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# Validation of Pipelle endometrial biopsy in patients with abnormal uterine bleeding in Kazakhstani healthcare setting

Gulzhanat Aimagambetova[1], Aiym Kaiyrlykyzy[2], Gauri Bapayeva[3], Talshyn Ukybassova[3], Kamila Kenbayeva[3], Bakytkali Ibrayimov[4], Alla Lyasova[5], Giulio Bonaldo[6], Giovanni Buzzaccarini[6,*], Marco Noventa[6], Antonio Simone Laganà[7], Milan Terzic[3,8,9]

[1] *Department of Biomedical Sciences, School of Medicine, Nazarbayev University, 020000 Nur-Sultan, Kazakhstan*

[2] *National Laboratory of Astana, Nazarbayev University, 010000 Nur-Sultan, Kazakhstan*

[3] *Clinical Academic Department of Women's Health, National Research Center of Mother and Child Health, University Medical Center, 020000, Nur-Sultan, Kazakhstan*

[4] *Department of Pathological Anatomy, National Research Center of Mother and Child Health, University Medical Center, 020000, Nur-Sultan, Kazakhstan*

[5] *Pathology bureau of Nur-Sultan city Administration, 010000 Nur-Sultan, Kazakhstan*

[6] *Department of Women and Children's Health, University of Padua, 35122 Padua, Italy*

[7] *Department of Obstetrics and Gynecology, "Filippo Del Ponte" Hospital, University of Insubria, 21100 Varese, Italy*

[8] *Department of Medicine, School of Medicine, Nazarbayev University, 020000 Nur-Sultan, Kazakhstan*

[9] *Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA*

*Correspondence: giovanni.buzzaccarini@gmail.com (Giovanni Buzzaccarini)

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*Background*: Abnormal uterine bleeding is a common sign which cover various conditions e/o pathologies. Different approaches are used to evaluate this condition. The aim of this study was to investigate the validity of Pipelle biopsy for endometrial sampling in Kazakhstani women with abnormal uterine bleeding. For this reason, we carried out a prospective study of 120 patients who underwent endometrial sampling due to abnormal uterine bleeding in a tertiary hospital setting in Kazakhstan. *Methods*: Statistics included descriptive analysis to evaluate the frequency of various endometrial conditions. The validity of Pipelle biopsy sampling was calculated by estimating sensitivity, specificity, accuracy, and positive and negative predictive values. For the Pipelle sampling validity assessment, we analyzed 120 samples, as 21 patients with insufficient samples were excluded. *Results*: Overall, concordance in histopathologic results was 92.93%. Pipelle sampling identified two cases of adenocarcinoma in our group. Moreover, endometrial hyperplasia was detected with 71.43% sensitivity, 98.82% specificity, PPV of 90.91% and NPV of 95.45%. However, the Pipelle reliability was low in cases of endometrial polyps. In conclusion, the Pipelle method was found to be valid for the diagnosis of endometrial hyperplasia and adenocarcinoma with high SN, SP, PPV and NPV. *Conclusions*: The Pipelle technique for evaluation of abnormal uterine bleeding in the Kazakhstani health care setting is a useful method with the highest efficacy in ruling out endometrial hyperplasia and diagnosing adenocarcinoma. If endometrial polyp was suspected under ultrasound scan in patients with abnormal uterine bleeding, physicians should consider other tools for endometrial sampling.

*Keywords*

Pipelle; Dilatation and curettage; Abnormal uterine bleeding; Postmenopausal bleeding; Endometrial hyperplasia

## 1. Introduction

Endometrial abnormalities are frequent problems in gynaecological patients in reproductive, pre- and postmenopausal periods. In the vast majority of cases, endometrial pathology appears as abnormal uterine bleeding (AUB), which is a broad term that describes abnormalities in the menstrual cycle involving frequency, regularity, duration, and volume of blood lost, excluding cases of pregnancy-related bleedings [1–3]. Up to one-third of reproductive age group women and more than two-thirds of peri- and postmenopausal women experience AUB requiring medical evaluation [1, 2].

Many endometrial sampling approaches have been developed and successfully used to identify benign endometrial pathologies and endometrial cancer (EC) in patients with AUB [4–8]. Endometrial biopsy techniques are represented by dilatation and curettage (D&C), aspiration office sampling techniques like the Vabra sampler and Pipelle device, and hysteroscopy [7, 8]. Well known as the "gold standard", D&C is a method for the diagnosis of endometrial pathology which was widely used in the past. However, the requirements for hospitalization and general anesthesia have made the procedure costly and less desirable. The office procedures, which

are more convenient and safer, less demanding, and inexpensive, such as the Pipelle biopsy device, have replaced the D&C technique with good patient acceptability [2, 7–10]. The Pipelle device is a flexible polypropylene tube that employs a suction mechanism [11]. The tube can be inserted into the endometrial cavity through the cervical canal without dilatation, which makes the technique favorable for use in an outpatient setting [2]. Although some studies have analyzed the efficacy of Pipelle biopsy for endometrial sampling and compared the Pipelle specimens with the D&C or hysterectomy specimens [2, 7–10], poor or no data are detectable from Kazakhstan.

Worldwide, the incidence of EC is increasing rapidly, with the highest disease burden reported in North America and Western Europe [12–14]. Kazakhstan has higher rates of mortality from endometrial malignancies compared to developed countries [15–17]. The introduction of Pipelle endometrial sampling in ambulatory care settings is necessary to improve the rate of early diagnosis of endometrial pathologies. As of January 2020, Pipelle biopsy is not commonly used in Kazakhstan and most endometrial tissue evaluations are performed using D&C. Therefore, the goal of the present study was to investigate the validity of the newly introduced endometrial sampling Pipelle into Kazakhstan and its consistency with D&C specimens.

In this article we analyze and discuss the results of our prospective study aimed at validating the Pipelle technique for endometrial sampling in the Kazakhstani health care setting. We have analyzed the concordance of histopathological results confirmed by Pipelle compared with D&C results. Pipelle endometrial sampling has recently been approved in Kazakhstan and our research is the first one in this field, investigating/assessing the reliability of Pipelle for endometrial biopsy in our clinical setting.

## 2. Materials and methods

### *2.1 Setting*

This cross-sectional study prospectively assessed patients who met the criteria for endometrial biopsy evaluation for abnormal pre- and post-menopausal bleeding. Recruitment took place in Clinical Academic Department of Women's Health of the University Medical Center (UMC), Nur-Sultan City, Kazakhstan, serving patients with gynecological pathologies as a tertiary care level institution. All trial procedures, protocols and data collections, and storage were approved by the Institutional Research Ethics Committee. Written informed consent was obtained from each participant.

### *2.2 Study participants*

Patients were approached if they had been signed up to undergo endometrial sampling through D&C within 3 months of recruitment. The endometrial samples were obtained just prior to hysteroscopy.

A consecutive sample of 120 participants was recruited. *Inclusion criteria* were age 18 years and older; with an intact uterus and cervix; endometrial biopsy recommendation due to (but not limited to) abnormal uterine bleeding and irregular cycles (for pre-menopausal women) or postmenopausal bleeding as an indication for the procedure. *Exclusion criteria* were cervical cancer, pregnancy, acute pelvic inflammatory disease, clotting disorders, acute cervical or vaginal infection, uterine anomalies/malformations, hysterectomy, previous endometrial ablation, or any intervention/procedure performed for Asherman's syndrome.

We considered both premenopausal and postmenopausal women, although abnormal bleeding has a different etiopathology. However, since our interest relies mainly in comparing Pipelle with the hysteroscopic and dilation and curettage method, we collected data from both groups.

### *2.3 Endometrial sample collection*

#### *2.3.1 Pipelle endometrial sampling*

In outpatient clinical settings, with the patient in the lithotomy position, bimanual examination is performed to determine the uterine size and position. After that, the cervix is centered in the speculum and cleansed with povidone-iodine solution. Without cervical dilatation and analgesia, probing of the cervix is performed gently with the uterine sound and the distance from the fundus to the external cervical is measured by the gradations on the uterine sound. The endometrial biopsy catheter tip is inserted into the cervix, avoiding contamination from the nearby tissues. The catheter tip is then inserted into the uterine fundus or until resistance is felt. Once the catheter is in the uterine cavity, the internal piston on the catheter is fully withdrawn, creating negative pressure and suction at the catheter tip. Endometrial tissue is aspirated from all the uterine walls, making several up and down passes to ensure that an adequate tissue sample is in the catheter. To remove the sample from the endometrial catheter, the piston is gently reinserted, forcing the tissue out of the catheter tip. If the tissue obtained is considered inadequate, the procedure is repeated in order to optimize sampling. Following this, the sample is placed in a container with ten percent formaldehyde and sent to the Department of Pathology for histopathological examination (HPE). Finally, it is mandatory to assert that samples were obtained independently from the menstrual phase.

#### *2.3.2 Hysteroscopy and dilation & curettage procedure*

Hysteroscopy and D&C are performed in the operating room under anesthesia according to the standard operating procedures for each sampling technique. Histopathology reports were categorized as proliferative, secretory, hyperplasia (simple or cystic), hyperplasia with atypia or complex hyperplasia and carcinoma.

### *2.4 Statistical methods*

The descriptive statistics of demographic and clinical characteristics, endometrial histopathology obtained by Pipelle biopsy and D&C were presented as frequencies and percentages. Continuous variables were reported as median with interquartile range. A two by two table was used for

**Table 1. Characteristics of patients undergoing Pipelle endometrial sampling.**

| | Sample of women undergoing Pipelle biopsy (n = 120) |
|---|---|
| Age, years | 42 (33–48) |
| BMI | 26.33 (21.95–30.99) |
| Menopausal status | |
| Premenopausal | 100 (83.33%) |
| Postmenopausal | 20 (16.67%) |
| Indication for biopsy | |
| Bleeding in reproductive age | 78 (65%) |
| Premenopausal bleeding | 26 (21.67%) |
| Postmenopausal bleeding | 16 (13.33%) |
| Having children | |
| No | 39 (32.50%) |
| Yes | 81 (67.50%) |
| Parity among women with children | 2 (1–3) |

Note: Continious variable presented as median (interquartile range), proportions as n (%).

calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the Pipelle versus Hysteroscopy/D&C, which was treated as the gold standard. Confidence intervals for sensitivity, specificity and accuracy are calculated using Clopper-Pearson confidence intervals. Confidence intervals for the predictive values are calculated using confidence intervals given by Mercaldo *et al.* 2007 [18]. The data was analyzed using Stata 13.

## 3. Results

Study population consisted of 120 patients who underwent endometrial sampling from January 2019 to September 2020 at the Clinical Academic Department of Women's Health of the UMC, Nur-Sultan City, Kazakhstan. Table 1 represents patients' features. The median age of the study group was 42 (33–48) years. The most common presenting indication for biopsy was bleeding in reproductive age (n = 78) followed by premenopausal bleeding (n = 26), and postmenopausal bleeding (n = 16). Tissue obtained for histopathology was 92.5% sufficient when the procedure was D&C/Hysteroscopy, while it was adequate in 82.5% of the Pipelle sampling cases. The performance of both D&C and Pipelle methods were very similar in the detection of the histologic appearance, as shown in Table 1. Between the two techniques, there is high concordance in histopathological diagnosis of proliferative and secretory endometrium, respectively 94.2% and 94.7%. The final sample for analysis consisted of 99 samples (21 patients with insufficient samples were excluded). Overall concordance in histopathological results was 92.93% (Table 2). However, since our samples were not related to the menstrual phase, it should be clearly considered that concordance is so high due to redistribution of concordance on histopathological reports. In particular, we found a 100% concordance in diagnosing adenocarcinoma (2 out of 2 cases). However, when considering only abnormal histological findings, the concordance is at the rate of 77.9%.

Table 3 shows the validity of the Pipelle technique in the identification of endometrial hyperplasia and adenocarcinoma. We found two cases of endometrial carcinoma diagnosed with Pipelle sampling and confirmed with D&C; 71.43% sensitivity, 98.82% specificity, PPV of 90.91%, NPV of 95.45%, and accuracy of 95.45% for endometrial hyperplasia.

Two cases of adenocarcinoma were identified: one postmenopausal woman and one premenopausal woman. Six of the 35 patients (17.14% [6.56; 33.65]). Five of the 35 patients (14.29%) had a polyp detected on D&C/Hysteroscopy biopsy but had no polyp visualized during Pipelle (Table 4). This can be attributed to aspiration sampling technique used in Pipelle biopsy. Using hysteroscopy as 'gold standard', the PPV of Pipelle endometrial samples in detecting endometrial polyps was 66.67%. The PPV was 66.67% in reproductive age women, 66.67% in premenopausal women and 50% in postmenopausal women. The PPV was 75% in reproductive age women, 66.67% in premenopausal women and 50% in postmenopausal women.

## 4. Discussion

We present the first study of Pipelle biopsy efficiency in Kazakhstani healthcare settings. With the growing number of endometrial cancer cases, it is crucially important to implement informative and reliable diagnostic methods into the clinical practice. Proper histological diagnosis is essential in order to choose further management and treatment options for AUB. The most important diagnostic step in the evaluation of AUB is an endometrial biopsy [8, 13, 14, 19, 20]. Different techniques of endometrial sampling were developed and used in clinical practice, including D&C, Pipelle sampling, hysteroscopy, etc. [8, 20, 21].

AUB is one of the main causes of office visits and constitutes more than 30% of patients attending gynecology outpatient departments [1, 2]. Since the XIXth century, when the most widely used technique for endometrial sampling, D&C, was invented by Recamier [8, 22] this procedure has become very useful and popular. For many decades, it has been the 'gold standard' method for endometrial sampling

**Table 2. Diagnostic consistency of histopathological reports obtained by D&C and Pipelle endometrial sampling techniques.**

| Endometrial histopathology report | Endometrial histopathology on Pipelle | Endometrial histopathology on D&C | Concordance in histopathological diagnosis |
|---|---|---|---|
| **Adenocarcinoma** | 2 | 2 | 100% |
| **Hyperplasia, including:** | 11 | 14 | 78.6% |
| Hyperplasia with atypia | 1 | 2 | 50% |
| Hyperplasia without atypia | 10 | 12 | 83.3% |
| **Proliferative** | 68 | 64 | 94.2% |
| **Secretory** | 18 | 19 | 94.7% |
| **Total** | **99** | **99** | **92.93%** |

**Table 3. Analysis of overall Pipelle biopsy reliability.**

| Endometrial characteristics | Sensitivity, % (95% CI) | Specificity, % (95% CI) | Positive predictive value, % (95% CI) | Negative predictive value, % (95% CI) | Accuracy, % (95% CI) |
|---|---|---|---|---|---|
| **Hyperplasia, including:** | 71.43 (41.90% to 91.61%) | 98.82 (93.62% to 99.97%) | 90.91 (58.08% to 98.63%) | 95.45 (90.17% to 97.96%) | 94.95 (88.61% to 98.34%) |
| Hyperplasia with atypia | 50 (1.26% to 98.74%) | 100 (96.27% to 100.00%) | 100 | 98.98 (96.04% to 99.74%) | 98.99 (94.50% to 99.97%) |
| Hyperplasia without atypia | 75 (42.81% to 94.51%) | 98.85 (93.76% to 99.97%) | 90.00 (55.51% to 98.48%) | 96.63 (91.49% to 98.71%) | 95.96 (89.98% to 98.89) |
| **Adenocarcinoma** | 100 (15.81% to 100.00%) | 100 (96.27% to 100.00%) | 100 | 100 | 100 (96.34% to 100.00%) |
| **Proliferative** | 96.88 (89.16% to 99.62%) | 82.86 (66.35% to 93.44%) | 91.18 (83.28% to 95.54%) | 93.55 (78.61% to 98.28%) | 91.92 (84.70% to 96.45%) |
| **Secretory** | 89.47 (66.86% to 98.70%) | 98.75 (93.23% to 99.97%) | 94.44 (70.67% to 99.17%) | 97.53 (91.41% to 99.32%) | 96.97 (91.40% to 99.37%) |

[2, 8, 19, 20, 23]. Imaging diagnostic follows or is helpful for an oncologic diagnosis, but this is not our study concern [24]. However, in some previous publications, it has been discussed that the uterine cavity scraping by D&C allows the evaluation of only up to 60% of the endometrial lining surface [8, 20, 25], while in 10% to 25% of cases D&C alone can fail to diagnose an endometrial pathology [2, 20, 26]. Together with some other disadvantages like risks of general anaesthesia, infections, bleeding and uterine perforation, D&C does not guarantee the obtainment of a sufficient sample of the endometrial lining [2, 8, 10, 25]. The above-mentioned disadvantages of D&C procedure have led to the development of a less invasive and more efficient method for endometrial sampling like the Pipelle device which is inexpensive, safe, and more convenient for use in an outpatient setting [2, 8]. In this study, we confirmed high validity of Pipelle biopsy for the detection of some endometrial pathology, but not all, and not in all age groups.

In the present study the most common symptom/indication for endometrial sampling was bleeding in reproductive age (n = 78, 65%) followed by premenopausal bleeding (n = 26, 21.67%), and postmenopausal bleeding (n = 16, 13.33%) ($P < 0.001$), which is in line with the previous researchers findings [2, 20]. Moreover, similarly to the cited studies [2, 20], the amount of our sample obtained for histological analysis was sufficient in 92.5% when the procedure was performed using D&C technique, while it was adequate only in 82.5% of cases by Pipelle sampling.

Discussing the reliability of the D&C procedure and Pipelle device, in our study the results of Pipelle sampling obtained for the diagnosis of endometrial hyperplasia and endometrial carcinoma were compared with Abdelazim *et al.* [20]. The results were also completely comparable with the study of Ilavarasi *et al.* [2] for endometrial carcinoma while it was slightly different for endometrial hyperplasia. For endometrial hyperplasia, our study shows SN of 71.43%, SP of 98.82%, PPV 90.91%, and NPV of 95.45%, while the study of Ilavarasi *et al.* [2] had SN, SP, PPV, and NPV of 64.2%, 88.8%, 94.1% and 85.5%, respectively. The higher reliability rates in our study might be attributed to the low number of cases.

The overall diagnosis consistency between D&C and Pipelle biopsy techniques in this study was quite high 92.93%. Both D&C and Pipelle methods were very similar in the detection of the histologic appearance of secretory and proliferative endometrium with high concordance. Our results were comparable with the results obtained in the study by Liu *et al.* [9], where the diagnosis consistency in terms of benign hyperplasia and endometrial cancer with Pipelle and D&C was 100%.

However, both D&C and Pipelle methods showed a limited capacity in the detection of endometrial polyps. In our study, in 17.29% of cases, a polyp was detected through D&C/Hysteroscopy biopsy and confirmed on Pipelle method (Table 4). Our results were much lower than the results of Seto *et al.* [27] which have shown that the PPV of Pipelle endometrial samples in detecting endometrial polyps was 56.3%. In their study, the probability of finding an endometrial polyp was higher in postmenopausal women (72.7%) compared to premenopausal women (53.7%) [27]. Our study showed that Pipelle had limited capacity in the

**Table 4. Reliability of Pipelle Biopsy for evaluation of endometrial polyps.**

| | Overall | Reproductive age | Premenopausal age | Postmenopausal age |
|---|---|---|---|---|
| Sensitivity, % (95% CI) | 17.14 (6.56% to 33.65%) | 12 (2.55% to 31.22%) | 25 (3.19% to 65.09%) | 50.00 (1.26% to 98.74%) |
| Specificity, % (95% CI) | 95.31 (86.91% to 99.02%) | 97.73 (87.98% to 99.94%) | 94.12 (71.31% to 99.85%) | 66.67 (9.43% to 99.16%) |
| Positive predictive value, % (95% CI) | 66.67 (34.75% to 88.25%) | 75 (87.98% to 99.94%) | 66.67 (17.43% to 94.99%) | 50.00 (10.75% to 89.25%) |
| Negative predictive value, % (95% CI) | 67.78 (64.18% to 71.17%) | 66.15 (62.68% to 69.46%) | 72.74 (63.73% to 80.19%) | 66.67 (28.76% to 90.83%) |
| Accuracy, % (95% CI) | 66.68 (57.53% to 76.73%) | 66.67 (54.29% to 77.56%) | 72 (50.61% to 87.93%) | 60 (14.66% to 94.73%) |

SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value.

detection/identification of endometrial polyps. Additionally, in cases with suspected endometrial polyps following ultrasonography, hysteroscopy is a preferable diagnostic tool. However, sonohysterogram could easily aid the targeted Pipelle usage in polyp's diagnosis. Further studies are needed in the Kazakhstan population in order to assess a greater Pipelle usefulness.

The results of our study confirm that the Pipelle sampling technique is valuable in detection of endometrial pathologies with high reliability in the diagnosis of endometrial hyperplasia and adenocarcinoma. Taking into consideration that Pipelle biopsy is a safe and inexpensive procedure without the requirement to administer analgesia it could be more widely used in an outpatient setting for evaluation of all cases of AUB. However, according to our results, Pipelle endometrial sampling procedure is not an excellent option for postmenopausal bleeding patients with thin endometrium. Other conditions or pathologies have not been investigated as suitable for Pipelle. For example, endometriosis is more efficiently diagnosed with ultrasound and laparoscopy [28–30]. Furthermore, istmocele, a common condition following cesarean section, is diagnosed with ultrasound and treated with hysteroscopy [31, 32]. Septate uterus and other morphologic anomalies still require other options such as ultrasound and its association with hysteroscopy [33, 34]. Finally, chronic endometritis (CE), a recent focus for infertility diagnosis and possible treatment, could be easily diagnosed with Pipelle and subsequent histologic exam [35]. For this reason, a prospective study should be assessed also considering CE possible outcome.

Our study has several limitations: the relatively small overall number of patients, a limited number of carcinoma cases, and the difference in the provider's experiences. Another limitation is the lack of follow-up of the unsuccessful specimens. In this report, we presented the preliminary data from our study. Recruitment of more cases into the study might enable a more accurate evaluation of the Pipelle method diagnostic validity and contribute to future recommendations.

## 5. Conclusions

In this preliminary study, we were able to obtain 82.5% of adequate samples by Pipelle biopsy. It had a high reliability and accuracy rate in diagnosing endometrial hyperplasia and adenocarcinoma. Thus, the Pipelle technique for evaluation of AUB is a valuable method for the diagnosis of endometrial pathologies with the highest efficacy in the identification of endometrial hyperplasia and adenocarcinoma. However, we should keep in mind that Pipelle has limited capacity in the detection/identification of endometrial polyps, especially in a postmenopausal age group. If the endometrial polyp is suspected on ultrasound scan, it is advisable to proceed with hysteroscopy.

## Author contributions

ASL, MT, GA GauB and GiuB designed the research study. KK, GauB, and TU performed the sample collection. BI and AL performed histological analysis. AK, GioB, AL, BI, GiuB, and MN performed data visualization and validation. MN and AK analyzed the data. GA, TU, KK, and AK wrote the manuscript. GiuB, MN, ASL, MT revised the manuscript. GA, AK, GauB, TU, KK, BI, AL, GiuB, GiBu, MN, ASL, and MT read and approved the final manuscript.

## Ethics approval and consent to participate

All study procedures, protocols, data collections and storage were approved by the Institutional Research Ethics Committee of Nazarbayev University and UMC (March 24, 2021) with approval code 392/24032021. Written informed consent was obtained from each participant.


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## Conflict of interest

The authors declare no conflict of interest.

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