

The accuracy of endometrial sampling for the diagnosis of patterns of endometrial pathology in women presenting with abnormal uterine bleeding

More conservative therapeutic approaches

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ABSTRACT

الأهداف: نريف الرحم غير الطبيعي (AUB) هو السبب الرئيسي لاستئصال الرحم ، والذي عادة ما يتم تشخيصه بأخذ عينات من بطانة الرحم قبل الجراحة. خططنا لهذه الدراسة لتقييم دقة تشخيص الأنماط النسيجية من بطانة الرحم في العينة التي تؤخذ قبل الجراحة في إشارة إلى التشخيص النسيجي النهائي بعد استئصال الرحم.

الطريقة: قمنا بمراجعة السجلات الطبية بأثر رجعي في الفترة ما بين 1 يناير 2011 و 31 ديسمبر 2015 في مستشفى أكاديمي في المملكة العربية السعودية وحددنا 43 حالة من حالات AUB تستوفي الشروط. تم تصنيف التشخيصات النسيجية في إما مجموعة أمراض طبيعية وحميدة (N/B) ، أو فئة سرطان وتضخم (Ca/H). واستخدمت مقاييس احصائية لمقارنة التشخيص النسيجي لأخذ عينات بطانة الرحم بالتشخيصات التالية لاستئصال الرحم وكابا كوهين لتقييم التوافق بين الطريقتين.

النتائج: كان العمر الوسيط لجميع المرضى 49 سنة. أظهر الفحص النسيجي قبل الجراحة حساسية 53.8% ، وخصوصية 90% ، و 70% و 81.8% القيم التنبؤية الإيجابية والسلبية ، و 30.1% و 18.2% معدلات الإيجابية والسلبية الكاذبة. على التوالي. كان معدل التوافق بين التشخيص النسيجي قبل الجراحة وبعد العملية الجراحية معتدل (K=0.469 ، 79.1%).

الخاتمة: دقة الفحص النسيجي قبل الجراحة كانت معتدلة. تشير نتائجنا إلى ضرورة اتخاذ القرارات السريرية الحذرة، وتقيد استئصال الرحم إلى النساء اللواتي لا يستجبن للتدابير العلاجية الأخرى.

Objectives: Abnormal uterine bleeding (AUB) is a leading cause of hysterectomies, the cause of which is usually diagnosed with preoperative endometrial sampling. We planned this study to assess the accuracy of diagnosing the histologic patterns of endometrium in the preoperative sample in reference to the final histologic diagnosis in hysterectomy.

Methods: We retrospectively reviewed medical charts between January 2011 and December 2015 at a tertiary hospital in Saudi Arabia and identified 43 cases of AUB with complete documentation. The histologic diagnoses were classified into normal and benign pathology group (N/B), or carcinoma and hyperplasia category (Ca/H). Measures of validity were used to compare endometrial sampling histological diagnoses to diagnoses following hysterectomy and Cohen's kappa to assess for agreement between the 2 modalities.

Results: The median age of all patients was 49 years. Preoperative histologic examination showed 53.8% sensitivity, 90% specificity, 70% positive predictive values and 81.8% negative predictive values, 30.1% false positive rates and 18.2% false negative rates. The agreement between preoperative and postoperative histologic diagnoses was moderate (79.1%, k=0.469).

Conclusion: The accuracy of preoperative histologic examination was moderate. Our findings recommend cautious clinical decision making and limiting hysterectomy to women who do not respond to other therapeutic measures.

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Abnormal uterine bleeding (AUB) is one of the most frequent, as well as complicated, gynecological complaints in clinical practice. AUB refers to any bleeding that differs from the normal menstrual pattern. This includes menorrhagia, oligomenorrhea, polymenorrhea, menometrorrhagia, mid-cycle spotting, acute abnormal bleeding, and dysfunctional uterine bleeding.¹ It affects up to 14% of women of reproductive age, and is responsible for approximately one quarter of gynecological surgeries.²

The spectrum of common pathologies that can be detected on histological examination of endometrial specimens from dilatation and curettage in AUB cases include atrophic endometrium, chronic endometritis, endometrial polyp, hyperplasia (H), and carcinoma (Ca). Women presenting with AUB after the age of 35 years require further evaluation, mainly to exclude endometrial Ca or its precursor hyperplasia. While an ultrasound might help in narrowing the possible etiologies of AUB, histologic diagnosis remains the gold standard for the diagnosis of mainly endometrial pathologies.³

Hysterectomy is a major surgery with a risk of serious complications, including ureteral and bladder injuries, hemorrhage, thrombo-embolic diseases, vault prolapse, and stroke, myocardial infarction and renal failure.⁴ Abnormal uterine bleeding is one of the most frequent indications for hysterectomy especially in developing countries. However, up to 40% of cases of AUB were not associated with any definite organic pathology.

The endometrium is a tissue that is easily accessible for sampling and histologic evaluation with minimal invasion by different techniques including biopsy, hysteroscopy, and dilation and curettage (D&C). Therefore, we investigated the histopathologic patterns of endometria in women presenting with AUB in a University hospital in the Eastern province of Saudi Arabia, with a view to evaluate the diagnostic accuracy of preoperative endometrial histological diagnosis in identifying endometrial pathology using findings from hysterectomy results as a reference standard.

Methods. This was a retrospective study conducted at a tertiary care academic center, King Fahd Hospital of the University, Saudi Arabia between January 2011

and December 2015. Ethical approval to conduct the study was granted by Imam Abdulrahman Bin Faisal, Dammam, Saudi Arabia Ethics Review Committee (IRB-2018-063-Med).

We reviewed medical records of all patients who had undergone hysterectomies with a diagnosis of AUB with a former endometrial sampling during the study period. We excluded cases that had unsatisfactory sampling and cases that were related to pregnancy complications. For patients with more than one pre-operative sampling, we used the latest results.

Using the patients' e-charts, we collected data on patients' ages at time of procedure, clinical presentation, endometrial histologic diagnoses' from both the preoperative sample and the hysterectomies.

Patients' ages were stratified into 3 groups; young (<40 years), premenopausal (40-50 years), and menopausal (>50 years). The histologic diagnoses were categorized into 2 major groups. All malignant and pre-malignant hyperplasia, with or without atypia, were all classified in the Ca/H category. Benign pathology (B) such as endometrial polyp, and chronic endometritis, as well as normal physiologic endometrium (N) whether proliferative, secretory, shedding or anovulatory/atrophic were classified into the second group which was referred to as normal or benign (N/B).

Statistical analysis. With reference to the final histologic findings from hysterectomy as the gold standard, the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and false positive (FPR) and false negative rates (FNR); of preoperative histological diagnosis was computed. Cohn's Kappa test was used to assess for agreement between the preoperative and post hysterectomy histologic diagnoses. Fisher's exact test was used to describe the association between age and the final diagnosis identified on hysterectomy. A 2-tailed $p < 0.05$ was considered as the cutoff point for statistical significance. All statistical analyses were conducted using GraphPad Prism software version 7.00 for windows (La Jolla, California, USA).

Results. A total of 51 women who had hysterectomy proceeded by preoperative endometrial sampling in the specified period were identified in the preliminary review. Among them, 7 patients who did not have conclusive diagnoses from the endometrial samplings, and one patient who had a molar pregnancy were excluded leaving 43 patients who met the criteria for inclusion in our analyses.

The median age of all patients was 49 years (range 39-76). While the majority of women (n=23, 53.5%)

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belong to the pre-menopausal age group, there was one patient aged less than 40 years (Table 1). The presenting clinical symptom was menorrhagia in 12 cases and postmenopausal bleeding in 8 cases. The nature of AUB was not specified in the remainder.

Histological diagnosis on endometrial sampling and hysterectomy. The final histologic diagnoses following hysterectomy was Ca/H in 13 cases (median age was 56 years (range: 45- 70); and normal histology or benign pathologic changes in 30 cases (median age: 47.5, range: 39-76 years).

Among the cases that ended up with diagnoses in Ca/H group (n=13), 7 were pre-operatively categorized as N/B categories. These under-diagnosed cases were first called as normal endometrium (4), a couple of endometrial polyps including one depicting atypia confined to the polyp, and a single case of chronic endometritis. The last one disclosed Ca in final pathology while the rest turned out to be hyperplasia.

Moreover, 2 cases of atypical hyperplasia were upgraded to endometrial Ca in hysterectomies (The International Federation of Gynecology and Obstetrics [FIGO] grade I & II), and there was a single case of Ca detected in biopsy upgraded from FIGO grade I to II in the final diagnosis. For the 30 cases ended to be in the N/B category, 3 were overcalled as hyperplasia without atypia preoperatively (Table 1).

Diagnostic accuracy of endometrial sampling. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and false positive rates (FPR) and false negative rates (FNR) of preoperative sampling histological diagnosis when compared to hysterectomy findings as gold standard were 58.3%, 90%, 70%, 81.8%, 30.1%, and 18.2% (Table 2).

Agreement between endometrial sampling and hysterectomy findings. The agreement between preoperative and postoperative histologic diagnoses was moderate (79.1%), $k=0.469$ (95% CI=0.176-0.762). Disagreement was mainly encountered in the diagnosis of hyperplasia. For the 6 cases labeled as hyperplasia in endometrial biopsies, only one of them had concordant results on hysterectomy. The others were upgraded to Ca (n=2) and downgraded as normal histology (n=3).

Six out of 7 cases first diagnosed as polyps (n=2) and normal histology (n=4) ended up being diagnosed as hyperplasia. Disagreement was also evident in polyps. Besides the aforementioned upgrading in 2 cases, downgrading to normal histology was also conspicuous.

The relationship between age group and final diagnoses. There was no association between age group and final diagnoses in our cohort ($p=0.104$).

Table 1 - Spectrum of preoperative and post-hysterectomies histological diagnoses for women with abnormal uterine bleeding in the Eastern province of Saudi Arabia between 2011 and 2015.

Diagnosis	<40 years		40-50 years		>50 years	
	Biopsy	Final	Biopsy	Final	Biopsy	Final
Carcinoma	0	0	0	0	3	6
Hyperplasia						
Non-atypical	0	0	2	2	2	2
Atypical	0	0	1	2	1	1
Chronic endometritis	0	0	1	0	1	0
Polyp	1	1	5	3	6	3
Normal						
Shedding	0	0	6	0	1	0
Proliferative	0	0	2	10	2	4
Secretory	0	0	6	4	0	0
Atrophic	0	0	0	2	3	3
Total	1		23		19	

Table 2 - Validity of preoperative endometrial pathologic diagnosis in identifying uterine pathology with hysterectomy specimens as reference Standard in women with abnormal uterine bleeding in the Eastern province of Saudi Arabia between 2011 and 2015.

Test	Percentage
Sensitivity	53.8
Specificity	90.0
Positive predictive value	70.0
Negative predictive value	81.8
False positive rate	30.1
False negative rate	18.2

Discussion. In this study, we assessed the preoperative histopathologic diagnoses of endometria in patients presenting with AUB with reference to the final diagnoses following hysterectomy. Our patients' median age was similar to other studies.⁴⁻⁶ The pattern of endometrial pathologic findings showed were either normal or benign diagnoses in hysterectomies of 53.5% and 16.3%; respectively. On the other hand, hyperplasia was detected in 16.3% and Ca in 14% of our cohort; all of the Ca cases were in the post-menopausal age group.

Normal physiologic patterns were also prominent in other international studies^{1,4,7} as well as in a previous Saudi study from Jeddah in the Western province. In this study, the frequency of hyperplasia was similar to our study with Ca constituting only 1.8% of their cases.⁸ The reason behind the conspicuous difference in the incidence of cancer in the 2 national reports might be partially attributed to having 30.5% of their patients younger than 40 years versus only 2.3% in this study.

In our study, the preoperative histologic examination had a specificity of 90% and a sensitivity of 53.8%. A low sensitivity has also been reported in other research studies.^{5,6,9} However, the sensitivity of

uterine sampling in the detection of high-grade tumors has been shown to be high.¹⁰ The main factor that compromises the sensitivity of endometrial sampling is the focal growth pattern. Focal lesions are likely to be missed during preoperative sampling. Epstein et al¹¹ showed that 58% of polyps, 50% cases of hyperplasia, and 11% cases of cancer were missed due to focality. Insufficient correlation between preoperative and post hysterectomies diagnoses of hyperplasia has also been confirmed by Gundem et al.¹²

We had 30.1% FPR and all were related to hyperplasia. Likewise, in a separate research study, a preoperative diagnosis of hyperplasia was confirmed in only 61.5% of hysterectomies.¹³ The researchers also found that time gap factor and hormonal therapy did not affect the agreement between preoperative histologic findings specimens and specimens following hysterectomies. In a Mexican study, endometrial biopsy had low sensitivity in predicting coexisting carcinoma with atypical hyperplasia; 3.2% of simple and 73.7% atypical hyperplasia were upgraded to Ca following excision.¹⁴ Therefore, this study recommended preparing frozen sections of specimens from preoperative sampling for all patients operated for atypical hyperplasia. Moreover, Erdem et al¹⁵ found that 25.1% of cases diagnosed as atypical hyperplasia using biopsies actually had coexisting Ca following excision, and 3% of them were high-risk cancers that had been overlooked during the examination of both biopsies and frozen sections.

Beside hyperplasia, polyps identified during preoperative histologic examination had different results following hysterectomy. Two of our patients initially diagnosed with polyps had hyperplasia following hysterectomy (upgrading). Downgrading from cancer/hyperplasia to normal physiologic endometrial tissue categories was also observed. This might results from total removal of the polyp preoperatively during uterine sampling. Polyps can also be missed due to their focal growth pattern. In a previous study, none of the 6 polyps seen following hysterectomy were detected during preoperative sampling.⁵

The overall agreement of preoperative and post-operative histologic examination was only moderate (79.1%, $k=0.469$). Comparable levels of agreement were found in other research studies (79.5% and 73%).^{6,13} Likewise, researchers who investigated the concordance level of preoperative and post hysterectomy histologic diagnoses specifically for endometrial hyperplasia ($k=0.011$) and cancer (72.5%) found even lower rates of agreement.^{16,17} Furthermore, the level of agreement between biopsy and hysterectomies for grading of tumors has also been shown to be moderate.¹⁸

Our results failed to document a significant association between age and the diagnosis of hyperplasia and carcinoma. Nevertheless, all malignant cases were restricted to the older age group. Hence, hyperplasia was the less favorable diagnosis that is usually seen in the premenopausal age group.

The current study was an original trial to assess the accuracy of preoperative histologic endometrial tissue diagnoses in women presenting with AUB in Saudi Arabia and the Arabian Gulf countries using findings following hysterectomy as a reference standard. However, there were some limitations to this study. A limited number of patients present with AUB to our center each year. Additionally, the assessment of endometrial histological tissues was carried out by different general pathologists who were not specialized in Gynecologic Pathology that work at our center on a rotational basis. This limits the generalizability of our findings. However, such limitations also apply to most centers worldwide. We also documented a limited sensitivity rate and moderate level of concordance between histologic diagnoses from preoperative endometrial samples and hysterectomies, consistently with other high volume centers. This supports our findings that show preoperative endometrial sampling has inherent limited level of accuracy.

In conclusion, the majority of our cohort had normal physiologic endometrial patterns, and AUB in these patients is therefore likely to be linked to myometrial or extra-uterine pathology that could be addressed with a less aggressive treatment modality than hysterectomy. The validity of preoperative endometrial tissue histologic examination in identifying uterine pathology is moderate, especially for patients with uterine hyperplasia. Therefore, our findings advocate for cautious clinical decision-making in such cases. Hysterectomy should be restricted to women who do not respond to other therapeutic measures.

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Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.