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Cytological and histological examination of the endometrium based on menstruation age groups

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Abstract

Introduction: Abnormal uterine bleeding (AUB) is one of the most common symptoms of endometrial cancer that necessitates endometrial biopsy.
Objectives: This study aimed to compare the cytological and histological findings in endometrial specimens among women with AUB in three different menstrual groups (pre-menopause, perimenopause, and post-menopause) and to evaluate the statistical accuracy of cytology compared to histopathology (gold standard).
Patients and Methods: This descriptive study was conducted on 78 women with AUB admitted to the gynecology and obstetrics unit of Shahid Beheshti hospital, Isfahan, Iran from 2018 to 2020. Patients were divided into three groups (pre-menopause, perimenopause, and post-menopause) based on their menstrual condition. Samples were obtained using endometrial curettage and cytobrush and were analyzed by two surgical pathologists. The results were described in four categories: negative, atypical endometrial cells of undetermined significance (AEC-US), atypical endometrial cells encompassing the spectrum of precursors to the malignant endometrial tumor (AEC-PEMT), and positive.
Results: Out of 78 samples, 36 (46.2%) were reported negative for epithelial abnormality, 15 (19.2%) were AEC-US, 9 (11.5%) were AEC-PEMT, and 18 (23.1%) were positive for epithelial lesions. There was a significant association between cytological findings and menstrual groups ($P = 0.004$). Positive results were more frequently reported in the post-menopausal group, whereas negative results were most common in the pre-menopause group. The sensitivity and specificity of cytological evaluation in the pre-menopause, perimenopause and post-menopause groups were 100% and 95% (accuracy: 100%, 95% CI: 0.94-1), 77% and 53%, (accuracy: 62%, 95% CI: 0.40-0.85), and 100% and 34% (accuracy: 41%, 95% CI: 0.20-0.61), respectively.
Conclusion: Cytological examination of the endometrium demonstrated high sensitivity in the pre-menopausal and post-menopausal women with AUB and can therefore be used as an efficient and valuable method of screening for endometrial neoplasia.

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Introduction

Endometrial cancer is one of the most common cancers in women worldwide, accounting for approximately 5% of all cancers and more than 2% of mortality related to cancer in women (1, 2). Endometrial cancer is characterized by the unchecked outgrowth of the endometrial stroma and glands which may be accompanied by reactive fibrosis and muscular metaplasia (3). Patients' symptoms are non-specific and include pelvic pain and subfertility. These symptoms may negatively affect the quality of life (4-9). Endometrial cancer risk is related to genetic, anthropometric, and lifestyle factors and some associated diseases (e.g., diabetes, polycystic ovarian syndrome) (10). Many factors that alter the amount of estrogen production, including parity, age at menarche, oral contraceptive use, and breastfeeding are also related to endometrial cancer (11).

Key point

Abnormal uterine bleeding is one of the most common symptoms that necessitates endometrial biopsy in pre-menopausal and post-menopausal women. This study aimed to evaluate the statistical accuracy of cytology compared to histopathology (gold standard) in endometrial specimens. Cytological examination of the endometrium demonstrated high sensitivity in the pre-menopausal and post-menopausal women with abnormal uterine bleeding and can therefore be used as an efficient and valuable method of screening for endometrial neoplasia.

The most important complaint among patients with endometrial cancer in postmenopausal period is abnormal uterine bleeding (AUB), observed in 60%-70% of patients. AUB is defined as any bleeding different from the regular menstrual pattern, such as menorrhagia, oligomenorrhea, polymenorrhea, menometrorrhagia, mid-

cycle spotting, acute abnormal bleeding, and dysfunctional uterine bleeding. A quarter of all gynecological surgeries are conducted for endometrial cancer, which affects approximately 14% of women in reproductive age. In order to diagnose endometrial cancer, patients undergo endometrial biopsy with cytological examination. Hysteroscopy allows direct visualization and targeted sampling of the endometrium and is currently the best tool for evaluation of endometrial cancer (12). The most common indication for hysterectomy is AUB, especially in developing countries. However, in approximately 40% of cases, AUB has not been associated with any definite organic pathology. Surgical procedures like hysterectomy can result in serious complications, including injuries to the ureter, bladder, blood vessels and heart (13).

Menopause occurs when women stop menstruating for an uninterrupted period. Age at menopause can contribute to the risk of many diseases (14) because women with delayed menopause have longer exposure to estrogens throughout their lifetime. Several studies have suggested that age at menopause is related to the occurrence of breast and liver cancers (14). However, the relationship between menopausal age and endometrial malignancy is not well established. Some studies have suggested that menopause occurring later in life was associated with increased risk of endometrial cancer (15), while some showed no significant relationship between menopausal age and endometrial cancer (16-18).

Objectives

In this study, we aimed to compare the cytological and histological findings in endometrial brush specimens among women presenting with AUB in three different menstrual groups (pre-menopause, perimenopause, and post-menopause). We also evaluated the statistical accuracy of cytology compared to histopathology (gold standard) in these specimens.

Patients and Methods

Study design

This descriptive study was conducted on women with abnormal uterine bleeding who were admitted to the gynecology and obstetrics unit of Shahid Beheshti hospital, Isfahan, Iran from 2018 to 2020.

The importance and method of obtaining an endocervical specimen were explained to the study subjects and written informed consent was obtained afterwards. All of the women who were new case of AUB with no previous history of malignancy or medical conditions or radiotherapy were included in this study. Around 78 women (aged 18-65 years old) were found eligible and underwent an endocervical curettage biopsy. Exclusion criteria consisted of pregnancy and use of psychotropic or anticoagulant medications or analgesics in the previous 24 hours or a monoamine oxidase inhibitor antidepressant in the last two weeks.

Patients were divided into three groups (pre-menopause, perimenopause, and post-menopause) based on their menstrual condition. Patients' primary demographic data (e.g., gender, age, and history of previous diseases) and gynecologic and routine clinical examinations were recorded. Gynecologic examination was conducted in the lithotomy position and cytology samples were obtained using endometrial brushes. The brushes were inserted into the cervical cavity without endoscopic anesthesia. The sample was drawn and placed on a slide after brushing using the thin-prep technique as used in Pap smears. A gynecologist collected the initial samples in a container labeled "A". After formal fractional curettage was performed, the endometrial curettage samples were collected in a container labeled "B". All collected specimens were analyzed by two surgical pathologists and the sum of their reports was included in the study.

In order to assess adequacy of endometrial specimen, the evaluation specimen cellularity (numerical criterion) is among the most important issues. The study conducted by Nimura et al (19) demonstrated the ≥10 clusters with ≥30 endometrial cells per cluster could be used as a specimen adequacy criterion for endometrial liquid based cytology in non-menopausal patients, while presence of 5 or more cell clusters was satisfactory in post-menopausal patients.

A cytobrush is a plastic tool used to obtain cells from the cervix during the procedure of a smear. Endometrial cell collection by cytobrush is a minimally invasive technique, similar to artificial insemination, which allows for evaluation of the molecular phenotype of the endometrium and uterine environment. It has been well demonstrated that the collected cells are representative of the dynamic changes that occur during different physiological and pathological conditions of the uterus.

The endometrial cytology results were described in four categories: negative, atypical endometrial cells of undetermined significance (AEC-US), atypical endometrial cells encompassing the spectrum of precursors to the malignant endometrial tumor (AEC-PEMT), and positive (Table 1) (20). The following cytological findings were reported as negative; [1] Uniform straight to curvilinear tubular or flat epithelial sheets with cohesion of the endometrial stromal cells (proliferative phase), [2] Honeycomb pattern with increased cytoplasm and accordion-pleated glands (the three-dimensional equivalent of saw-toothed glands) with rounded and vesicular nuclei with delicate chromatin pattern (secretory phase), and [3] Nuclear crowding and overlapping but not as striking as in proliferative endometrium (atrophic). The term AEC-US was used to describe the following findings: [1] Scant cytoplasm and isomorphic nuclei with finely granular chromatin that had small nucleoli or did not have nucleoli (simple endometrial hyperplasia) and [2] Benign endometrial disease caused by ovarian dysfunction, iatrogenic changes, or infection. Follow-up endometrial biopsy is not routinely suggested in such cases unless the

change persists on repeat cytology. The term AEC-PEMT was used for findings including clear cytoplasm and moderate nuclear pleomorphism (atypical endometrial hyperplasia).

In cases of malignancy, the cytology results of endometrial specimens demonstrate varied features based on the histotype and grade of differentiation of the tumor. In addition, the cytological findings of endometrial epithelial tumors will be different from those of mixed endometrial tumors, trophoblastic tumors, and non-endometrial tumors such as cervical, tubal or ovarian carcinoma. A directly collected endometrial specimen can also include non-pathological or hyperplastic endometrial cell aggregates. The most important cytology criteria for malignancy include loss of polarity, papillary cell clusters, discohesive cells, high nucleocytoplasmic ratio, coarse and/or marginated chromatin, nucleolar prominence, nuclear membrane indentation, cell cannibalism, scarcity of stromal cells, and necrosis (21).

Statistical analysis

SPSS software version 20.0 for windows (SPSS Inc., Chicago, IL) was conducted for statistical analysis. Qualitative data were reported using frequencies and percentages and quantitative data were reported using means and standard deviations (SD). To evaluate sensitivity, specificity, PPV (positive predictive value), and negative predictive value (NPV) of cytology compared to pathology, we used receiver operating characteristic (ROC) analysis with the significance level of < 0.05.

Results

This study was conducted on 78 women with AUB (mean age 51.28 ± 10.05, 35-76 years old). About 23 women (29.4%) were in the pre-menopause group, 26 women (33%) were in the perimenopause group, and 29 women (37%) were in the post-menopause group.

Out of 78 endometrial samples which underwent a cytological sample analysis, 36 (46.2%) were negative for epithelial abnormality, 15 (19.2%) were ASC-US, and nine (11.5%) were AEC-PEMT, and 18 (23.1%) were positive for epithelial lesions (Table 1). Out of 36 negative specimens, 18 (78.3%) were in the pre-menopause group, 11 (42.3%) were in the perimenopause group, and seven (24.1%) were in the post-menopause group. Out of 15 ASC-US specimens, three (13%) were in the pre-menopause group, seven (26.9%) were in the perimenopause group, and 5 (17.3%) were in the post-menopause group. Out of nine AEC-PMET specimens, one (4.3%) was in the pre-menopause group, 3 (11.5%) were in the perimenopause group, and five (17.3%) were in the post-menopause group. Out of 18 positive specimens, one (4.3%) was in the pre-menopause group, five (19.2%) were in the perimenopause group, and 12 (42.4%) were in the post-menopause group. There was a significant association between cytological findings and menstrual groups ($P=0.004$). Positive results were most frequently reported in the post-menopausal group, whereas negative results were most common in the pre-menopause group.

Out of 36 negative specimens, 19 (54.3%) were proliferative, six (17.1%) were secretory, eight (22.9%) were atrophic, and three (8.3%) were undetermined. There was a significant association between negative results and menstrual groups ($P=0.001$). However, no significant association was reported between menstrual groups and other cytological findings (AEC-US: $P=0.41$, AEC-PEMT: $P=0.25$).

According to the results of histology analysis, out of 78 specimens, 40 (51.3%) were negative, 11 (14.1%) were ASC-US, 2 (2.6%) were AEC-PEMT, and 25 (32.1%) were positive for epithelial lesions. Out of 40 negative specimens, 21 were in the pre-menopause group, 12 were in the perimenopause group, and seven were in the post-menopause group. Out of 11 AEC-US specimens, two were in the pre-menopause group, seven were in the perimenopause group, and two were in the post-menopause group. The two AEC-PEMT specimens were both in the post-menopause group. Out of 25 positive specimens, seven were in the perimenopause group and 18 were in the post-menopause group. There was a significant association between histology findings and menstrual groups ($P=0.001$). Negative results were most frequently

Table 1. The associations between menstrual groups and cytology and histology findings in women with AUB

		Menstrual groups			*P* value
		Pre-menopause No. (%)	Perimenopause No. (%)	Post-menopause No. (%)	
Cytologic findings	Negative	18 (78.3)	11 (42.3)	7 (24.1)	0.001
	ASC-US	3 (13)	7 (26.9)	5 (17.3)	0.41
	AEC-PEMT	1 (4.3)	3 (11.5)	5 (17.3)	0.25
	Epithelial lesion	1 (4.3)	5 (19.2)	12 (42.4)	0.004
Histology findings	Negative	21 (70)	12 (37.5)	7 (43.75)	0.001
	ASC-US	2 (6.6)	2 (6.2)	7 (43.75)	
	AEC-PEMT	0 (0)	0 (0)	2 (12.5)	
	Epithelial lesion	7 (23.3)	18 (56.2)	0 (0)	

reported in the pre-menopause group, whereas positive results were most common in the post-menopause group.

Out of 40 negative specimens reported in histology analysis, 29 (70.7%) were proliferative, 4 were secretory, 7 (17.1%) were atrophic and 1 was iatrogenic. There was a significant association between negative histology results and menstrual groups ($P=0.001$).

This study evaluated the quality of cytological analysis (microscopic analysis of pipeline collection) by estimating sensitivity, specificity, and accuracy values. Gold standard was the results of histologic analysis (hysteroscopic collection). In the pre-menopause group, the sensitivity and specificity values of cytological analysis were 100% and 5%, respectively (accuracy: 100%, 95% CI: 0.94-1). In the perimenopause group, the sensitivity and specificity values were 77% and 47%, respectively (accuracy: 62%, 95% CI: 0.40-0.85). The sensitivity and specificity values in the post-menopause group were 100% and 66%, respectively (accuracy: 41%, 95% CI: 0.20-0.61).

Discussion

Endometrial curettage biopsy is a minimally invasive test for the evaluation of endometrial tissue. In this study, we compared the results of cytological and histological evaluation of the endometrial samples between three different menstrual groups in women with AUB. We also assessed the statistical accuracy of cytological evaluation compared to histological evaluation (gold standard). The results showed a significant relationship between histological and cytological analysis results and menstrual groups. Most of the negative results were in the pre-menopause group. The sensitivity and specificity of cytological examination in the pre-menopause group were 100% and 5%, respectively, whereas for the perimenopause and post-menopause groups, these parameters were reported 77% and 47%, and 100% and 66%, respectively.

Gray and colleagues demonstrated that cytological evaluation had a higher sensitivity and specificity than endometrial biopsy and it could be used as a beneficial diagnostic tool to detect different types of endometrial neoplasia (21). Similar to this study, our study showed that cytological evaluation could effectively detect endometrial cancer with high sensitivity and specificity.

Okadome et al surveyed the cytological and histopathological analysis of endometrial samples in patients with AUB and demonstrated that endometrial aspiration cytology is a valuable method in detecting endometrial hyperplasia and neoplasia with an acceptable sensitivity (96.94% and 96.84%, respectively) (22). Papaefthimiou et al assessed the sensitivity and specificity of liquid-based cytological sampling obtained by three different sampling methods, including endometrial sampling, dilation and curettage, and also hysterectomy. They found that the sensitivity and specificity of endometrial sampling was 98.08% and 100%, respectively (23).

Akladios and colleagues demonstrated in a study conducted in 2015 that endometrial curettage findings had an excellent positive correlation in 81.3% of samples with histological examination results. The sensitivity and specificity of endometrial curettage were calculated as 87.3% and 96.9%, respectively (PPV; 95.4%, NPV; 91.9%) (24). In another study, Goksedef et al assessed the sensitivity and specificity of two exclusive diagnostic methods, endocervical curettage and endocervical brushing, in 104 patients. Statistical analysis showed that endocervical brushing had a higher sensitivity than endocervical curettage (100% compared to 88.8%), whereas endocervical curettage had higher specificity (90.9% compared to 72.7%). In this study, the frequency of negative and positive results in the cytological and histological examinations were reported 36.18% and 40.25%, respectively (25).

Conclusion

In our study, the accuracy of cytological examination of the endometrium was evident. This test demonstrated high sensitivity in the pre-menopausal and post-menopausal women with AUB and can therefore be conducted as an efficient and valuable method of screening for endometrial neoplasia.

Limitations of the study

One of our limitations was the small number of study patients. It is suggested that more people be investigated in the next studies.

Authors' contribution

Conceptualization: TA and YH; Methodology: NA and YH; Validation: NA; Formal Analysis: YH; Investigation: RR; Resources: RR; Data Curation: ARVD; Writing—Original Draft Preparation: RR; Writing—Review and Editing: RR; Visualization: YH; Supervision: TA; Project Administration: NA.

Conflicts of interest

The authors declare no conflict of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study. (ethical code #IR.MUI.MED.REC.1397.330). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Reza Rakhshan with registry number of 397703 at this university.

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