Management of Insufficient Endometrial Biopsy for Investigation of Premenopausal Abnormal Uterine Bleeding

Felix YF IU MBChB, MRCOG (UK)
Stephen PY YONG MBBS, FRCOG, FHKAM (O&G)
Hon-Cheung LEE MBBS, FRCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Tuen Mun, New Territories, Hong Kong

Objectives: To evaluate the risk of endometrial pathology and options of subsequent management in patients with abnormal uterine bleeding whose endometrial biopsies were reported as insufficient.
Methods: This was a retrospective study on insufficient endometrial biopsies performed for the investigation of premenopausal abnormal uterine bleeding in Pok Oi Hospital, Hong Kong, from 1 January 2009 to 31 December 2011. The subsequent management and outcomes were then analysed.
Results: A total of 2612 patients underwent outpatient endometrial biopsy during the study period. Among these, 133 (5.1%) of endometrial biopsies were reported as "insufficient tissue for diagnosis"; eight patients were lost to follow-up. The median (interquartile range) duration of follow-up for the remaining 125 (94%) patients was 384 (19-1113) days. A total of 49 (39%) patients had no further invasive investigations; of these, four patients eventually underwent hysterectomy for benign disease unrelated to endometrial hyperplasia or carcinoma. Overall, 76 (61%) patients had further investigations, 15 had repeat endometrial sampling and 61 had hysteroscopy with endometrial biopsy. Hysteroscopy showed polyps or fibroids in 16 (26%) patients; of these, nine underwent polypectomy or hysteroscopic resection. Endometrial hyperplasia or malignancy was not detected in any subject. Furthermore, endometrial hyperplasia did not develop de novo during the study period. There was one case (0.8%) of adenocarcinoma diagnosed 608 days after a normal repeat endometrial biopsy.
Conclusion: The risk of endometrial hyperplasia and carcinoma was low after an insufficient endometrial biopsy for premenopausal abnormal uterine bleeding. Patients with persistent symptoms should be further investigated. Benign polyps and fibroids amenable to hysteroscopic treatment were common and hysteroscopy should be considered when further investigation is indicated.
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Introduction

Abnormal uterine bleeding is a common reason for gynaecological consultation. It occurs when a woman experiences a change in her menstrual blood loss, or if the degree of blood loss or vaginal bleeding pattern differs from that experienced by the age-matched general female population. Normal menstruation and normal menstrual cycle are defined according to the regularity, frequency, amount, and duration of menstrual flow. Abnormal uterine bleeding can occur due to non-structural and structural causes[1,2]. It is an important presenting symptom of uterine cancer, which is the fourth most common cancer in Hong Kong women[3].

Outpatient endometrial biopsy without concurrent imaging is a commonly performed procedure for diagnosing endometrial hyperplasia and carcinoma when investigating abnormal uterine bleeding. It involves passing a sampler through the cervix to obtain endometrial tissue with suction. The sensitivity for identifying endometrial cancer varies between 70% and 100%, but the specificity is 100%[4]. The guideline published by the United Kingdom National Institute for Health and Clinical Excellence (NICE) recommends endometrial biopsy for abnormal uterine bleeding in women aged ≥45 years, and in those with persistent intermenstrual bleeding, treatment failure, or ineffective treatment[4].

An endometrial biopsy may be reported as "insufficient" when there is scanty or no endometrial tissue. Reported rates of insufficient outpatient endometrial biopsy for abnormal uterine bleeding range from 5-45.6%[5-12]. However, there are no standard criteria to define

Correspondence to: Dr Felix YF Iu
Email: iuyfoghk@gmail.com

what represents an insufficient endometrial biopsy. An insufficient biopsy may suggest that the uterine cavity has not been correctly sampled, but may also be consistent with atrophic endometrium without significant pathology[13].

The designation of a biopsy as insufficient may have medicolegal and management implications. Uterine malignancy missed in an insufficient biopsy can be a cause for litigation, especially if the insufficient biopsy is assumed to be normal and not investigated further. Additional investigations such as repeat biopsy or hysteroscopy may cause patient anxiety and inconvenience, additional morbidities, increased costs, and administrative burden. Despite this, there is no global consensus on whether an insufficient endometrial biopsy should be routinely investigated further.

Two guidelines lay out the protocol for management of women with premenopausal bleeding whose endometrial biopsies yield an insufficient sample. According to Cancer Australia[14], a national government agency working to reduce the impact of cancer on all Australians, "if insufficient material is obtained for a histological diagnosis, no further investigation is required in the absence of ongoing bleeding unless the woman has an endometrial thickness of over 12 mm for premenopausal women and 5 mm for peri-menopausal women." According to The Society of Obstetricians and Gynaecologists of Canada[15], "if an office endometrial biopsy cannot be performed or the sample is insufficient, then patients should be triaged according to their risk for endometrial cancer. Those felt to be at low risk for endometrial cancer or in whom atrophy is suspected or who are medically unfit, should proceed to transvaginal ultrasound. Those at high risk (i.e. obese, nulliparous, post-menopausal, diabetic women, or those taking tamoxifen) should proceed to D&C [dilation and curettage], with or without hysteroscopy, as a negative ultrasound would not necessarily be completely reassuring and a positive ultrasound would require tissue sampling regardless."

This study aimed to: (1) determine the risk of endometrial pathology in women with premenopausal abnormal uterine bleeding whose endometrial biopsies were reported as insufficient; and (2) evaluate the options for subsequent management. The findings from this study will be useful in the counselling and decision-making of further management of women with insufficient endometrial biopsies.

Methods

This was a retrospective observational study over a 3-year period from 2009 to 2011, carried out in Pok Oi Hospital, a subsidiary tertiary referral centre established by the Department of Obstetrics and Gynaecology, Tuen Mun Hospital of the New Territories West Cluster of Hong Kong. Patients with abnormal uterine bleeding who presented to the gynaecology clinic in Tuen Mun Hospital and Pok Oi Hospital were arranged for endometrial biopsy in the latter hospital at the clinician's discretion.

A dedicated half-day endometrial biopsy session was run twice weekly. Endometrial biopsy was performed using a 3-mm sampler (Endosampler, MedGyn Products Inc., Lombard [IL], US, or Pipet Curet, CooperSurgical, Trumbull [CT], US) with or without cervical priming with misoprostol. Mefenamic acid or paracetamol was prescribed for pain relief, as required. The procedures were performed by trainees in obstetrics and gynaecology with the assistance of registered nurses and health care assistants.

The target group of this study included all premenopausal women with abnormal uterine bleeding whose endometrial biopsies were reported as insufficient. Abnormal uterine bleeding is defined as a change in menstrual loss perceived by a woman, or a degree of menstrual loss or vaginal bleeding pattern that is different from that experienced by the age-matched general female population. Exclusion criteria were technical failure of the procedure and concurrent imaging such as hysteroscopy and ultrasonography.

The diagnosis of insufficient sample was based on the final report issued by the Department of Clinical Pathology, Tuen Mun Hospital, Hong Kong. There are no standard criteria for the histopathological diagnosis of insufficient sample, and no consensus within the department with regard to criteria for adequacy.

The histopathology reports were reviewed by specialists of our department. There was no protocol in our department for the management of an insufficient endometrial biopsy. The decision for further investigation was left to the individual clinician's discretion, taking into account the clinical condition of the patient and her wish.

The number of patients included in the study was generated from the Hospital Authority's Clinical Data Analysis and Reporting System. A list of endometrial biopsies reported as insufficient was obtained from the database of the Department of Clinical Pathology, Tuen Mun Hospital, Hong Kong. Other relevant clinical

information was obtained from the electronic (Hospital Authority's Clinical Management System) and written case notes.

The primary endpoint was a diagnosis of endometrial hyperplasia or malignancy. The patients were followed up in this study till: (1) diagnosis of endometrial hyperplasia or malignancy; (2) hysterectomy; (3) case closed by the attending clinician; or (4) end of the study period.

Results

A total of 2612 patients underwent outpatient endometrial biopsy for the investigation of premenopausal abnormal uterine bleeding from 1 January 2009 to 31 December 2011. In all, 133 (5.1%) cases were reported as "insufficient tissue for diagnosis". The uterine lengths taken by uterine sounding during the procedures were documented as at least 6 cm in all the cases studied. There was no documented technical failure, difficulty, or complication in any of these procedures. The median (interquartile range [IQR]) age of the patients was 48 (36-58) years. Overall, 33 patients had an enlarged uterus due to fibroids, and eight patients were lost to follow-up. The median (IQR) duration of follow-up in the remaining 125 (94%) patients was 384 (19-1113) days. Results of this study are summarised in the Figure.

A total of 49 (39%) patients had no further invasive investigations. Of these, 44 patients had no further menstrual symptoms or reached menopause; one patient had persistent symptoms but refused further investigation; and four patients eventually had hysterectomy for benign disease unrelated to endometrial hyperplasia or carcinoma, as confirmed on the final pathology reports. The median (IQR) duration of follow-up was 301 (19-1113) days for this group of patients.

Overall, 76 (61%) patients had further investigations;

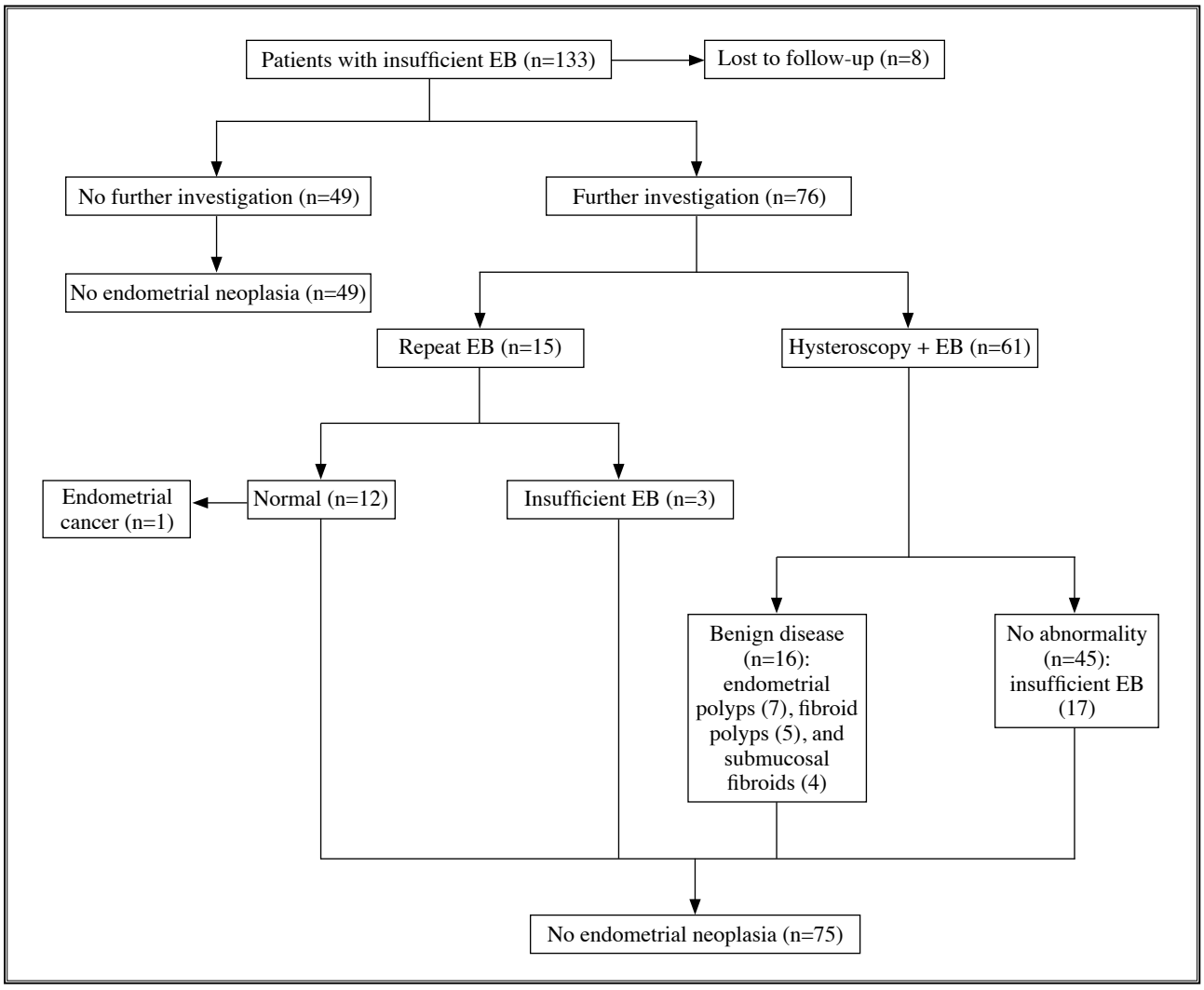

Figure. Summary of results of this study

Abbreviation: EB = endometrial biopsies

66 (87%) of whom were performed within 6 months of the initial endometrial biopsy (median, 69 days after the initial endometrial biopsy). Further investigations were arranged immediately after the initial insufficient biopsy for 55 patients, while 21 patients were initially observed and then investigated further for persistent symptoms.

Patients who had further investigation were divided into two groups. The first group included 15 patients who had repeat endometrial sampling. However, three biopsies yielded insufficient material for diagnosis again; one of these patients eventually underwent hysterectomy for intrauterine fibroid, and no pathology or recurrent symptoms were detected in the other two patients during the study period. The other 12 patients had normal results. However, a third endometrial biopsy was repeated 608 days later for irregular and prolonged menstrual bleeding in one patient who was diagnosed to have endometrioid adenocarcinoma. This was a 51-year-old woman with dysfunctional uterine bleeding and a normal-sized uterus whose first endometrial biopsy was reported as insufficient; a repeat endometrial biopsy performed 56 days later showed secretory endometrium. The third endometrial biopsy showed metaplastic squamous cells with focal areas suggestive of complex hyperplasia. Subsequent hysteroscopy showed normal findings but endometrial biopsy showed atypical glands (nuclear atypia). Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. The final pathological report was endometrioid adenocarcinoma stage 1A1 (with focal superficial invasion of myometrium).

The second group comprised 61 patients who underwent hysteroscopy with endometrial biopsy. In all, 16 (26%) had benign disease on hysteroscopy: seven had endometrial polyps, five had fibroid polyps, and four had submucosal fibroids. Of these, nine had hysteroscopic polypectomy / resection. No premalignant or malignant conditions were noted in the final pathology reports. The other 45 patients had normal hysteroscopic findings with 17 repeat endometrial biopsies still insufficient for diagnosis. Of the 61 patients in this group, five eventually had hysterectomy for persistent symptoms but there was no endometrial hyperplasia or malignancy detected on histopathological examination.

Discussion

Reported rates of insufficient outpatient endometrial biopsy for abnormal uterine bleeding, in both pre- and post-menopausal women in varying proportions, ranged from 5-45.6%[5-12]. In this study, 5.1% of endometrial biopsies for premenopausal abnormal uterine bleeding were reported as "insufficient tissue for diagnosis". The relatively low rate in our study was consistent with the exclusion of postmenopausal status, which is associated with higher rates of insufficient biopsy[6,11].

Farquhar et al[16] reported 46 (4.5%) cases of endometrial hyperplasia and five (0.5%) cases of endometrial cancer in 1033 women with premenopausal abnormal menstrual bleeding who underwent endometrial biopsy. However, the literature lacks clear data on the risk of serious endometrial pathology in cases with an insufficient endometrial biopsy[5]. Our study showed a 0.8% (1/125) risk of endometrial cancer in premenopausal abnormal uterine bleeding where an endometrial biopsy was reported as insufficient. This was similar to the 0.5% risk reported by Farquhar et al[16]; thus our study did not suggest an altered likelihood of endometrial cancer after an insufficient biopsy.

There was one case of adenocarcinoma diagnosed nearly 2 years after two endometrial biopsies that were insufficient and normal, respectively. It was unclear whether this represented a missed cancer in the initial two endometrial biopsies or the cancer only developed after the initial two biopsies. The natural history of endometrial cancer is not clearly understood, although the pathological diagnosis of endometrioid-type cancer in our case might suggest a relatively indolent tumour which may have developed from a background of hyperplasia and oestrogen excess[17,18].

Endometrial biopsy is not a perfect test. Only a small area of the endometrium is sampled by the endometrial biopsy, with a reported sensitivity between 70% and 100%[4,12,19]. Our study illustrated that a normal endometrial biopsy was not totally 'protective' against the development of endometrial cancer. However, there was no case of endometrial hyperplasia after an insufficient endometrial biopsy, and the only case of endometrial cancer presented with persistent symptoms. Thus, our data suggested that further invasive investigations were not always necessary in asymptomatic women. In keeping with the NICE guidance and Cancer Australia's diagnostic guide, it is important to further investigate persistent symptoms and unsatisfactory response to treatment, especially in the presence of risk factors for endometrial neoplasia[4,14].

Outpatient endometrial sampling has replaced D&C for the investigation of abnormal uterine bleeding[4]. The accuracy of outpatient sampling techniques compares

favourably to that of D&C; however, the latter procedure is associated with increased operative risks and costs[11,20-25]. The adequacy of histological samples obtained by endometrial sampling is also comparable to those obtained by D&C[22,23]. Theoretically, D&C may allow more thorough sampling of the uterine cavity, particularly when there is difficulty in the initial endometrial sampling due to uterine structural abnormality. Some authors have suggested the use of D&C for investigation of an insufficient endometrial sampling[15,25,26]. However, we have been unable to find studies directly comparing repeat endometrial sampling with D&C in the context of structural abnormality and insufficient endometrial sampling in premenopausal abnormal uterine bleeding.

When performed as an adjunct to endometrial sampling, hysteroscopy increases the rates of detecting polyps and submucosal fibroids, but not hyperplasia or malignancy[22,27]. Benign diseases such as fibroids and intrauterine polyps are common in women with premenopausal abnormal uterine bleeding. Approximately 30% of patients have uterine fibroids, and approximately 10% have polyps[4]. In our study, 26% (16/61) of patients who had hysteroscopy showed positive findings, and 15% (9/61) eventually had a therapeutic hysteroscopic procedure. A hysteroscopy should be considered when a repeat biopsy is warranted. The finding of atrophic endometrium on hysteroscopy may also provide reassurance even if the repeat biopsy is insufficient again.

Guidelines from Cancer Australia[14] and the Society of Obstetricians and Gynaecologists of Canada[15] recommend the use of transvaginal ultrasound for evaluation of endometrial thickness in the management of insufficient endometrial biopsy. While endometrial thickness is commonly measured when investigating postmenopausal bleeding, its role in premenopausal abnormal uterine bleeding is not well established and has not been directly studied in the context of an insufficient endometrial biopsy[28-31]. Further studies are needed to evaluate the role of transvaginal ultrasound as a screening tool for endometrial hyperplasia and malignancy in premenopausal women.

Given the relatively low risk of endometrial cancer in women with premenopausal abnormal uterine bleeding, our study was limited by its small sample size in determining the risk of serious pathology. The study lasted only 3 years. The risk of a new or 'missed' cancer presenting after 3 years was not evaluated. Some patients who became asymptomatic were reassured and discharged without long-term follow-up. It is possible that some of these discharged patients eventually developed significant pathology but were not seen again in our department. Thus, the risk of endometrial cancer might be underestimated in our study. The root problem of insufficient endometrial biopsy is the lack of a standard definition, as reflected by the wide variation in reported rates of insufficient sample. Thus, our conclusions have limited applicability to other units with different laboratories.

Conclusion

Endometrial biopsy is a well-established outpatient investigation for abnormal uterine bleeding. However, the current literature lacks strong evidence to guide the management of cases with an insufficient endometrial biopsy for premenopausal abnormal uterine bleeding. Our study showed that the risk of endometrial hyperplasia and malignancy was low, and further investigation was unlikely to be positive for serious pathology. However, an insufficient or normal endometrial biopsy is not 'protective' against endometrial cancer, and patients with persistent symptoms and risk factors should be further investigated. Our study also highlighted the high prevalence of benign polyps and fibroids that could be diagnosed and treated hysteroscopically. Thus, hysteroscopy should be considered when repeat biopsy is indicated.

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References

1. Fraser IS, Critchley HO, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. *Semin Reprod Med* 2011; 29:383-90.
2. Munro MG, Critchley HO, Broder MS, et al. FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynaecol Obstet* 2011; 113:3-13.
3. Department of Health, Hong Kong SAR. Hong Kong Cancer

Registry. Available from: http://www3.ha.org.hk/cancereg/statistics.html. Accessed 8 Feb 2013.
4. *NICE clinical guideline No. 44. Heavy menstrual bleeding*. London: National Institute for Health and Clinical Excellence; 2007.
5. Harmanli OH, Shunmugham S, Shen T, Houck KL, Chatwani AJ. The negative predictive value of "inadequate" endometrial biopsy in diagnosing endometrial neoplasia. *J Gynecol Surg* 2004; 20:13-6.
6. Critchley HO, Warner P, Lee AJ, Brechin S, Guise J, Graham B. Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status. *Health Technol Assess* 2004; 8:iii-iv,1-139.
7. Stovall TG, Ling FW, Morgan PL. A prospective, randomized comparison of the Pipelle endometrial sampling device with the Novak curette. *Am J Obstet Gynecol* 1991; 165:1287-90.
8. Ben-Baruch G, Seidman DS, Schiff E, Moran O, Menczer J. Outpatient endometrial sampling with the Pipelle curette. *Gynecol Obstet Invest* 1994; 37:260-2.
9. Teale GR, Dunster GD. The Pipelle endometrial suction curette: how useful is it in clinical practice? *J Obstet Gynaecol* 1998; 18:53-5.
10. Gordon SJ, Westgate J. The incidence and management of failed pipelle sampling in a general outpatient clinic. *Aust N Z J Obstet Gynaecol* 1999; 39:115-8.
11. Clark TJ, Mann CH, Shah N, Song F, Khan KS, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic qualitative review. *BJOG* 2002; 109:313-21.
12. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial hyperplasia. *Acta Obstet Gynecol Scand* 2001; 80:784-93.
13. Philips V, McCluggage WG. Results of a questionnaire regarding criteria for adequacy of endometrial biopsies. *J Clin Pathol* 2005; 58:417-9.
14. Cancer Australia. *Abnormal vaginal bleeding in pre- and peri-menopausal women: a diagnostic guide for general practitioners and gynaecologists*. Surry Hills: Cancer Australia; 2011.
15. SOGC clinical practice guideline No. 86. Diagnosis of endometrial cancer in women with abnormal vaginal bleeding. *J Soc Obstet Gynaecol Can* 2000; 22:102-4.
16. Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. *Am J Obstet Gynecol* 1999; 181:525-9.
17. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983; 15:10-7.
18. Palmer JE, Perunovic B, Tidy JA. Endometrial hyperplasia. *The Obstetrician & Gynaecologist* 2008; 10:211-6.
19. Rodriguez GC, Yaqub N, King ME. A comparison of the Pipelle device and the Vabra aspirator as measured by endometrial denudation in hysterectomy specimens: the Pipelle device samples significantly less of the endometrial surface than the Vabra aspirator. *Am J Obstet Gynecol* 1993; 168:1-55.
20. Stovall TG, Solomon SK, Ling FW. Endometrial sampling prior to hysterectomy. *Obstet Gynecol* 1989; 73:405-9.
21. Dijkhuizen FP, Mol BW, Brölmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. *Cancer* 2000; 89:1765-72.
22. Tahir MM, Bigrigg MA, Browning JJ, Brookes ST, Smith PA. A randomised controlled trial comparing transvaginal ultrasound, outpatient hysteroscopy and endometrial biopsy with inpatient hysteroscopy and curettage. *Br J Obstet Gynaecol* 1999; 106:1259-64.
23. Grimes DA. Diagnostic dilation and curettage: a reappraisal. *Am J Obstet Gynecol* 1982; 142:1-6.
24. Feldman S, Berkowitz RS, Tosteson AN. Cost-effectiveness of strategies to evaluate postmenopausal bleeding. *Obstet Gynecol* 1993; 81:968-75.
25. Chambers JT, Chambers SK. Endometrial sampling: When? Where? Why? With what? *Clin Obstet Gynecol* 1992; 35:28-39.
26. Yarandi F, Izadi-Mood N, Eftekhar Z, Shojaei H, Sarmadi S. Diagnostic accuracy of dilatation and curettage for abnormal uterine bleeding. *J Obstet Gynaecol Res* 2010; 36:1049-52.
27. Ben-Yehuda OM, Kim YB, Leuchter RS. Does hysteroscopy improve upon the sensitivity of dilatation and curettage in the diagnosis of endometrial hyperplasia or carcinoma? *Gynecol Oncol* 1998; 68:4-7.
28. Paraskevaidis E, Kalantaridou SN, Papadimitriou D, et al. Transvaginal uterine ultrasonography compared with endometrial biopsy for the detection of endometrial disease in perimenopausal women with uterine bleeding. *Anticancer Res* 2002; 22:1829-32.
29. Getpook C, Wattanakumtornkul S. Endometrial thickness screening in premenopausal women with abnormal uterine bleeding. *J Obstet Gynaecol Res* 2006; 32:588-92.
30. Muneyyirci-Delale O, Gupta A, Abraham C, Chandrareddy A, Bowers CH Jr, Cutler JB. Management of dysfunctional uterine bleeding based on endometrial thickness. *Int J Womens Health* 2010; 2:297-302.
31. Ozdemir S, Celik C, Gezginç K, Kıreşi D, Esen H. Evaluation of endometrial thickness with transvaginal ultrasonography and histopathology in premenopausal women with abnormal vaginal bleeding. *Arch Gynecol Obstet* 2010; 282:395-9.