting that both types of IUDs led to changes in the maturation of cervicovaginal epithelial cells and influenced inflammatory processes [15]. While our study did not include subgroup analyses based on IUD types, future research could benefit from examining these differences in greater detail.

In a meta-analysis by Rowe et al. (2021), IUD use was underlined as a factor affecting the adequacy of endometrial biopsy materials, particularly in premenopausal women [14]. The observation of higher pathology categories in individuals using IUDs in our study is consistent with these findings and define the importance of considering IUD use as a key factor in diagnostic processes.

This study is one of the few retrospective studies evaluating the impact of IUD use on endometrial biopsy results. One of its strengths is its large sample size (n=409) and the detailed analysis of the relationship between pathological findings and IUD use.

However, the study also has some limitations. First, the retrospective design increases the risk of bias due to a lack of standardization in data collection. Second, the lack of differentiation between types of IUDs (copper or hormonal) limits the ability to investigate the specific effects of different IUD types on endometrial biopsy outcomes. Future studies should address these limitations through prospective designs and more comprehensive analyses.

Our findings emphasize the need for careful evaluation of biopsy materials from individuals using IUDs. Specifically, inflammatory changes should be considered in diagnostic processes, and the increased likelihood of advanced pathology categories in IUD users should be acknowledged. In clinical practice, strategies to improve diagnostic accuracy in evaluating biopsy materials from IUD users should be developed, considering the potential effects of inflammatory processes.

This study underlines the potential impacts of IUD use on endometrial biopsy results and provides a valuable contribution to the literature. Our findings demonstrate that the inflammatory changes induced by IUDs in endometrial tissue should be considered in diagnostic processes. Future prospective and more comprehensive studies will help to provide a clearer understanding of the effects of IUD use on endometrial biopsy outcomes.

5. Conclusion

This retrospective study evaluated the effects of IUD use on endometrial biopsy outcomes. Higher pathology categories were observed in individuals using IUDs, suggesting that inflammatory changes may influence the diagnostic adequacy of biopsy materials. Notably, the significantly higher proportion of unclassifiable pathology categories in the IUD group supports the role of inflammation in endometrial pathological processes.

Additionally, a negative relationship was identified between endometrial thickness and pathology category, indicating that thinner endometrial structures may be associated with more

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advanced pathological changes. Although the effect of IUD use on endometrial thickness was not found to be statistically significant, further investigation with larger sample sizes is warranted to explore this relationship in greater detail.

In conclusion, this study underlines the impact of IUD use on endometrial biopsy outcomes, emphasizing the importance of considering the inflammatory changes induced by IUDs when evaluating biopsy materials. These findings provide a basis for improving diagnostic processes and guiding future research aimed at better understanding the effects of IUDs on endometrial pathology.

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Consent for publication: None.

Availability of data and material: Ethics committee permission was granted by Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee, Kayseri, Turkey. Data requests can be directed to this committee to ensure long-term accessibility and stability. Please find the contact information below: Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee. Phone: +90352 315 77 00. Email: kayserisehir@saglik.gov.tr.

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