



RISK FACTORS AND HYSTEROSCOPIC RESULTS FOR INSUFFICIENT TISSUE FROM ENDOMETRIAL BIOPSY

Endometriyal Biyopsi Sonrası Yetersiz Doku Tanısının Olası Risk Faktörleri ve Histeroskopik Sonuçları

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The ethical approval was obtained from Bakirköy Dr. Sadi Konuk Training and Research Hospital local ethics committee (Approval number: 2018/237).

Abstract

Aim: The aim of this study was to determine risk factors that may play a role in the diagnosis of insufficient endometrial tissue and to evaluate the office hysteroscopy findings of these patients.

Materials and Methods: The clinical data and results of insufficient endometrial tissue in the medical records of patients at Bakırköy Dr. Sadi Konuk Teaching and Research hospital from August 2018 to November 2019 were analyzed retrospectively.

Results: Endometrial biopsy procedures were applied to 1560 patients during the period evaluated for the study. The pathology report of 81 patients (5.2%) was evaluated insufficient endometrial tissue. The results of the 64 patients were analyzed in the study. The mean age of the patients in the study was 52.1 years (range= 32-78 years). Results of 64 patients undergoing hysteroscopy; normal hysteroscopic findings (22 patients; 34%), endometrial polyp (18 patients; 28%), appearance of submucous myoma (6 patients; 10%) and atrophic endometrial appearance (18 patients; 28%) were evaluated.

Conclusion: We point out that insufficient endometrial tissue diagnosis can be detected more often in postmenopausal cases over 60 years of age and in patients with large uterine fibroids. Additionally, we emphasize that hysteroscopy can guide the clinician for definitive diagnosis in patients with insufficient endometrial tissue.

Keywords: Endometrial biopsy, hysteroscopy, insufficient endometrial tissue, inadequate sampling.

Öz

Amaç: Bu çalışmanın amacı yetersiz endometriyal doku tanısında rol oynayabilecek risk faktörlerini belirlemek ve bu hastaların ofis histeroskopi bulgularını değerlendirmektir.

Materyal ve Metot: Ağustos 2018-Kasım 2019 tarihleri arasında Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma hastanesinde yetersiz endometriyal doku tanılı hastaların klinik verileri ve sonuçları retrospektif olarak incelendi.

Bulgular: Çalışma için değerlendirilen süre boyunca 1560 hastaya endometriyal biyopsi işlemleri uygulandı. 81 hastanın (% 5.2) patoloji raporu yetersiz endometriyal doku olarak değerlendirildi. Çalışma kriterleri eşliğinde 64 hastanın sonuçları analiz edildi. Çalışmadaki hastaların yaş ortalaması 52,1 (dağılım = 32-78) idi. Histeroskopi uygulanan 64 hastanın sonuçları; normal histeroskopik bulgular (22 hasta; % 34), endometriyal polip (18 hasta; % 28), submuköz miyom görünümü (6 hasta; % 10) ve atrofik endometriyal görünüm (18 hasta; % 28) olarak değerlendirildi.

Sonuç: 60 yaşın üzerindeki postmenopozal olgularda ve büyük çaplı miyomu olan hastalarda yetersiz endometriyal doku tanısının daha sık tespit edebileceğine dikkat çekmekteyiz. Ek olarak, histeroskopin yetersiz endometriyal doku tanılı hastalarda uygun tanı için klinisyene rehberlik edebileceğini vurgulamaktayız.

Anahtar Kelimeler: Endometriyal biyopsi, histeroskopi, yetersiz endometriyal değerlendirme, yetersiz örnekleme.

INTRODUCTION

Endometrial biopsy is a procedure that is frequently used in gynecology clinics that determine patient management by examining endometrial tissue. This procedure is widely performed to investigate for various endometrial pathologies, such as endometrial hyperplasia and endometrial carcinoma, in women who have an abnormally thick endometrium on imaging, or abnormal uterine bleeding ^{1,2}.

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Previous studies showed that endometrial tissue sampling can be provided with dilatation and curettage (D&C) or pipelle biopsy techniques. D&C has been used as a gold standart procedure for endometrial tissue biopsy for many years. However, the need or possibility for hospital admission, cervical dilatation requirement and the cost has made it less favorable ³. The pipelle biopsy technique also has developed in the following years and has started to be used frequently in gynecology clinics.

An important problem of these effective methods used in the evaluation of endometrial tissues is "insufficient tissue for diagnosis" mentioned in the pathology reports. Previous studies suggests that insufficient endometrial tissue comprise 2% to 60% of all samples ⁴⁻⁶. Multiple factors contribute to such variation, including the patient's age, parity, endometrial thickness, the sampling device, as well as the provider's technique ⁷. Additionally, it is a fact that there are no diagnostic criteria among the pathologists in the diagnosis of insufficient endometrial tissue and may vary according to different pathologist examining.

In literature, there is no consensus in the management of insufficient endometrial biopsy result. Repetition of the sampling procedures, follow-up without any additional method, hysteroscopy and radiologic follow-up are the management modalities in the diagnosis of insufficient endometrial tissue ^{8,9}. Hysteroscopy is the diagnostic and treatment method that increase in popularity for endometrial pathologies. Advancing technology led to changes in the use of diagnostic hysteroscopy, leading to the developed of thin- walled Bettocchi-type office hysteroscopy ¹⁰. This development has enabled more widespread and effective use of hysteroscopy. Therefore, office hysteroscopy is frequently used for imaging endometrial cavity in patients with insufficient endometrial tissue diagnosis.

Our study was aimed to determine the risk factors that may play a role in the diagnosis of insufficient endometrial tissue and to evaluate the office hysteroscopy findings of these patients.

MATERIALS AND METHODS

The retrospective observational study was carried out between August 2018 and November 2019 at our tertiary referral clinic at the department of obstetrics and gynecology. The ethical approval was obtained from our hospital's local ethics committee (Approval number: 2018/237). The patients who underwent endometrial sampling procedure for different gynecological complaints were included in the study. The patients who could not performed endometrial sampling due to pain intolerance or failure of cervical canal dilatation were excluded from the study. Informed consent forms were obtained from each patients participating in the study.

Physical examination, medical history and routine gynecologic evaluation results in all women were analyzed. The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m²). Patients with insufficient endometrial tissue result firstly screened with a high resolution ultrasound. Ultrasonographic measurements were performed with a high-resolution ultrasound (Samsung-HS70A, Samsung Healthcare Systems, South Korea) by the same physician (S.Y.). The analysis were conducted with transvaginal transducer in gynecologic mode to obtain endometrial

thickness measurements. After that, patients with insufficient endometrial tissue pathology result were evaluated by hysteroscopy and repeated endometrial tissue biopsy.

Endometrial sampling procedures

Endometrial biopsies were performed by residents in obstetric and gynecology clinic via pipelle or D&C with the preference of experts. These procedures were performed in a specific outpatient clinic on all weekdays. All the clinicians followed the standart instutional biopsy methods for each sampling technique. In both methods, vagina and cervix were cleaned with antiseptic solution (povidone iodine) after bimanual examination. After the cervix held with teneculum, the uterus was placed in the appropriate position.

Pipelle device comprises a transparent and flexible outher sheath made of piropropilen and a piston mechanism inside. The dimensions of the pipelle were 3.1 mm in outer-diameter, 2.6 mm in inner-diameter and 23.5 cm in length. Pipelle biopsy procedure was performed without cervical misoprostol administiration. Negative pressure is generated by retracting the plunger inside the device. The endometrial tissue samples were aspirated by turning the device back and forth and clockwise in the endometrial cavity. Afterwards, the pipelle was removed and the piston was pushed forward and the material was discharged into the container containing 10% formoline.

In the D&C procedure, sufficient cervical dilatation was achieved with hegar dilators. Endometrial sampling was performed by determining the appropriate currette number for each patient. The collected material was discharged into a container containing 10% formoline. The specimens were sent to the pathology laboratory for histopathologic evaluation.

Office hysteroscopy procedure

Hysteroscopic procedures were performed using 5 mm Bettocchi B.I.O.H. Office Hysteroscope (Karl Storz GmbH&Co. Tuttlingen, Germany). Hopkins II rod telescope and continous current outher sheath were used as hysteroscopy equipments. Video recording and photographing were performed by Telepack video monitor system. The uterine cavity was visualized with a hysteroscope without cervical dilatation. Cavity distension was provided with saline solution. In cases where endocervical canal, whole cavity, and both tubal ostium could be observed, the procedure was considered sufficient and included in the study. Evaluating the uterine cavity; normal endometrial cavity findings, endometrial polyps, submucous fibroids, atrophic endometrial appearance were detected and recorded. After hysteroscopy, repeated endometrial biopsy procedure was performed via D&C technique.

Statistical analysis

The medical data of patients and clinical outcomes were analyzed. Data examination was completed with SPSS (version 20.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as frequencies in the text and tables.

RESULTS

Endometrial biopsy procedures were applied to 1560 patients in our hospital during the period evaluated for the study. The pathology report of 81 patients (5.2%) was evaluated insufficient not available. The results of the remaining 64 patients were analyzed in the study. The follow-chart of the study was shown in Figure 1.

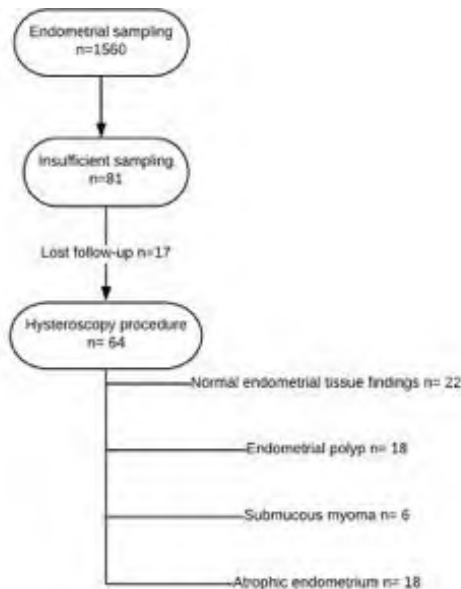


Figure 1. Flow chart of the study.

The demographic characteristics and clinical data of the study population are presented in Table 1. The mean age of the patients in the study was 52.1 years (range= 32-70 years). The mean BMI was found to 32.1 ± 4.1 kg/m² (range= 24.9-41.6). The mean parity of the patients was 1.5 ± 0.7 (range 0-4). The results of 7 nulliparous patients were analyzed. 38 patients had only normal spontaneous birth, 22 patients gave birth with both types of delivery. 28 patients (43.7%) were premenopausal and 36 patients (56.3%) were postmenopausal. The most common endometrial biopsy indication was abnormal uterine bleeding (83%). Endometrial sampling procedures of 30 patients (47%) were performed with pipelle technique and 34 patients (53%) with D&C technique. All patients were evaluated for transvaginal ultrasound in terms of endometrial thickness and if detected fibroid size. The mean endometrial thickness was 8.1 ± 3.7 mm. The endometrial thickness was less than 8 mm in 35 patients (55%) and over 8 mm in 29 patients (45%). Ultrasonographic examination of 6 patients revealed myoma uteri. The mean myoma size was 9.6 cm (range=6-14 cm).

Table 1. Characteristics of women with insufficient endometrial tissue diagnosis

Characteristics	Value *
Age, y	
Mean±SD, (min-max)	52.1±10.4 (32-70)
<40, y	8 (13%)
40-60, y	31 (48%)
>60	25 (39%)
Parity	
Mean±SD, (min-max)	1.5±0.7 (0-4)
Nulliparity	7 (11%)
Multiparity	57 (89%)
Previous vaginal birth	
Yes	34 (53%)
No	30 (47%)
BMI (kg/m²)	
Mean±SD, (min-max)	32.1±4.1 (24.9-41.6)

Table 1. Characteristics of women with insufficient endometrial tissue diagnosis (continuation)

Characteristics	Value *
Indications for endometrial sampling	
AUB	53 (83%)
Non-AUB	11 (17%)
Endometrial sampling procedure	
Pipelle	30 (47%)
D&C	34 (53%)
Menopausal status	
Premenopausal	28 (44%)
Postmenopausal	36 (56%)
Endometrial thickness (mm)	
Mean±SD, min-max)	8.1±3.7 (3-16)
Less than 8 mm	35 (55%)
8mm or more	29 (45%)
Hormonal treatment before procedure	
Yes	20 (31%)
No	44 (69%)

BMI body mass index, SD standart deviation, AUB anormal uterine bleeding, D&C dilatation and curettage. *Values are designed as a number and percentage of patient unless specified otherwise

Results of 64 patients undergoing hysteroscopy; normal hysteroscopic findings (22 patients; 34%), endometrial polyp (18 patients; 28%), appearance of submucous myoma (6 patients; 10%) and atrophic endometrial appearance (18 patients; 28%) were evaluated (Table 2). Repeated endometrial procedure results after hysteroscopy; normal endometrial tissue (26 patients; 45%), endometrial polyp (17 patients; 27%), insufficient endometrial tissue (13 patients; 20%) and atrophic endometrium (8 patients; 12%) were analyzed (Table 3). No pathology report revealed malignant endometrial tissues.

Table 2. Office hysteroscopy results of the patients

Hysteroscopic appearance	Patients n (%)*
Normal endometrial tissue findings	22 (34%)
Endometrial polyp	18 (28%)
Submucous myoma	6 (10%)
Atrophic endometrium	18 (28%)

*Values are designed as a number and percentage

Table 3. Repeated endometrial sampling results after hysteroscopy

Histopathologic result	Patients n (%)*
Normal endometrial tissue	26 (41%)
Endometrial polyp	17 (27%)
Insufficient endometrial tissue	13 (20%)
Atrophic endometrium	8 (12%)

*Values are designed as a number and percentage

DISCUSSION

Inadequate pathologic tissue diagnosis that obtained by uterine biopsy procedures is common in gynecology practice. Herein, we analyze pathologic results of 1560 patients with outpatient endometrial sampling at our clinic within one year. Additionally, this study was conducted to analyze the clinical characteristics of patients with insufficient endometrial tissue diagnosis and to evaluate the results of hysteroscopy in these patients management.

Reported rates of inadequate tissue diagnosis after uterine biopsy procedures, in both pre- and post-menopausal women in varying proportions, ranged from 5-45.6¹¹⁻¹³. In our study, insufficient endometrial tissue was found to be 5.2% regardless of endometrial biopsy technique. The reason for variable percentage of insufficient endometrial tissue in clinical studies, it can be considered that sample changes in the studies such as patient's age, menopausal status, presence of uterine fibroids and variety of endometrial tissue procedures^{14,15}.

In the present study, 56% of patients with insufficient endometrial tissue were evaluated as postmenopausal. Xie et al. showed that postmenopausal period enhanced the rate of insufficient tissue diagnosis after uterine biopsy procedures ¹⁶. Additionally, another study also demonstrated that postmenopausal period affect the success of obtaining endometrial tissue ¹⁴. In our study, 18 patients with atrophic endometrial hysteroscopic imaging were in postmenopausal period. In other words, endometrial atrophy was detected hysteroscopically, in one of the two patients with insufficient endometrial tissue diagnosis were in the postmenopausal period. It is clear that endometrial atrophy that occurs naturally in the postmenopausal period will decrease the amount of endometrial tissue taken for sampling or may cause endometrial tissue to never be obtained.

The studies reported that with an annual increase in patient age, an average of %4 rise in the rate of inadequate pathologic diagnosis following uterine biopsy procedures ^{14,17}. Another study showed that patients with an age above 60 years had an increased rates of inadequate endometrial tissue diagnosis ¹⁸. However, Adembekov et al. stated that the patient's age above 55 years did not increase the rate of inadequate tissue diagnosis ¹⁹. In our study, 39% of the women were 60 years of age and 48% of women were between 40-60 years of age.

Guidelines from cancer Australia ²⁰ and The Society of Obstetricians and Gynecologists of Canada ²¹ recommend the use of vaginal ultrasound imaging for evaluation of endometrial lining in the management of insufficient endometrial biopsy. A study reported that the measurement of endometrial lining below 5 mm reduced the success of obtaining enough tissue for pathologic evaluation ¹⁴. Additionally, another study reported that the transvaginal ultrasound measurement of endometrial lining below 12 mm increased the rate of inadequate endometrial tissue ¹⁷. In our study, 54% of patients were less than 8 mm in endometrial thickness. In addition to the effect of endometrial thickness on insufficient tissue diagnosis, we suggest that patients with insufficient endometrial tissue should be evaluated with high-resolution transvaginal ultrasound in order to better guide for the correct endometrial diagnosis.

D&C was the standard procedure for maintaining endometrial tissue. Recently, pipelle seems to perform as well or better than any other procedures in terms of sampling adequacy ²². In our study, biopsies performed with both techniques were evaluated with insufficient endometrial tissue diagnosis with a close percentage. We think that these techniques have no superiority to each other in the evaluation of endometrial sampling.

Aue-Aungkul et al. reported that nulliparity, previously normal labor history or active hormone therapy did not contribute to the possibility of inadequate endometrial tissue diagnosis ²³. In our study, 7 patients (11%) had nulliparous, 34 patients (53%) had normal birth and 20 patients (31%) were using hormone therapy for abnormal uterine bleeding. In light of these analysis, we think that these variables cannot be effective in the diagnosis of insufficient endometrial tissue. Further detailed studies with subgroups are needed on this subject.

When performed as an adjunct to endometrial sampling, hysteroscopy increases the rates to detecting polyps and submucous fibroids²⁴. Furthermore, many departments evaluate hysteroscopically patients with insufficient endometrial tissue. In our study, abnormal findings were found 66% of hysteroscopy results in patients with insufficient endometrial tissue diagnosis. 6 patients (10%) had myoma with submucous component. Remarkably, the mean fibroid size was as high as 9 cm. We believe that large-sized fibroids may cause difficulties in the sampling of endometrial tissue due to the pressure of fibroids on the endometrial cavity. Therefore, endometrial sampling with hysteroscopy becomes more important with large-sized fibroids. Additionally, one of the benefits of hysteroscopy in insufficient endometrial tissue management is the determination of atrophic endometrial diagnosis and insuring the diagnosis in the possibility of the failure of the second endometrial biopsy again.

Some authors have suggested that the use of D&C for investigation of an insufficient endometrial sampling²⁴. In our clinic, we perform simultaneous D&C with hysteroscopy in all insufficient endometrial tissue diagnosis. Previous studies indicated that approximately 6%-7% of women with insufficient endometrial tissue samples were subsequently found to be have atypical endometrial hyperplasia or endometrial cancer¹⁵. In addition to this cancerous possibility, Kandil et al. suggest that second sampling procedures showed a failure rate of about 23%¹⁸. We showed that the failure of second sampling biopsy was found to be 20%. However, second biopsy results showed no signs of endometrial hyperplasia or cancer in our analysis. Despite the second endometrial biopsy, approximately 20% of the patients still do not have endometrial tissue diagnosis. Therefore, this undiagnosed condition increases the importance of hysteroscopy in the management of patients with insufficient tissue diagnosis.

Firstly; the main limitation of our study is the retrospective design. Secondly; the study evaluates one-year follow-up, that prevents the evaluation of serious pathologies such as endometrial cancer in the following years. Thirdly; as a basic limitation, the definition of insufficient endometrial tissue pathologic diagnosis varies and this definition reflects highly variable pathology reports. Despite these limitations, the strength of the study that the study was conducted in a single center which all insufficient endometrial tissue cases were evaluated hysteroscopically by same physician to establish a management standard.

In conclusion, endometrial tissue sampling is a frequently used but not a perfect method in endometrial pathology examination. We point out that insufficient endometrial tissue diagnosis can be more often detected in postmenopausal cases over 60 years of age and in patients with large uterine fibroids. Additionally, we emphasize that hysteroscopy can guide the clinician for definitive diagnosis in patients with insufficient endometrial tissue. Future studies should focus on creating guidelines for insufficient endometrial tissue diagnosis and identify variables that will reduce the insufficient endometrial tissue cases in practice.

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