Comparison of Office Hysteroscopy, Transvaginal Ultrasonography and Endometrial Biopsy in Evaluation of Abnormal Uterine Bleeding

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ABSTRACT

Objective: A comparison between office hysteroscopy, transvaginal ultrasonography and endometrial biopsy was performed, in terms of detection of intrauterine lesions. A secondary objective was assessment of evaluatory approach in the management of abnormal uterine bleeding in an outpatient setting.

Design: Prospective observational study.

Material and Methods: A total of 54 women were evaluated for abnormal uterine bleeding. Assessment included performance of an endometrial biopsy, a transvaginal ultrasound scan followed by office hysteroscopy. Results of hysteroscopy were taken as the gold standard. Sensitivity and specificity of the investigations were assessed. The bleeding pattern was classified as heavy regular, irregular, postmenopausal and heavy or unscheduled bleeding on hormone replacement therapy.

Results: The incidence of focal intrauterine lesions in patients presenting with abnormal bleeding was 52% for all ages and 31% for the postmenopausal group. Seventy-five percent of the patients with Hb < 11 gm% and 67% with an enlarged uterus harbored a focal pathology. The incidence of lesions in patients with heavy regular bleeding was 74%. The sensitivity and specificity of transvaginal ultrasound when compared with results of hysteroscopy was 0.60 and 0.88 respectively. A normal endometrial biopsy had a negative predictive value of 51%. The sensitivity and specificity of endometrial biopsy were 0.04 and 0.83, respectively.

Conclusion: Both transvaginal ultrasound and endometrial biopsy exhibited poor sensitivity for detection of focal intrauterine lesions. Considering the significantly high incidence of intrauterine lesions in patients presenting with abnormal bleeding, the most cost-effective approach appears to be proceeding with hysteroscopy early in assessment.

Key Words: Abnormal uterine bleeding, Office hysteroscopy, Endometrial biopsy, Transvaginal ultrasound scan.

INTRODUCTION

Abnormal uterine bleeding (AUB) accounts for a significant proportion of gynecological referrals. Evaluation of the problem has included investigations ranging from the traditional diagnostic dilatation and curettage (D&C), office based endometrial biopsy (EMBx), to pelvic ultrasonography for evaluation of endometrial/myometrial pathology contributing to the presentation. Diagnostic hysteroscopy for direct assessment of the uterine cavity has been a relatively recent acquisition in the armamentarium of the gynecologists. In an outpatient setting, the entire evaluatory workup takes at least two to three visits prior to arriving at a definitive diagnosis and commencement of appropriate therapy.

In the current scenario of increasing cost awareness and an ever-increasing litigious environment, a balance has to be achieved between the practice of "blanket" medicine aiming at performance of all investigations possibly contributing to a diagnosis versus a condition appropriate approach.

The study presented was undertaken to evaluate the sensitivity and specificity of EMBx and transvaginal ultrasound for detection of intrauterine lesions compared with results of office hysteroscopy (OH), which were taken as the gold standard. A secondary objective of the study was to evaluate the protocol for assessment of the common problem of AUB. Appropriate management could thus be instituted at the earliest possible opportunity, minimizing the number of unnecessary investigations as well as the numerical patient visits to the clinic, without compromising the quality of patient care.

DESIGN

Prospective observational study conducted at the Department of Gynecology at Massachusetts General Hospital (MGH) between January, 1995, and September, 1996.

MATERIALS AND METHODS

Patients attending the gynecology department at MGH with complaints of abnormal uterine bleeding were evaluated for inclusion in the study. The catchment population was from the resident managed gynecology clinic and from practices of two attending physicians with a special interest in reproductive endocrinology. AUB was defined as either cyclic excessive bleeding, irregular menstrual cycles, post-
menopausal bleeding, and excessive or unscheduled withdrawal bleeding on hormone replacement therapy (HRT).

Each patient presenting underwent a preliminary assessment by history and clinical examination; pap smear status was evaluated and updated if indicated. The bleeding pattern was categorized as regular or irregular. The uterine size was assessed clinically and determined as normal or enlarged.

The study protocol aimed at obtaining an outpatient endometrial biopsy (EMBx) usually at the initial presentation, followed by a transvaginal pelvic ultrasound (TVS). An office hysteroscopy (OH) was then scheduled at a subsequent visit. Other than OH, the other investigations were performed without consideration of the phase of the menstrual cycle; OH was scheduled in the early proliferative phase of the menstrual cycle in patients complaining of regular AUB.

The EMBx was performed using a Pipelle biopsy sampler (Unimar, Inc. Connecticut). Aseptic precautions were employed by cleansing the cervix with betadine prior to insertion of the catheter. Antibiotic prophylaxis was given if indicated, using Doxycycline 100 mg bid for 5 days.

The TVS was performed in an office setting by one of the two attendings in gynecology. The uterine anatomy and the adnexae were visualized using a 7.5 MHz vaginal probe transducer (General Electric, Milwaukee, RT 3200 Advantage II real time sector scanner). Appearance of the endometrial stripe was commented upon as either normal or abnormal; a specific note was made of any focal lesion seen in terms of impression of an endometrial polyp, submucous fibroid, intramural fibroid, suspicion of hyperplasia or endometrial carcinoma. The contour of the endometrial stripe was assessed in the midline sagittal plane and the point of maximum thickness of the stripe (ET) was measured on a frozen image at 1.5x magnification.

Office hysteroscopy (OH) was performed using a 3.6 mm single channel flexible hystroscope (HYF-P Olympus America, NY) with a fiberoptic cold light source; normal saline was used as the distending medium and the procedure was performed under direct video monitoring.

A total of 54 patients completed the study and underwent EMBx, TVS and OH. In none of the OH procedures was cervical dilatation required, nor was any form of local anesthetic used.

Baseline laboratory investigations included a complete blood count, results for which were available for 47 patients. The results of OH were taken as the "gold standard" for detection of intracavitary pathology as a contributing factor to the clinical presentation. Sensitivity and specificity of the EMBx and TVS in detecting the intracavitary lesions were calculated. The sensitivity of clinical finding of an enlarged uterus and the pattern of bleeding in predicting an intracavitary lesion were also estimated, as was the association of significant anemia (Hb < 11 gm%) and the incidence of concomitant intrauterine lesions. An age-related prevalence of intracavitary lesions (submucous fibroids / polyps / endometrial hyperplasia / chronic endometritis / endometrial cancer) was calculated in the study population.

Statistical analysis was performed using unpaired t tests using the statistical package GraphPAD in Stat version 1.01. A 'P' value of < 0.05 was considered as statistically significant.

**RESULTS**

The age range for the patients was 19 - 74 years. Thirteen patients were postmenopausal. Fifty-two percent of the patients presenting with abnormal uterine bleeding had evidence of an intracavitary lesion as detected by office hysteroscopy. Congenital uterine anomalies detected incidentally on OH included one case each of a unicornuate, and bicornuate and two cases of septate uterus.

(TVS) performed detected a distortion of the endometrial cavity suggestive of a focal pathology in 20 patients. A subsequent OH confirmed the diagnosis in 17/20 cases where a focal lesion was suspected (Table 1). However, of the 34 patients in whom TVS showed a normal endometrium, OH confirmed 11 false negative cases. The sensitivity of an abnormal transvaginal ultrasound scan when compared to office hysteroscopy for detection of an intracavitary lesion was thus calculated as 0.60. The specificity for a normal TVS was determined as 0.88. Of the 11 false negative TVS results, OH demonstrated five cases of endometrial polyp and six submucous myomas; in 5/6 of the latter there was

| TVS          | Office hysteroscopy |
|--------------|----------------------|
| Abnormal     | Normal | Total |
| Abnormal     | 17     | 3     | 20   |
| Normal       | 11     | 23    | 34   |
| Total        | 28     | 26    | 54   |

TVS: Transvaginal ultrasound
ultrasonic impression of intramural fibroids.

Of the 54 patients who underwent TVS, a specific mention of the thickness of the endometrial stripe was available in 28, the thickness of the endometrium (ET) ranging from 1.8 mm to 25 mm. When correlating the thickness in mm with the presence of intracavitary lesions confirmed by OH, it was noted that the ET ≤ 6 mm had a negative predictive value of 92%; ET of ≥ 10 mm had a positive predictive value of 89%.

The highest prevalence of intracavitary lesions was seen in the age group of 36-40 years (71%); in the < 30 years age group, the incidence was 50%, the difference in the prevalence between the different ages not being of statistical significance (Table 2). Submucous myomas were the most common lesions seen in the younger patients; an increasing incidence of endometrial polyps was seen with increasing age, polyps being the most frequently diagnosed pathology in the postmenopausal women, as shown in earlier studies.\(^1\)

| Age (years) | Number of patients | Abnormal OH | Percentage |
|-------------|--------------------|-------------|------------|
| ≤ 35        | 6                  | 3           | 50%        |
| 36-40       | 14                 | 10          | 71%        |
| 41-50       | 20                 | 11          | 55%        |
| >51         | 14                 | 5           | 36%        |

The endometrial biopsy (EMBx) specimens were considered adequate for reporting in 49/54 cases; two samples had inadequate tissue and three specimens showed menstrual blood, making interpretation difficult. No evidence of pathology was seen in 44/49 specimens. Of the patients with a normal EMBx, 19 were true negative and 25 were false negative, when compared to results of OH (Table 3). The negative predictive value of a normal EMBx was calculated as 51%. In 5/49 biopsy specimens, a pathology was detected and included fragments of endometrial polyp in two cases; office hysteroscopy confirmed the presence of a residual polyp in one of these patients. There was evidence of chronic endometritis in one patient, in whom an endometrial polyp was detected on hysteroscopy, and focal hyperplasia within a secretory endometrium was shown in the fourth patient, who had a normal appearing endometrial cavity on OH. The sensitivity of endometrial biopsy was 0.04 with a specificity of 0.83. No pathological evidence of endometrial carcinoma was detected in the EMBx specimens available, which included 14 specimens from postmenopausal patients. The incidence of inconclusive sampling was 9% and that of focal endometrial hyperplasia was 2%.

Of the 13 postmenopausal patients, the age range was 47-74 years; seven patients were on some form of HRT for a period of at least three months prior to the presentation. The prevalence of intracavitary lesions in the postmenopausal group was 31% (4/13); two of the lesions were confirmed to be benign endometrial polyps on histology and the third was a submucous myoma; in the fourth patient the biopsy of an irregular focal area of the endometrium provided a benign proliferative histological specimen. Results of TVS specifically noted endometrial thickness in 10 postmenopausal patients, the thickness ranging from 1.8 mm - 15 mm. In 7/10 patients, the ET was < 6 mm and 6/7 had a normal uterine cavity of OH; the seventh patient, a 72-year-old woman, was noted to have an area of endometrial irregularity on the anterior uterine wall and a directed biopsy performed showed histological evidence of proliferative endometrium with no evidence of malignancy. Of the three postmenopausal patients in whom a TVS showed an endometrial thickness of greater than 6 mm, all were found to have an endometrial polyp on OH. Thus taking the ET of 6 mm as the cut-off in the postmenopausal women, the positive predictive value for detection of intracavitary lesions for ET > 6 mm was determined to be 100%, whereas the negative predictive value for an ET of < 6 mm was also calculated as 100%.

Of the 54 patients included in the evaluation, 26 underwent definitive surgical management for the presenting problem; two patients had a normal uterine cavity and opted to undergo endometrial ablation, whereas 24 had operative hysteroscopic resection of the focal lesion. Histopathological tissue diagnosis was available for 23/24 of these cases. The most common histological diagnosis was a submucous myoma, seen in 65%, followed by benign endometrial polyps in 26% of the resected lesions; in 5%, a combination of the two existed. There was no evi-

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Table 2.
Age related prevalence of intracavitary lesions determined by OH.

| Age (years) | Number of patients | Abnormal OH | Percentage |
|-------------|--------------------|-------------|------------|
| ≤ 35        | 6                  | 3           | 50%        |
| 36-40       | 14                 | 10          | 71%        |
| 41-50       | 20                 | 11          | 55%        |
| >51         | 14                 | 5           | 36%        |

Table 3.
Detection of intracavitary uterine lesions: Comparison of results of office hysteroscopy to endometrial biopsy.

| Endometrial biopsy | Office hysteroscopy |
|--------------------|---------------------|
| Normal             | Abnormal            |
|                    | Normal              |
|                   | Total               |
| Normal            | 1                   | 4             | 5 |
| Abnormal          | 25                  | 19            | 44 |
| Total             | 26                  | 23            | 49* |

* Interpretation for 5/54 EMBx specimen was inconclusive. See Text.
cence of focal atypia in any of the histology specimens.

The uterus was classified as normal in size on clinical examination in 63% of the patients (36/54). Of the 18 enlarged uteri, 12 showed an intracavitary lesion on OH, giving a PPV of 67%. In eight of the 47 patients in whom a CBC was available, the hemoglobin was less than 11 gm%; 6/8 (75%) of these patients had an abnormal finding on OH. Nineteen of the 54 patients were experiencing heavy, though regular menstrual flow; of these, 14 (74%) had an abnormal OH compared to 14/35 (40%) of those presenting with irregular bleeding, the difference in the prevalence of lesions being statistically significant ($P=0.008$).

**Table 4.**

Pattern of abnormal uterine bleeding and associated uterine intracavitary abnormalities.

| Bleeding pattern | Number of patients | Intracavitary lesion of OH |
|------------------|--------------------|---------------------------|
| Regular heavy    | 19                 | 14a*                      |
| Irregular and/or heavy | 35             | 14b*                      |
| Total            | 54                 | 28                        |

Difference between a and b is statistically significant $P<0.05$

**DISCUSSION**

The high incidence of intrauterine lesions (52%) in our patient population presenting with abnormal uterine bleeding (AUB) is consistent with results of earlier studies.1 The traditional approach to evaluation of AUB in an outpatient setting has included an endometrial sampling following a preliminary assessment based on the history and clinical examination. The patient commonly makes an average of two to three clinic visits, depending on the urgency of presentation, before being commenced on a specific treatment protocol.

In the present era of cost containment and capping of procedure related reimbursements, the physicians should be acquainted not only with the relative informative yield but also the cost per investigation, so as to channelize their diagnostic approach. The aim of management is to thus minimize the cost incurred per patient, while adhering to the principals of the standard of care.

Diagnostic hysteroscopy, though being increasingly employed for evaluation of AUB, is still underutilized. Since the introduction of the hysteroscopic technique, the procedure has undergone significant modifications, contributing to an increase in patient acceptance. Introduction of fiberoptics, reduction in the caliber of the endoscopes, use of simpler distending media and availability of safer local infiltrative anesthetics have all contributed to an increasing utilization of this technique in evaluation of the uterine cavity. Baskett et al.2 in a recent commentary on the efficiency of a one-stop menstrual clinic have demonstrated the cost and clinical effectiveness of utilizing hysteroscopy as a preliminary investigation performed at the initial visit in selected patients. The results of our study agree with their rationale. More than 50% of all diagnostic hysteroscopies, however, are still being performed in the operating room (OR), and this trend could be attributed to a combination of a lack of awareness on the part of the physician and perhaps nonavailability of smaller caliber endoscopes. Compared to TVS, hysteroscopy allows for a direct visualization of the endometrial cavity and hence detection of any focal lesion. It offers the additional opportunity of obtaining a directed biopsy in the same setting if indicated, thus obviating the need for a separate scheduling of the procedure. Studies have demonstrated a superior yield of directed biopsies compared to D&C in providing representative histological specimens.3,4 In terms of cost containment, the procedure being performed by the investigating gynecologist precludes the involvement, and hence need for reimbursement of an additional specialist. Furthermore, it dictates the need for a histological specimen if indicated, and allows for a directed biopsy, ensuring provision of a representative specimen of the focal pathology for evaluation. Performing an OH early in the evaluation in appropriately selected patients would render utilization of any further investigation like EMBx or TVS unnecessary. The net result would ensure cost containment by reduction in the number of patient visits for investigational purposes, and by enabling the physician to embark on an appropriate management plan at the earliest opportunity, contribute significantly to patient satisfaction.

The significant incidence of intrauterine lesions in the postmenopausal patients evaluated (31%) is comparable to other studies5,6 and underscores the importance of direct visualization of the uterine cavity in this subgroup. Since this represents the patient population at the highest risk for significant uterine pathology, i.e. endometrial carcinoma, and because the hysteroscopic appearances of early lesions are well recognized,7 the argument is further strengthened in favor for an early visualization of the cavity. An insight into the clinical staging of an existing endometrial carcinoma would be an additional benefit contributing to the final management plan.

The high incidence of intracavitary lesions seen in the patients with clinically enlarged uteri (62%) and in those with significant anemia (80%) underscores the importance of proceeding with OH early in the evaluatory process in this subcategory of patients. The rationale for attempting to evaluate the endometrial
specimen histologically, obtained by either D&C or outpatient biopsy, is to provide an early diagnosis of a significant pathology, namely endometrial cancer and/or endometrial hyperplasia. While the risk of such an occurrence is high in a subset of patients, i.e. postmenopausal women with abnormal bleeding (10%), anovulatory patients and those with a history of prior endometrial hyperplasia, the yield of endometrial sampling from the rest of the patient population in terms of obtaining a pathological diagnosis is negligible. This is consistent with our data and the questions the almost universal practice of biopsying the endometrium in any patient presenting with AUB. In our experience, an expenditure of approximately $250 for an EMBx could be easily avoided in the majority of premenopausal patients with AUB. An EMBx, however, has a definite place in the diagnostic workup of postmenopausal patients as well as those premenopausal patients who are at high risk for endometrial hyperplasia. The high propensity of missing focal intrauterine lesions like submucous myomas and polyps with D&C is well documented in recent literature.\textsuperscript{3,4,8,9} Moreover, the alleged therapeutic effect of D&C in the management of AUB remains questionable.\textsuperscript{3,4,10}

Most of the data available on the diagnostic accuracy of TVS in evaluation of abnormal uterine bleeding is relevant only for the postmenopausal patients.\textsuperscript{11,12} The general consensus of opinion is that an endometrial thickness of less than 5-6 mm in a patient presenting with postmenopausal bleeding does not warrant an extensive workup, as the risk of endometrial carcinoma and/or hyperplasia is negligible;\textsuperscript{11,13} The sensitivity and specificity of TVS in detecting focal intrauterine lesions in the study presented is comparable to the results shown by Tombin et al. (0.54 and 0.40, respectively). Scheduling the ultrasound evaluation in the follicular phase of the menstrual cycle in the premenopausal patients may enhance the sensitivity since the hyperechoic secretory endometrium may mask the endometrial polyps.\textsuperscript{14,15} Presence of intramural myomas may obscure the endometrial stripe, thus contributing to a significant incidence of false negative interpretations, as shown in our series. The majority of pelvic ultrasound scans are still being performed by the radiologists; the cost of a TVS ranges from $250-$400, depending on the involvement of the radiology department. Furthermore, an impression of an intracavitary lesion directs the management towards performance of a hysteroscopic procedure for the ultimate diagnosis and management.

CONCLUSION

There is a high incidence of intracavitary uterine pathology in patients presenting with abnormal uterine bleeding. This is especially true when considering the 35-50 years age group who present with heavy regular bleeding, clinically enlarged uteri and significant anemia. The relatively poor sensitivity of both endometrial biopsy and transvaginal ultrasound in the detection of intrauterine focal pathology encourage us to propose that OH be utilized as a first line investigation in these patient evaluations. The cost-benefit analysis of investigations like EMBx and TVS as well as the financial burden of clinic visits during the entire evaluatory process further strengthens the validity of the proposed approach.

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