

Endometrial Sampling Methods: A Case Report and Literature Review

Endometriyal Örnekleme Yöntemleri: Bir Olgu Sunumu ve Literatür Değerlendirmesi

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ABSTRACT The evaluation of the uterine cavity and endometrial thickness measurement via ultrasound examination are the first-line researching methods in the case of abnormal uterine bleeding. Various endometrial sampling methods have been developed for diagnosis of uterine malignancies. Pipelle aspirator is an easy, inexpensive, minimally invasive and useful outpatient procedure for diagnosis in patients with abnormal uterine bleeding. Leiomyosarcoma is an aggressive gynaecologic malignance and constitutes 13% of all uterine sarcomas. Because leiomyosarcoma originates from myometrium, it is difficult to diagnose with endometrial sampling. So, leiomyosarcoma is usually diagnosed by the examination of hysterectomy/myomectomy materials. A case of leiomyosarcoma diagnosed by Pipelle endometrial sampling in a postmenopausal woman with diabetes mellitus and hypertension was reported in this case report. Leiomyosarcoma of the uterus was diagnosed histopathologically (severe nuclear atypia, increased mitotic activity and coagulative tumour-cell necrosis). This case illustrates the importance of Pipelle endometrial sampling in the diagnosis of uterine malignancies.

Key Words: Uterine hemorrhage; pathology; leiomyosarcoma

ÖZET Anormal kanamanın varlığında ilk yapılması gereken, ultrason muayenesi ile uterus kavitesinin değerlendirilmesi ve endometriyal kalınlığın ölçülmesidir. Uterusun malign hastalıklarının tanısı için, çeşitli endometriyal örnekleme yöntemleri geliştirilmiştir. Pipelle aspiratör; uygulanımı kolay, ucuz, minimal invaziv ve faydalı bir yöntem olarak, anormal uterin kanaması olan hastalıkların tanısı için ayaktan takip edilen hastalarda uygulanan bir yöntemdir. Leiomyosarkom agresif seyirli bir jinekolojik malign hastalık olup tüm uterin sarkomların %13'ünü oluşturur. Leiomyosarkom myometriumdan köken aldığı için, endometriyal örnekleme ile tanısının konulması zordur. Bu sebeple, leiomyosarkom tanısı genellikle histerektomi/miyomektomi materyallerinin incelenmesi sırasında konulur. Bu yazıda, diyabet ve hipertansiyonu olan bir postmenopozal kadında, pipelle endometriyal örnekleme ile tanısı konulan leiomyosarkom vakası sunuldu. Uterustaki leiomyosarkom histopatolojik olarak tanımlandı (şiddetli nükleer atipi, artmış mitotik aktivite, koagülatif tümör-hücre nekrozu). Bu vaka uterusun malign hastalıklarının tanısında Pipelle endometriyal örnekleme yönteminin önemini göstermektedir.

Anahtar Kelimeler: Uterus kanamaları; patoloji; leiomyosarkom

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Abnormal uterine bleeding may be occur in premenopausal, perimenopausal or postmenopausal periods and it is one of the major symptoms in patients with uterine malignancy. Especially, postmenopausal women with abnormal uterine bleeding should be evaluated in terms of uterine malignancy. However, abnormal uterine bleeding may be a precursor for a uterine benign focal lesion such as fibroid or polyp.¹ The

evaluation of the uterine cavity and endometrial thickness measurement via ultrasound examination are the initial non-invasive methods in the case of abnormal uterine bleeding. Saline infusion sonography should be performed in the event of suspicious focal endometrial pathology by ultrasonography.² It was reported that endometrial sampling should be applied if the endometrial thickness is measured as 5 mm or greater in postmenopausal women.³

Various endometrial sampling methods including Tao brush, Pipelle, dilatation-curettage, vabra aspirator and hysteroscopy have been developed for diagnosis of uterine malignancies. Pipelle aspirator is an easy, inexpensive, minimally invasive and useful outpatient procedure for diagnosis in patients with abnormal uterine bleeding.⁴ In a study researching the role and clinical value of Pipelle sampling in women with postmenopausal bleeding and endometrial thickness > 4 mm; the use of Pipelle sampling reduced the need of hysteroscopy and endometrial biopsy in 61.5% of cases.⁵

Leiomyosarcoma is an aggressive gynaecologic malignance comprising 1.3% of uterine malignancies.⁶ Abdominal pain (35%), abnormal vaginal bleeding (53%) and abdominal mass (14%) are the most common symptoms of the disease.⁷ The most significant risk factors for leiomyosarcoma are nulliparity, obesity, diabetes mellitus, hypertension, exposure to irradiation and long use of estrogens as hormone replacement therapy or tamoxifen.⁸⁻¹¹ We present a case of leiomyosarcoma diagnosis by Pipelle (aspiration) endometrial sampling.

CASE REPORT

A 60-year-old para 5 postmenopausal woman was admitted to the Gynecology Clinic because of intermittent vaginal bleeding of 3 months duration. She was also suffering from mild abdominal pain and bloating. Her last childbirth was 20 years ago. She had hypertension for ten years requiring the use of antihypertensive drugs. Also she had been treated by insulin for 10 years due to type 2 diabetes. She had no family history of malignant uterine disease.

On physical examination, blood pressure was 140/90 mmHg and heart rate was 80 bpm. Body mass index was 28 kg/m². There were no abnormal findings in the abdomen, chest or breast. The liver, spleen and kidneys were not palpable. Pelvic examination showed normal cervix and a slightly tender uterus of normal size. Transvaginal ultrasonography demonstrated an uterus (the size of 8×5×6 cm) with heterogeneous material visualized within endometrial cavity measuring 11×20.4 mm (Figure 1). The ovaries were hypoplastic and acid was not available in the abdomen. The patient's hemoglobin was 9 g/dl. The CA-125 was at 60 U/ml (normal range 0-23 U/ml) and other tumor markers including carcino-embryonic antigen, alpha feto-protein, CA-19-9 and 15-3 were within normal range. Chest x-ray showed no nodules in the lungs. In magnetic resonance imaging (MRI) scan of the pelvis, there was no invasion of adjacent structures. Also the ovaries were normal in appearance and no pelvic or inguinal lymphadenopathy was seen.

Endometrial sampling with Pipelle aspirator was planned for diagnosing endometrial pathology. Endometrial sampling was performed in the dorsal lithotomy position under anaesthesia. For maintenance of anaesthesia, midazolam at 0.1 mg/kg, 50µg fentanyl and 3 L/minute of O₂ with a face mask were administered. After the cervix was held with tenaculum forceps, a Pipelle was inserted through cervical canal and endometrial samples were aspirated. The curettage specimens were fixed in formalin for pathology. Immunohistochemical staining showed that the neoplastic cells were positive for desmin, vimentin, smooth muscle actin; 5% positive for p53; negative for CD10, CK19 and

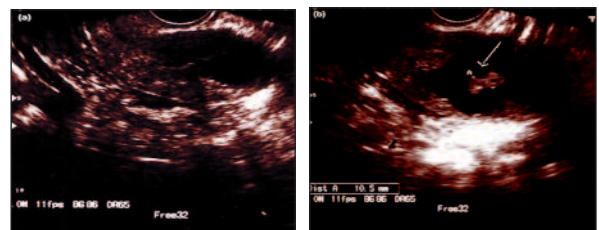


FIGURE 1: Grey-scale images of the uterine cavity with echoic and anechoic compartments.

pankeratin and Ki-67 was approximately 15%. Based on these findings, the diagnosis was defined as 'leiomyosarcoma' with a comment that the presence of nuclear atypia, increased proliferative activity and coagulative cell necrosis (Figure 2).

The patient was informed about the disease and the operation was explained in detail. The patient preferred a university hospital for the operation. During the telephone follow-up, it was discovered that the patient had undergone an operation of total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) with peritoneal washings, omental biopsy and sampling of pelvic and para-aortal lymph nodes. Also the specimen report was compatible with Stage IB low-grade leiomyosarcoma (tumor limited to uterus with a size of 8 cm and without pelvic spread). Written informed consent was obtained from the patient for publication of this case report.

DISCUSSION AND LITERATURE REVIEW

An ideal endometrial sampling method should be minimal invasive, painless, cheap and easily applicable. It also should provide adequate and high-quality tissue samples for histopathological

diagnosis without major complications.¹² Previously, dilatation and curettage (D&C) was the most commonly used method for endometrial sampling. Nowadays, because D&C is an expensive and invasive method and requires general anesthesia and hospitalization, it has been replaced by aspiration techniques.

Pipelle (Figure 3a), which is a flexible sampler with a polypropylene sheath is widely preferred by gynecologists to provide endometrial sample in patients with abnormal uterine bleeding.^{4,5} There are numerous studies in the literature comparing the effectiveness of Pipelle with D&C in patients with endometrial pathology (Table 1). These studies indicated the important role of pipelle in the diagnosis of endometrial pathology. On the other hand, pipelle was found to be more effective to obtain endometrial tissue for histological diagnosis compared with the Vabra aspirator with lower average cost per patient and higher procedure success rate.⁴

The Pipelle Mark II sampler (Figure 3b) was designed to collect both histological and cytological samples in patients with endometrial atrophy. Studies showed that outpatient Pipelle Mark II endometrial sampling is a reliable technique in the

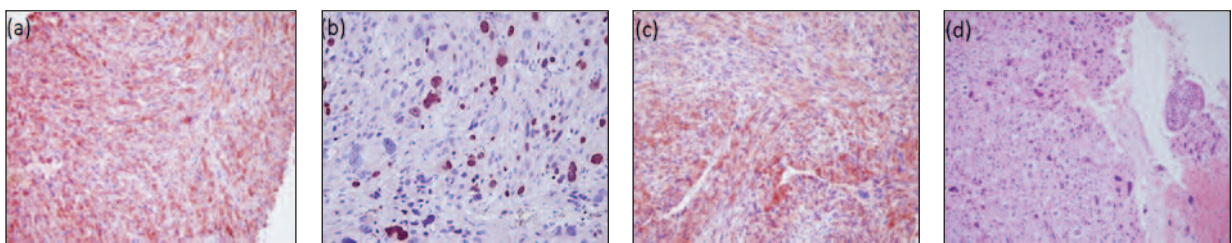


FIGURE 2: (a) Endometrial biopsy showing immunoreactivity for desmin (Immunoperoxidase staining, $\times 200$). (b) Endometrial biopsy showing nuclear immunoreactivity for Ki-67 antigen (Immunoperoxidase staining, $\times 200$). (c) Endometrial biopsy showing immunoreactivity for muscle-specific actin (Immunoperoxidase staining, $\times 200$). (d) Endometrial biopsy showing nuclear atypia, increased proliferative activity and coagulative cell necrosis (hematoxylin-eosin, $\times 200$).

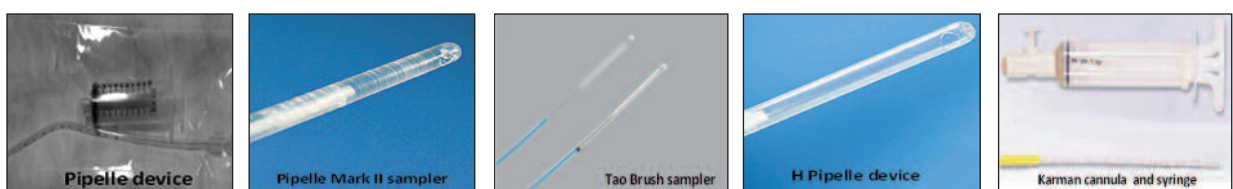


FIGURE 3: Endometrial sampling devices (a) Pipelle device. (b) Pipelle Mark II sampler (c) Tao Brush sampler (d) H Pipelle device (e) Karman cannula and syringe.

TABLE 1: Studies in the literature comparing the effectiveness of Pipelle with D&C.

Author (Year, ref. number)	Number of patients	Conclusion
Kazandi et al. ¹³	82	Both two methods are nearly equally successful in the evaluation of pathologies that involve the entire endometrium. But Pipelle biopsies provide limited diagnostic accuracy in cases with focal pathologies.
Demirkiran et al. ¹⁴	673	Both two methods have almost equal success rate in the diagnosis of endometrial pathologies while both methods are not adequate for focal endometrial pathologies. Pipelle biopsy is a cheaper and easier technique compared to D&C.
Fakhar et al. ¹⁵	100	Pipelle and D&C are safe methods for endometrial sampling for histopathological examination with a high sensitivity and specificity for detection of endometrial hyperplasia and malignancy.
Huang et al. ¹⁶	278	Preoperative endometrial sampling with Pipelle or curettage is sensitive and accurate for the diagnosis of high-grade endometrial tumors.
Bunyavejchevin et al. ¹⁷	30	The sensitivity and specificity of Pipelle in endometrial tissue samplings are similar to fractional curettage: Pipelle is a more simple, easy and painless method compared with fractional curettage

investigation of postmenopausal bleeding and provides adequate samples for histological and cytological analysis in women with endometrial atrophy. The use of the Pipelle Mark II sampler also reduced the rate of false negative results for endometrial cancer.^{18,19}

The Tao Brush sampler (Figure 3c) is introduced into the endometrial cavity and provides a sampling of endometrial cells via a disposable sheath. This method is inexpensive, simple and does not require anesthesia. Wu et al. described 633 cases using the Tao Brush for endometrial biopsy in an outpatient setting.²⁰ This method was found to be 100% sensitive and 96% specific for identify endometrial carcinoma in their study. In another study; the Tao Brush method provided a more adequate specimen (72%) for pathological assessment compared with Pipelle sampler (44%).²¹ Del Priore et al. researched the correlation between the pathology of endometrial samples obtained with Tao Brush or Pipelle and final diagnosis in hysterectomy material.²² They reported 95.5% sensitivity for the Tao Brush and 86% sensitivity for Pipelle to detect or exclude endometrial cancer. They concluded that endometrial cancer can be reliably detected and excluded using these two distinct office biopsy devices simultaneously during one office visit. In another study, Mossa et al. compared the efficacy in detecting early-stage cancer

of the outpatient endometrial sampling cytology with conventional biopsy in postmenopausal women with abnormal uterine bleeding and/or abnormal endometrial thickness at ultrasound.²³ They reported that endometrial sampling with an endometrial brush device is a reliable and well tolerated method to detect early-stage cancer in postmenopausal women with high risk for endometrial cancer.

Outpatient hysteroscopy, is performed with a speculum, tenaculum and hysteroscopy is another endometrial sampling method and it has a high success rate with good patient tolerability for detection of endometrial and intra-uterine abnormalities.^{24,25} Hysteroscopy provides direct visualization of the endometrium and direct endometrial biopsies may be obtained using office 5-mm operative hysteroscopy via miniaturized forceps. Hysteroscopy also allows the elimination of detected endometrial pathologies during the procedure such as intrauterine adhesions, submucous myomas or endometrial polyps.²⁴ Leone et al. compared the quantity and quality of endometrial tissue sample at saline contrast sonohysterography with that obtained by directed endometrial biopsy by operative hysteroscopy in patients with endometrial abnormalities.²⁶ Sonohysterographic endometrial sampling provided adequate and good tissue samples compared with extended curettage

of the endometrium after hysteroscopy in their study. In Liberis et al. study, specificity, sensitivity and positive predictive values of hysteroscopy to distinguish endometrial benign pathology such as cervical polyps, endometrial fibroma were 100% and specificity, sensitivity and positive predictive values were 88.9%, 42.3%, 94.3% in cases with atrophic endometrium, respectively.²⁷ Additionally, hysteroscopy had a specificity of 91.3%, a sensitivity of 91.3% and positive predictive values of 99.5% for the detection of endometrial malignancy in their study.²⁷ In another study reviewing the hysteroscopic reports of 25 menopausal patients treated by hysterectomy, the correlation was found between the pathologic findings on the uterine specimen and the diagnoses obtained by hysteroscopic view.²⁸ Also, sensitivity, specificity, and negative and positive predictive values of hysteroscopy to foresee a diagnosis of infiltrating carcinoma were 84.6%, 100%, 87.5%, and 100%, respectively in patients with a diagnosis of atypical hyperplasia on endometrial biopsy.

The vaginoscopic approach to hysteroscopy via hydro-distension of vagina without speculum and tenaculum is named as “no touch” hysteroscopy. This method was found to be effective and comfortable to evaluate the endometrial cavity in older women. Because additional interventions and instruments are required, providing endometrial biopsy during the procedure is both difficult and uncomfortable.^{29,30} The H Pipelle device (Figure 3d) has been developed based on the Pipelle to facilitate endometrial sampling after “no touch” hysteroscopy and it obtained an adequate endometrial biopsy without the need for additional instruments such as vaginal speculum and tenaculum.^{31,32} Nqu et al. compared the efficiency in evaluation of the endometrial cavity of vaginoscopic hysteroscopy using the H Pipelle with traditional hysteroscopy using the standard Pipelle.³³ They reported similar biopsy adequacy, pain score and procedure duration in two approaches.

Leiomyosarcoma constitutes 13% of all uterine sarcomas and the most common symptom is abnormal vaginal bleeding.³⁴ The incidence rate

was approximately 0.4 per 100,000 for leiomyosarcoma in the Nordic countries.³⁴ Uterine muscle, the connective tissue of blood vessels or a previously existing leiomyoma may be the source of leiomyosarcoma in uterus. It was reported that sarcomatous transformation in benign uterine leiomyomas may be seen at 0.1–0.8 percent.³⁴ It is difficult to diagnose of leiomyosarcoma with endometrial sampling, because it originates from myometrium. So, leiomyosarcoma is usually diagnosed by the examination of hysterectomy/myomectomy materials.³⁶ On the other hand, imaging methods such as computed tomography and MRI can not reliably distinguish between leiomyoma and leiomyosarcoma.³⁷ However, these imaging methods are used to assess size of tumour, to view metastases in the pelvic tissues and to identify tumour stage. It was reported that malignant degeneration should be considered on MR images of any degenerated leiomyoma showing an irregular contour.³⁸ Also, most experts suspect sarcoma in the case of rapidly growing uterine leiomyoma or uterus. However, this condition is reported in only 0.27–2.6% of women diagnosed with leiomyosarcoma.³⁶ In this case, the patient had intermittent vaginal bleeding as a symptom, a normal sized uterus with heterogeneous material in the endometrial cavity ultrasonographically and no pelvic spread on MR image.

According to our literature data, leiomyosarcomas diagnosed with Pipelle endometrial sampling has not been previously reported. Pipelle device has some advantages and disadvantages in the detection of endometrial pathology (Table 2).³⁹ Although pipelle device is simple, cheap and creates no severe pain for the patient, it samples only 4.2% of the endometrial surface area when the total surface area was taken into consideration.⁴⁰ Pipelle also provides limited diagnostic accuracy in cases with focal pathologies and direct biopsy methods such as hysteroscopy are advised in cases with suspected focal pathologies following ultrasonography.¹³ On the other hand, preoperative endometrial sampling with Pipelle was found to be sensitive and accurate for the diagnosis of high-grade endometrial tumors.¹⁶ Size and type of tumor and its location

TABLE 2: The advantages and disadvantages of Pipelle endometrial sampling in the detection of endometrial pathology.

Advantages of Pipelle	<ul style="list-style-type: none"> . A few minutes are sufficient for procedure. . It is well tolerated by the patient because of it creates less pain. . It is cheap technique. . It does not require anesthesia and hospitalization. . It has very low risk for uterine perforation. . It has a high degree of sensitivity and specificity for the detection of endometrial carcinoma.
Disadvantages of Pipelle	<ul style="list-style-type: none"> . Procedure may be painful especially for nulliparous women. . Failed insertion of Pipelle may occur. . It is not adequate for focal endometrial pathologies. . It provides diagnosis of endometrial pathologies without any therapeutic benefit.

within the uterine cavity, the mechanism of sampling and preparation method influence the detection of uterine cancer by Pipelle device.⁴¹

We reported a case of uterine leiomyosarcoma diagnosed by Pipelle endometrial sampling and it

was diagnosed histopathologically including severe nuclear atypia, increased mitotic activity and coagulative tumour-cell necrosis. This case illustrates the importance of Pipelle endometrial sampling in the diagnosis of uterine leiomyosarcoma.

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