10.5005/jp-journals-10032-1120

RESEARCH ARTICLE

Pipelle Endometrial Biopsy *vs* Dilatation and Curettage to Diagnose Endometrial Diseases in Abnormal Uterine Bleeding

[1]Nikhitha Chandrashekar, [2]Jyothi GS, [3]Prasanna Shetty

ABSTRACT

Aim: The objective of this study was to assess the adequacy of the sample aspirated in order to make a definite diagnosis of endometrial disease in abnormal uterine bleeding (AUB) and to draw comparisons between the histopathological findings of Pipelle endometrial aspiration biopsy and dilatation and curettage (D&C).

Materials and methods: Pipelle endometrial biopsy and D&C samples were collected from 100 patients with AUB in the Department of the Obstetrics and Gynecology and sent to the Department of Pathology of a tertiary care hospital for adequacy of the sample and for histopathological analysis.

Results: The Pipelle sample was adequate in 73% of the cases and inadequate in 27% compared with D&C, which showed 85% and 15%, respectively. About 53% of cases were comparable between D&C and Pipelle and 37% were discordant. For endometrial hyperplasia using Pipelle aspirator, the sensitivity was 58.8%, specificity was 91.6%, positive predictive value (PPV) was 58.8%, negative predictive value (NPV) was 91.6%, and concordance was 86%. For detection of endometrial carcinoma using Pipelle, the sensitivity was 50%, specificity was 99%, PPV was 50%, NPV was 99%, and concordance rate was 98%.

Conclusion: It is more convenient and cost-effective for patients to undergo pipelle biopsy to confirm normalcy and rule out endometrial hyperplasia rather than undergoing D&C initially. Out of the 27% of inadequate samples, 14.8% had fibroids and 11.1% had polyps, thus showing that tumors localized to a polyp or a small area of endometrium went undetected with Pipelle.

Clinical significance: Due to the high specificity and NPV and low sensitivity and PPV in diagnosing endometrial lesions and carcinomas, pipelle is suitable for women with a low risk of cancer. In cases where the diagnosis is hyperplasia on Pipelle, the patients are advised to undergo hysteroscopic-guided D&C following pipelle to confirm the diagnosis. This is also applicable for cases of polyps and fibroids.

Keywords: Abnormal uterine bleeding, Dilatation and curettage, Endometrial biopsy, Pipelle de Cornier.

[1]Intern, [2,3]Professor

[1,2]Department of Obstetrics and Gynecology, M. S. Ramaiah Medical College, Bengaluru, Karnataka, India

[3]Department of Pathology, M. S. Ramaiah Medical College Bengaluru, Karnataka, India

Corresponding Author: Nikhitha Chandrashekar, Intern Department of Obstetrics and Gynecology, M. S. Ramaiah Medical College, Bengaluru, Karnataka, India, Phone: +918023615818 e-mail: nikhic@gmail.com

How to cite this article: Chandrashekar N, Jyothi GS, Shetty P. Pipelle Endometrial Biopsy *vs* Dilatation and Curettage to Diagnose Endometrial Diseases in Abnormal Uterine Bleeding. J South Asian Feder Menopause Soc 2017;5(2):123-128.

Source of support: The authors extend their most sincere gratitude to the Medical Education and Research Trust (MERT) for granting funds of 10,000 INR to pursue this study.

Conflict of interest: None

Date of received: 26 July 2017

Date of acceptance: 19 September 2017

Date of publication: December 2017

INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as bleeding, i.e., excessive or occurs outside of the normal cyclic menstruation and accounts for two-thirds of hysterectomies. AUB is the commonest presenting symptom in the gynecology outpatient department accounting for 70% of all gynecological cases in peri- and postmenopausal years.[1] Because of its broad range of differential diagnosis, the diagnosis of AUB can be quite challenging. Despite a detailed history, various blood tests, and a thorough pelvic examination often involving transvaginal ultrasonography, the cause of the bleeding is established in only 50 to 60% of the cases.[2]

Dilatation and curettage is the most commonly used diagnostic technique for AUB. This method has been found to be inconvenient as it involves high costs of hospitalization and use of operation theater, bed shortages, complications and risk of anesthesia. Therefore, as an alternative method, Pipelle endometrial aspiration biopsy can be used as a safe, simple, inexpensive, and reliable outpatient procedure to assess the endometrial pathology. Pipelle is a flexible instrument made of soft plastic polypropylene material and works using a suction mechanism. It can be inserted into the cervical canal without dilatation. It is ideal for obtaining endometrial biopsy in outpatient settings.

It is useful in the workup of AUB, cancer screening, detection, and follow-up of precancerous hyperplasia and atypia, endometrial dating, and infertility.[3] Recently, endometrial aspiration biopsy has been found to be successful for diagnosing extrauterine malignancies as well

as low-grade endometrial sarcomas. The efficacy of the Pipelle has been studied and conflicting results have been obtained with different studies. It is generally felt that a positive biopsy can save time and cost, and avoid inconvenience to a patient, but a nonspecific finding should be interpreted with caution.[4]

Thus, further studies are needed to determine the efficacy of Pipelle as a tool for endometrial biopsy and establish the reliability of Pipelle biopsy, so that the number of traditional D&Cs done under general anesthesia could be reduced to a minimum. The present study is done to evaluate the efficacy of endometrial aspiration in comparison with D&C in the diagnosis of AUB, taking D&C histopathology findings as standard.

AIMS AND OBJECTIVES

- To assess the adequacy of the sample aspirated with regard to making a definite diagnosis.
- To draw comparisons between the histopathological findings of Pipelle endometrial biopsy and D&C.

MATERIALS AND METHODS

This is a prospective study done on patients presenting with AUB for a period of 1 year from June 2015 to June 2016 in the Department of Obstetrics and Gynecology in collaboration with the Department of Pathology of a tertiary hospital in South India. This study has been approved by the Ethics Committee of our institute.

The present study included patients of premenopausal, perimenopausal, and postmenopausal age groups between 30 and 65 years, who presented with complaints of AUB, and in need of D&C and willing to give written informed consent for pipelle endometrial biopsy. Data were also collected on a proforma sheet that included history, general physical examination, and local examination. Information was obtained regarding adequacy of the sample as well as a comparison of histopathological examination (HPE) reports of pipelle endometrial biopsy with D&C. Exclusion criteria included patients with acute pelvic inflammatory disorder of the genital tract, pregnancy, gross evidence of cervical malignancy, and acute cervical and vaginal infections.

METHOD OF COLLECTION OF DATA

Patient was put in dorsal position. First, we performed the procedure of endometrial aspiration. The cervix was held with tenaculum/volsellum forceps during insertion of the aspirator (pipelle curette) into the cervical canal. After reaching the fundus of the uterus, the piston was pulled back to provide negative pressure. Endometrial tissue was aspirated. The biopsy specimen was placed in a bottle labeled 1, containing 10% formaldehyde for tissue processing. The D&C procedure was performed after endometrial aspiration biopsy, by dilatation of the cervix and using a sharp curette to sample the endometrial tissue. This biopsy specimen was placed in a bottle labeled 2, containing 10% formaldehyde for HPE. Both samples were evaluated in the pathology department of our institution. The adequacy of the sample and the histopathological report were interpreted by the same pathologist. Histopathological findings were categorized into six groups, such as normal, focal lesions, hyperplasia, atypia, atrophy, and insufficient material.[5] Pipelle endometrial aspiration biopsy and D&C samples were collected from 100 patients with AUB in the Department of the Obstetrics and Gynecology and sent to the Department of Pathology of a tertiary hospital, for histopathological analysis.

STATISTICAL ANALYSIS

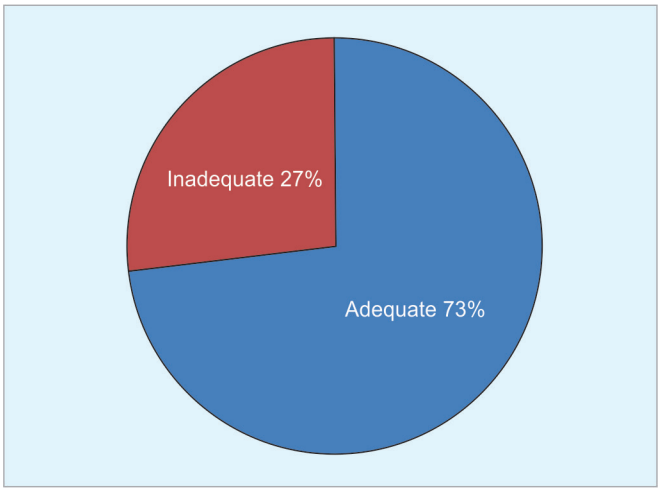
The qualitative parameters, such as HPE findings were expressed in terms of frequency and percentages. Sensitivity, specificity, NPV, and PPV of endometrial aspiration HPE were computed using 2 × 2 tables. To validate the endometrial aspiration technique, D&C histopathology was considered as the golden standard.

RESULTS

The findings are tabulated as follows:

Graph 1 illustrates that 73 (73%) samples out of the 100 were adequate and 27 (27%) were inadequate using pipelle. By the method of D&C, 87 (87%) were adequate samples and 13 (13%) were inadequate.

Table 1 shows the endometrial HPE of the inadequate pipelle samples, the highest being proliferative endometrium at 33.3%. About 40.7% of the inadequate pipelle samples came back inadequate by D&C as well. Table 2 depicts the pathologies present in the patients who had inadequate pipelle samples. These include postmenopausal



Graph 1: Adequacy of sample by Pipelle aspiration

Table 1: Endometrial HPE of cases with inadequate samples by Pipelle

Endometrial lesion	*Number (n = 27)*	*Percentage*
Proliferative endometrium	9	33.3
Secretory endometrium	4	14.8
SEH	3	11.1
Complex endometrial hyperplasia	0	–
Endometrial polyp	3	11.1
Atrophic endometrium	1	3.7
No opinion	11	40.7

Table 2: Pathologies present in inadequate samples

Probable cause for inadequacy	*Number (n = 27)*	*Percentage*
Postmenopausal bleeding	6	22.2
Fibroid	4	14.8
Polyp	3	11.1
Cervical stenosis	1	3.7
Vaginal mass	1	3.7

Table 3: Histopathological diagnosis by Pipelle biopsy and D&C

	Pipelle biopsy		*D&C*	
Diagnosis	*Number (n = 100)*	*%*	*Number (n = 100)*	*%*
Proliferative endometrium	36	36	40	40
Secretory endometrium	18	18	22	22
Simple hyperplasia	15	15	16	16
Complex hyperplasia	0	0	–	–
Complex hyperplasia with atypia	2	2	–	–
Adenocarcinoma	1	1	2	2
Atrophic endometrium	1	1	0	0
Polyp	0	–	3	3
SCC	1	1	0	0
Hormonal imbalance	–	–	3	3
Scanty tissue	27	27	15	15

bleeding, fibroids, polyps, cervical stenosis, and vaginal masses. Table 3 shows the endometrial HPE using pipelle and D&C. The most common finding in both pipelle and D&C was proliferative endometrium followed by secretory endometrium. Malignancy like adenocarcinoma was seen in 2% of the D&C HPE and 1% by pipelle. Table 4 shows the discordant and concordant histopathological findings between pipelle and D&C. There were 37 (37%) discordant cases. Pipelle biopsy was comparable with D&C in 53% of the cases. The maximum was proliferative endometrium with 49%. Table 5 shows the sensitivity, specificity, accuracy rate, PPV, and NPV of the Pipelle de Cornier device in detecting endometrial hyperplasia and carcinoma. The specificity and NPV in both hyperplasia and carcinoma were the highest values.

DISCUSSION

Pipelle biopsy is a safe, simple, cost-effective, and less painful alternative to D&C. It can be done on an outpatient department basis and does not require general anesthesia. In this study, the primary objective was to assess the adequacy of the sample in order to make a definitive diagnosis. The adequacy rate using pipelle aspirator was 73% compared with D&C, which was 87%. This shows a 14% difference in outcome of adequacy between the two, which is not a significant difference. Thus, pipelle

Table 4: Comparison between Pipelle and D&C HPE

	Pipelle HPE not comparable to D&C HPE		*Pipelle biopsy comparable to D&C*
Endometrial HPE	*Number (%) n = 037 (37)*	*D &C HPE – number (percentage)*	*Number (%)*
Proliferative endometrium	10 (27)	Simple hyperplasia w/o atypia: 3 (30) Secretory: 2 (20) Hormonal imbalance: 1 (10) Scanty tissue: 4 (40)	26 (49)
Secretory endometrium	2 (5.4)	Proliferative: 1 (50) Adenocarcinoma: 1 (50)	17 (32)
SEH without atypia	5 (13.5)	Proliferative: 2 (40) Secretory: 1 (20) Hormonal imbalance: 1 (20) No opinion: 1 (20)	9 (16.9)
Complex endometrial hyperplasia with atypia	1 (2.7)	Simple hyperplasia w/o atypia: 1 (100)	
Adenocarcinoma			1 (1.8)
Scanty tissue	17 (45.9)	Proliferative endometrium: 9 (52.9) Secretory endometrium: 4 (23.5) SEH w/o atypia: 3 (17.6) Endometrial polyp: 1 (5.9)	
Atrophic	1 (2.7)	Proliferative: 1 (100)	
SCC	1 (2.7)	No opinion: 1 (100)	

Table 5: Validity of Pipelle endometrial sampling for endometrial hyperplasia and endometrial carcinoma

Validity of PES	*Endometrial hyperplasia (%)*	*Endometrial carcinoma (%)*
Sensitivity rate	58.8	50
Specificity rate	91.6	99
Accuracy rate	86	98
PPV	58.8	50
NPV	91.6	99

holds good with regard to sample adequacy. Our study draws parallel to a study done by Giannecopoulos et al[6] wherein the adequacy rate was 76.4% and the inadequacy rate was 21%.

Out of the total inadequate samples by pipelle, 11.1% was diagnosed with endometrial polyps on D&C. This is in concurrence with a study by Guido et al[7] wherein 5 of the 11 patients with false negative results had benign tumors present in the form of an endometrial polyp. Three of the 11 patients had disease localized to <5% of the surface area of the endometrium. They, therefore, concluded that tumors localized to a polyp or a small area of endometrium may go undetected with pipelle. An additional hysteroscopic-guided D&C is required for definitive diagnosis in these cases. Six (22.2%) of the inadequate samples were postmenopausal bleeding. Thus, the inability to obtain adequate endometrial tissue might have been due to the thin endometrial lining. Four (14.8%) of the inadequate samples were cases of fibroid, so the inadequacy may have been due to the decreased endometrial surface available for sampling. One case (3.7%) had cervical stenosis and 1 (3.7%) had a vaginal mass and, hence, there was difficulty in negotiating the pipelle into the cervical canal to reach the endometrial surface leading to inadequate sample. The results are also comparable to a study conducted by Tanriverdi et al,[8] where the adequacy rate was 77.2% and the inadequacy rate was 22.8%. The authors concluded that pipelle sampling should be reserved for those patients with only a minimal risk for endometrial carcinoma, hyperplasia, and polyps. In the study by Batool et al,[9] results show that pipelle is less efficient than other methods as a screening tool as only a small proportion of the endometrial surface could be sampled.

The secondary objective was to draw comparisons between the histopathological findings of pipelle endometrial biopsy and D&C. There were 37 cases (37%) with discordant reports between pipelle and D&C. Out of the ten cases that were diagnosed as proliferative by pipelle, 3 (30%) were diagnosed as simple hyperplasia without atypia, 2 (20%) as secretory, 1 (10%) as hormonal imbalance, and 4 (40%) as scanty tissue on D&C. Out of the 2 cases diagnosed with secretory endometrium, 1 (50%) was proliferative and 1 (50%) adenocarcinoma by D&C. Out of 5 simple endometrial hyperplasia (SEH) without atypia, 2 (40%) were proliferative, 1 (20%) secretory, 1 (20%) hormonal imbalance, and 1 (20%) scanty tissue. The sample that was diagnosed as complex hyperplasia with atypia by pipelle was reported as simple hyperplasia without atypia on D&C. Out of 17 scanty tissues by pipelle, 9 (52.9%) were proliferative, 4 (23.5%) were secretory, 3 (17.6%) SEH without atypia, and 1 (5.9%) polyp by D&C. One proliferative endometrium was diagnosed as atrophic by pipelle and one squamous cell carcinoma (SCC) by pipelle gave no opinion by D&C.

Out of all the 7 cases of discrepancy between pipelle and D&C regarding simple hyperplasia, only 3 (6.3%) cases of simple hyperplasia were diagnosed incorrectly by pipelle as proliferative. In 3 (6.3%) cases, simple hyperplasia was not diagnosed due to the insufficiency of the sample. And one sample diagnosed as SEH on D&C was complex hyperplasia with atypia on pipelle. The rest of the 9 (19.1%) cases were comparable using both methods. This evidence proves that pipelle is an efficient method in detecting hyperplasia, but D&C still remains the gold standard.

Using pipelle, 1 (2.7%) sample was diagnosed as complex hyperplasia with atypia, but by D&C, it was shown to be simple hyperplasia without atypia. The pipelle device also diagnosed 5 cases that were normal on D&C as simple hyperplasia without atypia. The reason for discrepancy in the diagnosis could be due to difference in the areas of the endometrium sampled as some areas may be differentiated more than other regions. This shows that the pipelle device is suitable for diagnosing premalignant lesions. One sample was shown to be SCC on pipelle, which gave no opinion on D&C, showing some evidence that pipelle is an effective method of diagnosing endometrial carcinomas. The aspirator surpasses the D&C, as it has an ability to suction the loose malignant cells that are present in the endometrium.

Pipelle biopsy was comparable with D&C in 53% of the cases. The sensitivity of Pipelle de Cornier device in detecting endometrial hyperplasia was 58.8%, specificity was 91.6%, concordance was 86%, PPV was 58.8%, and NPV was 91.6%. From the above findings, we can decipher that the pipelle device would be more useful in ruling out endometrial hyperplasia and carcinoma than in diagnosing them, as the specificity and NPV are in the higher range with 91.6% each and sensitivity and PPV derived in our study were in the lower range (58.8%). Thus, the test should be limited to patients who have low risk for hyperplasia and endometrial carcinoma for confirming normalcy rather than for detecting hyperplasia itself. Our study is comparable to a study by Fuat Demirkiran et al,[5] wherein sensitivity of pipelle

biopsy in detection of hyperplasia was 67% and NPV of pipelle biopsy was 99% for malignancy. It showed that neither pipelle nor D&C is an adequate method for focal endometrial pathologies. Both biopsy methods are not perfect, but pipelle biopsy is a cheaper and easier technique compared with D&C, and ultrasonographic findings of endometrium should be considered prior to endometrial biopsy.

In our study for detection of endometrial carcinoma, out of the two adenocarcinomas diagnosed by D&C, using pipelle, one gave the same diagnosis as D&C, but the second one showed hypersecretory changes. Although using pipelle one SCC was identified, the same sample came back inadequate using D&C. Similarly, in a study by Ferry et al,[4] poor results were obtained in well-differentiated, low volume, and minimally invasive tumors, i.e., most early tumors, precluding its use as a screening tool. A positive biopsy can save patients the time, cost, and inconvenience of a D&C. However, in light of these findings, a nonspecific finding should be interpreted with caution.

Our study is comparable to a study by Bunyavejchevin et al[10] wherein the sensitivity and specificity of pipelle in endometrial tissue samplings compared with fractional curettage were 87.5% and 100%, respectively. In their study, 1 out of 3 cases of endometrial adenocarcinoma could not be diagnosed by pipelle. They concluded that the use of pipelle to replace fractional curettage in the management of postmenopausal bleeding should be done with caution. False negative results could occur in focal disease of malignancy of the endometrium. Contrary to our study, a study by Yasmin et al[11] has shown 100% sensitivity and 94% specificity for diagnosing endometrial hyperplasia using pipelle and 75% sensitivity and 100% specificity for endometrial carcinoma. In addition, a study by Abdelazim et al[12] showed 100% sensitivity, 100% specificity, and 100% accuracy for diagnosing endometrial hyperplasia as well as carcinoma. In this study also, 97.9% of the sample collected by pipelle was adequate for HPE.

In our study, the sensitivity was 50%, PPV was 50%, specificity was 99%, NPV was 99%, and concordance rate was 98% for diagnosing endometrial carcinomas. The low rate of sensitivity may be because the number of cases of carcinoma was limited to two. Thus, the values obtained may not adequately demonstrate the accuracy of pipelle in diagnosing endometrial cancer. To obtain more fruitful results with respect to endometrial carcinoma, a larger sample size inclusive of more postmenopausal women who are predisposed to endometrial carcinoma should be included in such a study.

As pipelle is an inexpensive, painless, easy method, the benefits outweigh the risks and it would be more cost-effective for patients to undergo pipelle to confirm normalcy and rule out hyperplasia rather than undergoing D&C at the very beginning.

CONCLUSION

In the present study, it is seen that the ability of pipelle to obtain adequate sample is good, with a rate of 73%. It is comparable to the method of D&C, which had an adequacy of 87%. So, with regard to obtaining adequate sample, pipelle shows equivocal results compared with D&C. The inadequacy of sample (27%) was due to the reasons that 22.2% cases had postmenopausal bleeding, 14.8% had fibroids, and 11.1% had polyps. Tumors localized to a polyp or a small area of endometrium were undetected with pipelle. An additional hysteroscopic-guided D&C is required for definitive diagnosis in these cases.

With respect to the diagnosis of endometrial hyperplasia, the method of pipelle aspiration showed high NPV and specificity at 91.6% and, hence, it can be used as a method to confirm normalcy in patients with low risk of endometrial hyperplasia. As the PPV and sensitivity was 58.8% each, it should be used more as a method to confirm the absence of hyperplasia than to diagnose its presence. Thus, pipelle is an effective tool for patients with low risk of cancer. As the concordance between the D&C and pipelle was 86%, we can see that the two show parallel results.

Owing to the small sample size of two cases, we are unable to come to an accurate result regarding the efficacy of pipelle in diagnosing endometrial carcinomas.

Due to the affordability and acceptability and being a less painful method, pipelle procedure is suitable for all females of reproductive age group with low risk of cancer to confirm normalcy and rule out hyperplasia. It can be done on an outpatient basis so there will be good compliance among patients. It will be of great help in detecting the cancer before it progresses to the end stages. If such cases are detected by pipelle as hyperplasia, the patients will be advised to undergo hysteroscopic-guided D&C after pipelle. This would prevent unnecessary D&C from being done in normal women and limit D&C to those at risk of developing carcinoma.

In cases of endometrial polyps or fibroids diagnosed on ultrasonogram and patients with vaginal mass or cervical stenosis, those patients would be advised to directly undergo D&C. This is owing to insufficiency of sample obtained in such patients using pipelle.

CLINICAL SIGNIFICANCE

In cases where the diagnosis is hyperplasia on pipelle, the patients are advised to undergo hysteroscopic-guided D&C

following pipelle to confirm the diagnosis. This will prevent unnecessary painful and expensive D&Cs from being done in normal women and limit the procedure only to those at risk of developing carcinoma. This is also applicable for cases of polyps and fibroids, as out of the 27% of inadequate samples, 14.8% had fibroids and 11.1% had polyps, thus showing us that tumors localized to a polyp or a small area of endometrium went undetected with pipelle.

REFERENCES

1. Shams G. Comparison of Pipelle de Cornier with conventional dilatation and curettage in terms of patients' acceptability. J Postgrad Med Inst 2012;26(4):418-421.
2. Kotdawala P, Kotdawala S, Nagar N. Evaluation of endometrium in peri-menopausal abnormal uterine bleeding. J Midlife Health 2013 Jan-Mar;4(1):18-21.
3. Zuber TJ. Endometrial biopsy. Am Fam Physician 2001 Mar 15;63(6):1131-1135.
4. Ferry J, Farnsworth A, Webster M, Wren B. The efficacy of the pipelle endometrial biopsy in detecting endometrial carcinoma. Aust N Z J Obstet Gynaecol 1993 Feb;33(1):76-78.
5. Demirkiran F, Yavuz E, Erenel H, Bese T, Arvas M, Sanioglu C. Which is the best technique for endometrial sampling? Aspiration (pipelle) versus dilatation and curettage (D&C). Arch Gynecol Obstet 2012 Nov;286(5):1277-1282.
6. Giannecopoulos C, Karakitsos P, Stergiou E, Koutroumbi E, Giannikos L, Kyrcou K. Uterobrush and Pipelle endometrial samplers in diagnosis of endometrial pathology. Eur J Gynaecol Oncol 1996;17:451-452.
7. Guido RS, Kanbour-Shakir A, Rulin M, Christopherson W. Pipelle endometrial sampling: sensitivity in the detection of endometrial cancer. J Reprod Med 1995 Aug;40(8):553-555.
8. Tanriverdi HA, Barut A, Gün BD, Kaya E. Is pipelle biopsy really adequate for diagnosing endometrial disease? Med Sci Monit 2004 Jun;10(6):CR271-CR274.
9. Batool T, Reginald PW, Hughes JH. Outpatient pipelle endometrial biopsy in the investigation of postmenopausal bleeding. Br J Obstet Gynaecol 1994 Jun;101(6):545-546.
10. Bunyavejchevin S, Triratanachat S, Kankeow K, Limpaphayom K. Pipelle versus fractional curettage for the endometrial sampling in postmenopausal women. J Med Assoc Thai 2001 Jun;84 Suppl 1:S326-S330.
11. Yasmin F, Farrukh R, Kamal F. Efficacy of pipelle as a tool for endometrial biopsy. Biomedica 2007 Jul-Dec;23:116-119.
12. Abdelazim IA, Aboelezz A, AbdulKareem AF. Pipelle endometrial sampling versus conventional dilatation & curettage in patients with abnormal uterine bleeding. J Turk Ger Gynecol Assoc 2013 Mar 1;14(1):1-5.