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The Analysıs of Endometrıal Samplıng on Results Reported as Insufficıent Samples

Insufficıent Endometrıal Samplıng

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Abstract

Objectıve

The aim of this study is to evaluate the pathology results of second endometrial samplings performed in cases where the initial endometrial sampling was reported as insufficient material by the pathology unit.

Materıal Method

This study analyzed the results of 6,612 patients who underwent endometrial sampling at Prof. Dr. Cemil Taşçıoğlu City Hospital between 2019 and 2023, using the hospital's electronic record system. Data from 615 patients whose samples were reported as insufficient and 257 patients who underwent repeat procedures were included in the study. Patients were evaluated based on age, parity, menopausal status, indication for endometrial sampling, endometrial thickness, and the type of anesthesia used.

Statistical Method:

For statistical analysis, SPSS 15.0 for Windows was used. Descriptive statistics were presented as numbers and percentages for categorical variables, and as mean, standard deviation, minimum, maximum, and median for numerical variables. Since the assumption of normal distribution was not met, comparisons of numerical variables between more than two independent groups were performed using the Kruskal-Wallis test, while comparisons between two groups were conducted using the Mann-Whitney U test. Subgroup analyses were interpreted using Bonferroni correction. Proportions between groups were compared using the Chi-square test. A significance level of $p<0.05$ was considered statistically significant.

Fındıngs

The files of 6612 patients were reviewed. Pathology results of 615 (9.3%) of these patients were evaluated as inadequate specimens. According to hospital data, 257 of these 615 patients underwent repeat endometrial biopsy, 105 (40.8%) of whom had an unsatisfactory result. Of the 152 patients with an adequate sample, atrophy (34.2%), endometrial polyp (32.2%), hormonal effect (25.7%) and malignancy (7.9%) were diagnosed in the second endometrial sampling.

Conclusion

The detection of malignancy in 7.9% of patients who underwent repeat sampling after an initial insufficient endometrial pathology result highlights the importance of repeating the procedure, especially in older patients. Additionally, the fact that 40.8% of repeat samplings also resulted in insufficient specimens suggests that alternative methods should be considered for second endometrial samplings.

Keywords: Endometrial sampling, İnsufficient samplıng, endometrial malignancy

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Introduction:

There are no universally accepted pathological criteria for reporting endometrial samples with limited tissue, and there is no consensus on the clinical follow-up of patients with such samples.

Endometrial sampling is a method used to obtain endometrial tissue for histological examination in women with abnormal uterine bleeding or increased endometrial thickness [1]. This procedure is typically performed to investigate significant endometrial pathologies, including endometrial hyperplasia and endometrial carcinoma, in women with abnormally thick endometrium on imaging, atypical glandular cells on cervical smears, or postmenopausal bleeding [2,3].

Previous studies have demonstrated that the performance of endometrial sampling is comparable to dilation and curettage (D&C) or manual vacuum aspiration [4,5]. In cases of postmenopausal bleeding, endometrial sampling has been shown to have a 90% sensitivity and 99-100% specificity for diagnosing endometrial hyperplasia or endometrial cancer, comparable to D&C or hysteroscopy-guided biopsy, which are considered the reference standards [6].

A key limitation of endometrial sampling is the small volume of obtained tissue. In 6-33% of cases, endometrial sampling provides insufficient tissue for a definitive pathological diagnosis [7,8]. Among postmenopausal women who undergo endometrial sampling for abnormal uterine bleeding and receive non-diagnostic results, approximately 6% are later found to have significant endometrial lesions upon further evaluation [9,10]. Therefore, it is crucial to identify patients in whom endometrial sampling may provide insufficient tissue, as alternative endometrial evaluation methods may be more appropriate.

The aim of this study is to assess the frequency of insufficient tissue following endometrial sampling, analyze the outcomes, and evaluate predictive factors. An insufficient endometrial sample does not rule out endometrial carcinoma; therefore, additional histopathological examination is recommended.

To predict insufficient endometrial tissue among samples, seven clinical variables were analyzed, including age, parity, menopausal status, indication for endometrial sampling, use of anesthesia, endometrial thickness, and repeat endometrial sampling. In addition to the large sample size, one of the strengths of this study is the analysis of a vast amount of patient data and potential risk factors leading to insufficient sampling, allowing us to determine the predictive impact of various cofactors.

Table 1

	Age	**Gravida** n (%)		**Menapoz** n (%)		**Endometrial thickness** n (%)		**Anesthesia** n (%)		**Total n (%)**	**2nd time insufficient sample n (%)**
Indication	Mean ±SD Min-Max (Median)	Nullipar	Multipar	Premenapoz	Postmenapoz	<8 mm	≥8 mm	Local	General		
Postmenopausal bleeding	57,5±7,6 46-89 (56)	5 (2,5)	192 (97,5)	6 (3,0)	191 (97,0)	147 (74,6)	50 (25,4)	138 (70,1)	59 (29,9)	197 (32,0)	32 (30.4)
Postmenopausal fluid collection[Ø]	65,8±8,5 47-85 (67)	0 (0,0)	25 (100)	0 (0,0)	25 (100)	13 (52,0)	12 (48,0)	18 (72,0)	7 (28,0)	25 (4,1)	1 (0.9)
Increased endometrial	58,6±7,7 44-88	5 (3,5)	138 (96,5)	7 (4,9)	136 (95,1)	39 (27,3	104 (72,7	86 (60,1	57 (39,9)	143 (23,3	40 (38.0)

thickness¥	(58)					)	)	)		)		
Abnormal uterine bleeding Ø£¥	43,9±6,1 26-54 (44)	26 (51,0)	25 (49,0)	49 (96,1)	2 (3,9)	26 (51,0)	25 (49,0)	29 (56,9)	22 (43,1)	51 (8,3)	3 (2.9)	
Menometrorrhagia Ø£¥	45,1±4,8 32-60 (45)	23 (48,9)	24 (51,1)	42 (89,4)	5 (10,6)	37 (78,7)	10 (21,3)	38 (80,9)	9 (19,1)	47 (7,6)	3 (2.9)	
Endometrial polyp* # ¥	52,8±14, 0 28-78 (51)	8 (30,8)	18 (69,2)	9 (34,6)	17 (65,4)	10 (38,5)	16 (61,5)	15 (57,7)	11 (42,3)	26 (4,2)	4 (3.9)	
Premenopausal endometrial fluid collection Ø£¥	46,0±4,6 38-49 (48)	2 (40,0)	3 (60,0)	3 (60,0)	2 (40,0)	4 (80,0)	1 (20,0)	4 (80,0)	1 (20,0)	5 (0,8)	2 (1.9)	
Breast ca Ø * # £¥	50,5±9,9 34-89 (49)	40 (58,0)	29 (42,0)	25 (36,2)	44 (63,8)	35 (50,7)	34 (49,3)	45 (65,2)	24 (34,8)	69 (11,2)	15 (14.3)	
Myoma uteri Ø * # £ ¥	52,2±9,1 36-74 (51,5)	9 (23,7)	29 (76,3)	15 (39,5)	23 (60,5)	25 (65,8)	13 (34,2)	32 (84,2)	6 (15,8)	38 (6,2)	5 (4.8)	
Cervical pathology (polyps/precancerous lesions /chondyloma)* (# ¥)	55,9±8,7 41-68 (55)	3 (21,4)	11 (78,6)	4 (28,6)	10 (71,4)	14 (100)	0 (0,0)	11 (78,6)	3 (21,4)	14 (2,3)	0 (0,0)	
Total	54,6±9,8 26-89 (53)	121 (19,7)	494 (80,3)	160 (26,0)	455 (74,0)	350 (56,9)	265 (43,1)	416 (67,6)	199 (32,4)	**615**	105	
p	<0,001	<0,001		<0,001		<0,001		0,028				

Age Ø Different from postmenopausal bleeding* Different from menometrorrhagia # Different from abnormal uterine bleeding£ Different from increased endometrial thickness¥ Different from postmenopausal fluid collection

Table 2a

	Age	**Gravida** n (%)			**Menapoz** n (%)			**Endometrial thickness** n (%)			**Anesthesia** n (%)			**Total (n=152)**
histopatoloji	Ort.±SD Min-Maks (Median)	Nullipar (n=36)	Multipar (n=116)	p	Premenapoz (n=51)	Postmenapoz (n=101)	p	<8 mm (n=79)	≥8 mm (n=73)	p	Local (n=104)	General (n=48)	p	
Atrofi	57,3±8,2 34-76 (55,5)	4 (11,1)	48 (41,4)	0,001	8 (15,7)	44 (43,6)	0,001	35 (44,3)	17 (23,3)	0,006	32 (30,8)	20 (41,7)	0,188	52 (34,2)
Endometrial polip	53,8±10,6 35-77 (52)	12 (33,3)	37 (31,9)	0,872	17 (33,3)	32 (31,7)	0,837	18 (22,8)	31 (42,5)	0,009	37 (35,6)	12 (25,0)	0,195	49 (32,2)
Hormonal etki (E/P)	46,4±7,3 33-67 (45)	20 (55,6)	19 (16,4)	<0,001	26 (51,0)	13 (12,9)	<0,001	21 (26,6)	18 (24,7)	0,786	27 (26,0)	12 (25,0)	0,900	39 (25,7)
Malignite	62,3±7,3 51-73 (64,5)	0 (0,0)	12 (10,3)	0,070	0 (0,0)	12 (11,9)	0,009	5 (6,3)	7 (9,6)	0,456	8 (7,7)	4 (8,3)	1,000	12 (7,9)
p	<0,001													

Table 2b

		Age
		p
Atrophy	**Endometrial polyp**	0,053
	Hormonal effect (E/P)	<0,001
	Malignancy	0,047
Endometrial polyp	**Hormonal effect (E/P)**	0,001
	Malignancy	0,011
Hormonal effect (E/P)	**Malignancy**	<0,001

There was a statistically significant difference in the ages of patients with different histopathologic results (p<0.001). The ages of patients with hormonal effect (E/P) were significantly lower than those with atrophy, endometrial polyps and malignancy (p<0.001 p=0.001 p<0.001). The result of atrophy was significantly higher in multiparous patients compared to nulliparous patients, while the result of hormonal effect was significantly lower (p=0.001 p<0.001). Postmenopausal patients had significantly higher atrophy and malignancy results and significantly lower hormonal effect results compared to premenopausal patients (p=0.001 p=0.009 p<0.001). Endometrial thickness <8 mm was statistically significantly higher for atrophy and statistically significantly lower for endometrial polyps than those with ≥8 mm (p=0.006 p=0.009).

Findings:

The files of 6612 patients were reviewed. The pathology results of 615 (9.3%) of these patients were evaluated as inadequate specimens. According to the hospital data, 257 of these 615 patients underwent a second PC procedure and 105 (40.8%) of them were again evaluated as inadequate. The results of the 152 patients who had an adequate second pc result were atrophy (34.2%), endometrial polyp (32.2%), hormonal effect (25.7%) and malignancy (7.9%)

Table 1 compares the age, gravida, menopausal status, endometrial thickness and anesthesia status of patients with insufficient specimens according to their indications. Postmenopausal patients with postmenopausal bleeding (32%) and postmenopausal patients with increased endometrial thickness (23.3%) the most common indications for inadequate specimens. In the 2nd PC, the patients with unsatisfactory results were mostly in these two indications; postmenopausal bleeding (30.4%) and postmenopausal endometrial thickness increase (38.0%).

Sample sizes were calculated at confidence levels between 80%-99% with a 5% margin of error from the 6000 endometrial sample population in our hospital. The minimum population of the study was accepted as 598 endometrial samples with a confidence level of 99% and the study was completed with 615 samples.

Discussion:

Insufficient endometrial sampling is generally observed in older patients. For an abnormal clinical outcome to occur in endometrial tissue, it must be exposed to prolonged hormonal influence. From this perspective, it is expected that age would be statistically significant. In our study, age was found to be a significant factor (p < 0.001). Similarly, in the study conducted by Kandil D. et al., it was reported that insufficient specimens were predominantly found in older patients [11]. Insufficient endometrial sampling was detected in 5.8% of younger patients and 14.6% of older patients. The average ages by pathology result were as follows: atrophy (55.5), endometrial polyp (52), hormonal effect (45), malignancy (64.5).

Our study yielded similar results, confirming that patients diagnosed with atrophy, endometrial polyps, and malignancy had a higher average age. The histopathological diagnosis of hormonal effect is expected to be more common in premenopausal younger patients, and our study supports this finding.

Performing this procedure under general anesthesia may seem more comfortable for the surgeon. However, in our study, the type of

anesthesia did not show a statistically significant effect on insufficient endometrial sampling results ($p > 0.05$). Similar findings have been reported in the literature [12]. The fact that most patients were multiparous and that the procedure was performed in a high-volume center likely reduced the impact of anesthesia type on the results.

The fact that 7.9% of patients who underwent repeat endometrial sampling due to insufficient specimens were ultimately diagnosed with malignancy underscores the necessity and importance of a second intervention. The malignancy rate of 7.9% in repeat sampling particularly highlights the critical need for repeating the procedure in older patients. The statistically higher average age of patients with a final diagnosis of malignancy, compared to those with other pathology results, explains the higher incidence of malignancy in postmenopausal patients.

All patients diagnosed with malignancy upon repeat sampling were postmenopausal and multiparous. Malignancy is typically an age-related issue, which explains its higher frequency in postmenopausal patients. The literature suggests that in multiparous patients, each subsequent pregnancy is associated with a reduced risk of endometrial malignancy, likely due to progesterone activity during pregnancy [13]. However, in our study, the exclusive occurrence of malignancy in multiparous patients might be due to increased obesity after childbirth, leading to postmenopausal peripheral estrogenic effects. Weight gained during pregnancy is not completely lost postpartum, which can lead to progressive weight gain with multiple pregnancies, potentially contributing to obesity [14].

The absence of malignancy in premenopausal and nulliparous patients who underwent a second biopsy following an initial insufficient sample is notable. The lack of malignancy in premenopausal patients can be explained by insufficient hormonal exposure or young age, while its absence in nulliparous patients might be coincidental in our study. Among patients whose initial pathology results were insufficient, those who underwent repeat sampling and were diagnosed with malignancy showed no significant differences in endometrial thickness or anesthesia type.

The histopathological diagnosis of hormonal effect is expected to be more common in younger patients, and our study supports this, as the nulliparous and premenopausal patient groups were statistically significantly higher in this category ($p < 0.001$). However, there was no significant difference in terms of anesthesia type or endometrial thickness in patients with this pathology result.

In our study, menopause, endometrial thickness <8mm, and multiparity were found to be statistically significantly associated with atrophy as a histopathological outcome. The higher prevalence of atrophy in postmenopausal patients and those with thin endometrium can be attributed to reduced hormonal activity (hypoestrogenic state) in older age [15]. The higher prevalence of atrophy in multiparous patients, compared to nulliparous patients, may be due to hormonal differences during pregnancy, particularly progestogenic effects. The continuous hormonal exposure in nulliparous patients may result in a lower frequency of atrophy, or exposure to progesterone during pregnancy may lead to a higher incidence of atrophy in multiparous patients at older ages.

Conclusion:

The 7.9% malignancy rate in repeat sampling of patients with insufficient endometrial tissue in the pathology result highlights the importance of repeating the procedure, especially in older patients.

The fact that 40.8% of patients who underwent repeat sampling after an insufficient initial pathology result again received an insufficient result indicates that alternative approaches should be considered for second endometrial samplings.

Availability of Data and Materials

All data points generated or analyzed during this study

are included in this article and there are no further underlying data necessary to reproduce the results.

Author Contributions

RA designed the research study. FŞ, VM, Tİ, DA, SS performed the research and analyzed the data. All authors contributed to editorial changes in the manuscript. All authors

read and approved the final manuscript.

Ethics Approval and Consent to Participate

The retrospective study received ethical approval from

the Istanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee, with approval number: 2022/365. Written permission has also been obtained from

the institutions where the research was conducted, and informed consent has been obtained from the patients. The study was conducted in accordance with the Principles of

the Declaration of Helsinki.

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