REVIEW ARTICLE

Evaluation of endometrium in peri-menopausal abnormal uterine bleeding

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ABSTRACT

Abnormal Uterine Bleeding (AUB) is one of the most common health problems encountered by women. It affects about 20% women of reproductive age, and accounts for almost two thirds of all hysterectomies. Gynaecologists are often unable to identify the cause of abnormal bleeding even after a thorough history and physical examination. Diagnostic evaluations and treatment modalities have been evolving over time. The onus in AUB management is to exclude complex endometrial hyperplasia and endometrial cancer. From D and C + EUA under general anesthesia the shift to more accurate procedures like hysteroscopy and vision directed biopsy was welcome. But the current minimally invasive procedures like sonohysterography, office vacuum aspiration (Pipelle) and the use of office hysteroscopy have revolutionized the management of AUB. We have tried to review the current literature and guidelines for evaluation of endometrium with the twin goals of finding an accurate reason causing the AUB and to rule out endometrial cancer or a potential for the cancer in future. We have also attempted to compare the current procedures and their present perspective vis-à-vis each other. Histological assessment is the final word, but obtaining a sample for histology makes it more accurate, and we have reviewed these techniques to enhance accuracy in diagnosis. Hysteroscopy and directed biopsy is the 'gold standard' approach for most accurate evaluation of endometrium to rule out focal endometrial Ca. Blind endometrial biopsies should no longer be performed as the sole diagnostic strategy in perimenopausal as well as in postmenopausal women with AUB. A single-stop approach, especially in high risk women (Obesity, diabetes, family history of endometrial, ovarian or breast cancer) as well as in women with endometrial hyperplasia of combining the office hysteroscopy, directed biopsy in presence of a focal lesion, and vacuum sampling of endometrium in normal looking endometrium, all without anesthesia is the most minimally invasive and yet accurate approach in current practice.

Key Words: Abnormal uterine bleeding, endometrium, peri-menopause

INTRODUCTION

Abnormal uterine bleeding (AUB) is one of the most common presenting complaints encountered in a Gynecologist's office and accounts for almost 10% consultations in any busy out-patient clinic. AUB is defined as 'bleeding that is excessive or occurs outside of normal cyclic menstruation' and accounts for two-thirds of hysterectomies. 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 (TVS), the cause of the bleeding is established in only 50-60% of the cases.

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The International Federation of Gynecology and Obstetrics working group on menstrual disorders has recently developed a classification system (PALM-COEIN) for causes of the AUB in non-gravid women of reproductive age.[1] There are nine main categories, which are arranged according to the acronym PALM-COEIN: Polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified. According to the proposed classification system, non-specific term like dysfunctional uterine bleeding should be abandoned to favor a more specific etiology like ovulatory dysfunction.

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Besides systemic, iatrogenic or hormonal age-related causes, an endometrial pathology (polyps, submucous myomas endometrial hyperplasia, and endometrial carcinoma) should always be suspected, and evaluation appears to be mandatory. Infectious endometritis can also be a cause for irregular bleeding and even endometrial atrophy may, at times, manifest as abnormal bleeding. Diagnosis and treatment of endometrial pathology can nowadays benefit from well-established techniques, ranging from clinical examination to TVS, saline infusion sonohysterography (SIS), hysterosalpingography, hysteroscop (HYS), and endometrial biopsy.[2]

The major challenge to address is to allay the worries about possible uterine cancer while treating a lady for AUB in peri-menopause and post-menopause. One would feel a bit queasy about giving hormone therapy without ruling out a precancerous neoplasia like suspicious hyperplasia or sub-clinical endometrial cancer. A visual and the histological assessment of the endometrium; therefore remains the cornerstone in the current practice. Both dilatation and curettage (D and C) (for histology) as well as HYS with dilatation of the cervix (for visual assessment) required anesthesia. This led to delayed intervention and at times late diagnosis. With the advent of office HYS, as well as vacuum devices for endometrial sampling this stumbling block (need for anesthesia) in early assessment of the endometrium is now averted.

Although relatively uncommon, chronic endometritis also leads to AUB in 5-15% of all AUB. Various organisms (Chlamydia, Tuberculosis, Neisseria, Group B streptococcus, Mycoplasma and many viruses) produce non-specific inflammation of the endometrium. The classic clinical symptoms of pelvic inflammatory disease, such as low abdominal pain, mild fever, and heaviness might be present. Specific Hysteroscopic findings have been described and immuno-histochemical stains are also developed for an accurate diagnosis.

EVALUATION OF ENDOMETRIUM

Evaluation of the endometrium as a cause of AUB is mainly three in modes;

- Imaging of patterns endometrium by transvaginal ultrasound, hysterosonography (SHG) and to some extent a magnetic resonance imaging (MRI)
- Visual assessment by HYS and
- Cellular assessment by microscopic evaluation of endometrial samples

Imaging of the endometrium and uterus

TVS

TVS is an inexpensive, non-invasive and a convenient way to indirectly visualize the endometrial cavity. Therefore, it is recommended as a 1st line diagnostic tool for assessing uterine pathology in reproductive age women presenting with AUB.

Since its introduction in the mid-1980s, TVS has become the standard way to image the female pelvis in the gynecologic community and has served as an important adjunct to the radiologist/sonologist. End-fire endoluminal probes of 5-9 MHz have been used. There is continuing interest in the role of spectral and color Doppler imaging for the endometrium.

The endometrium of the ovulating reproductive-age woman fluctuates in single-layer thickness from 2 mm in the early follicular phase to 6 mm in the late luteal phase. Typically, endometrial thickness is actually measured and reported as the sum of the two adjacent layers of the endometrium, a measurement called the endometrial echo complex (EEC). Consequently, the EEC in the menstrual phase is typically 4 mm and up to 12 mm in the late luteal phase.

It is difficult to define the exact cause of abnormal or irregular uterine bleeding AUB in the premenopausal patient; however, pathologic conditions of the endometrium or myometrium often are factors. Anovulatory cycles are a common cause, but hyperplasia, polyps, submucous myomas, and carcinoma are possible and are of concern to the patients. Merce, *et al*.[3] described the role of spectral Doppler in the evaluation of the endometrium in patients with AUB. As with other Doppler evaluations attempting to separate benign from malignant histologies, the positive predictive value is poor and the information does not influence the eventual diagnostic or therapeutic outcome.

Mathew, *et al*., in their study, found that sensitivity of TVS in detection of these abnormalities was 54%, whereas the specificity was 100%. Positive predictive value was 100% and negative predictive value was 81.1%. TVS and HYS were in agreement in 84.5% cases The percentage of abnormal findings detected by HYS and TVS was 33.6% and 18.2%, respectively. This difference is statistically significant. Based on the above results, they concluded that HYS is superior to TVS for the exclusion of intrauterine abnormalities in premenopausal women.[4]

Saline infusion sonohysterography

SIS is a technique in which a catheter is placed into the endometrial cavity and sterile saline is instilled to separate the walls of the endometrium. In 1993, a study by Parson and Lense[5] in the Journal of Clinical Ultrasound termed the technique sonohysterography (SHG). This technique has been known by many names, including SHG, hysterosonography, TVS with fluid contrast augmentation,[6] and finally, SIS.[7]

A catheter is placed in the uterine cavity (size fr. 8) with a stilette to provide stiffness to the catheter) through cervical os and sterile saline is injected into the endometrial canal which distends the cavity, pushing the opposed walls of the endometrium apart. The anechoic fluid is then juxtaposed against the echogenic endometrium, giving finer detail of the uterine lining. Complete sonographic evaluation of the endometrial cavity is performed in both the coronal and sagittal planes. In addition, 3-dimensional (3D) imaging has been advocated to get a better global view of the uterine cavity.[8] The catheter balloon is then deflated, and evaluation of the lower uterine segment and endocervical region is performed. Doppler evaluation can be quite helpful for distinguishing blood clots from polypoid lesions.[9]

SIS can distinguish focal lesions from diffuse endometrial thickening. Polyps are focal lesions. TVS cannot distinguish endometrial hyperplasia from benign polyps because both conditions can cause thickening of the endometrium are hyperechoic and can contain cystic spaces.[10] With SIS, endometrial hyperplasia typically appears as diffuse thickening of the endometrium, although it can occasionally appear as a focal area of endometrial thickening.[11] In a study by Jorizzo, *et al*.[12] on endometrial hyperplasia, cysts were seen in 57% of patients, and concomitant endometrial polyps were found in 26% of patients. In a study by Dubinsky, *et al*.[13] of 28 women with diffuse thickening of the endometrium, all 28 had either a secretory or proliferative endometrium at biopsy. This underscores the importance of the timing of SIS in menstruating women; the procedure should be performed as early as possible after the cessation of menses, ideally on days 4-6 of the menstrual cycle.

Most commonly, endometrial cancer appears as fairly diffuse thickening of the endometrium, which cannot be differentiated from endometrial hyperplasia.[11] Endometrial cancer can also be seen as an inhomogeneous focal mass. A recent article reported that the uterine cavities of women with endometrial cancer were poorly distensible, and this was the most consistent finding in this pathology and stretch-ability of uterus may be considered a diagnostic sign of endometrial Ca.[14] This sign, however, needs to be considered keeping in mind the fact that the myometrium will contribute much more to the expansibility of uterus than the endometrium and we do not have any studies about differential expansibility of uterus as a whole!

Endometrial hyperplasia is increased with incidence of 1.3-20% in tamoxifen-treated women.[15] SIS and TVS have been advocated as tools for evaluating these women. Fong, *et al*.[16] evaluated asymptomatic post-menopausal women being treated with tamoxifen and found endometrial abnormalities in 40% of their study group. TVS had a sensitivity of 85% and specificity of 56% compared with SIS, which had a sensitivity of 90% and a specificity of 79%. Tepper, *et al*.[17] prospectively evaluated asymptomatic women with a history of breast cancer and tamoxifen therapy who had a thickened endometrium. They defined a thickened endometrium as >8 mm on TVS. The incidence of endometrial abnormalities in the study group was 32%. A study by Hann, *et al*.[18] evaluated 46 sonohysterograms in patients who received tamoxifen for a mean of 2.6 years. SIS revealed endometrial polyps in 62% of patients; 12% had a thickened endometrium, and 8% had subendometrial cysts. 63% of sonohysterograms with prior negative endometrial biopsy results had endometrial abnormalities, including 10 polyps. These authors also found that in 14% of cases, the finding of a normal endometrium on SIS allowed these patients to avoid further intervention.

A more specific diagnosis can be made with SIS over TVS, further intervention can sometimes be obviated on the basis of the increased confidence of negative SIS findings. Some authors are advocating 3D imaging of the uterus with either multiplanar reconstructions or surface-rendering techniques.[19] As 3D imaging has become standard practice in computed tomography and MRI, sonography may soon follow.

As SIS shows focal lesions with such exquisite detail, the next step may be to obtain biopsies of endometrial abnormalities with real-time sonography guidance. Dubinsky, *et al*.[20] published a study in which biopsy of focal lesions was performed in conjunction with SIS. Under direct sonographic guidance, the endometrial canal was distended with saline, and sonographically guided biopsy was performed. There were technical difficulties with leakage of the saline during the biopsy as well as limited steer-ability of the biopsy device.

The basic limitation of all imaging techniques has been the diagnosis of cellular changes in the endometrium. As of now the best use of ultrasonography along with SIS in pre-menopausal AUB is to rule out organic pathologies such as a fibroid, adenomyosis, polyp etc., It has been proposed to use the 'thick endometrium' as a screening tool to select patients for histological assessment. Various cut-offs have been proposed for this screening (most common is >12 mm thickness of the endometrium). However, this has been found to be quite inaccurate and a blind adherence to this is not recommended. As against that, a cut-off of >4 mm thickness of the endometrium in post-menopausal bleeding has been fairly predictive and almost 99% patients with endometrial cancer would have >4 mm thickness of the endometrium. This cut-off is employed by many institutions as a screening and is

recommended. If, however, a repeat episode of bleeding occurs post-menopause with a thin endometrium (<4 mm), a biopsy of endometrium becomes necessary to rule out that 1% chance of endometrial cancer.[21,22]

HYS

A hysteroscopic evaluation of the endometrial cavity and visually directed biopsy for histo-pathological evaluation is considered the gold standard for assessing the endometrium and detecting or ruling out endometrial cancer in current Gynec practice. The major problem with a regular HYS was the need for general anesthesia. High blood pressure and diabetes are quite frequent in peri-menopausal age and have been a great deterrent for early diagnosis of endometrial Ca. The advent of office HYS, with no need for anesthesia, has become a boon in dealing with peri-menopausal AUB and postmenopausal uterine bleeding. One concern was also voiced about the possibility of using liquid distension medium leading to peritoneal migration of neoplastic cells and peritoneal metastasis. This concern would be equally true for SIS also. This worry, however, has been refuted by prospective trials, showing clearly that there is no increased risk of developing cancer metastasis in this event.[23,24]

Multiple micro-polyps (1 mm or less in size) are fairly diagnostic of endometritis. Coupled with clinical symptoms, stromal edema and local hyperemia micro-polyps make a case of chronic endometritis. Further evaluation by immuno-histochemistry and broad spectrum antimicrobials are in order.

The availability of small-diameter hysteroscopes and small operative instruments, have expanded the use of this procedure, enabling HYS to be performed in an awaken patient in an office setting. As intracavitary lesions are common in women with complaints of AUB, HYS constitutes an important diagnostic tool and an out-patient HYS is being increasingly utilized for the diagnosis in a "1-stop" approach. In this one stop approach, an office HYS is performed and at the same time an endometrial sampling is performed with a vacuum device and the pathology like polyps is treated by excision simultaneously.

For better diagnostic accuracy, ideally, HYS should be scheduled in the follicular phase after the cessation of menstruation. Irregular proliferative or luteal phase endometrium may have irregular topography and can be falsely interpreted as endometrial polyps.

Loverro, *et al*.[25] in their study found that Positive predictive value of HYS in the diagnosis of endometrial hyperplasia accounted for 63%. In fact, Hysteroscopic diagnosis of endometrial hyperplasia was confirmed at pathologic examination in 81 out of 128 patients. Sensitivity and specificity of the endoscopic procedure accounted for 98% and 95%, respectively. Negative predictive value accounted for 99% as only two cases of atypical hyperplasia were missed at HYS.

The high diagnostic accuracy, associated with a minimal trauma, renders HYS the ideal procedure for both diagnosis and follow-up of conservative management of endometrial hyperplasia. In experienced hands, the accuracy of visual assessment of endometrium has matched the histological assessment to the tune of 95%.

Endometrial biopsy

It is very vital to evaluate the endometrial histopathology in a woman who has no improvement in her bleeding pattern following a course of therapy of 3 months. The society of obstetricians and gynecologists of Canada guidelines diagnosis of endometrial cancer in women with abnormal vaginal bleeding (2000) reviewed the evidence for endometrial sampling and contained an algorithm, which suggests a course of management in assessing the endometrium.[26]

A blind D and C used to be a gold standard procedure for all women with AUB in 40 + age group! However, a classic article questioned the efficacy and highlighted the limitations of this procedure. In 10-25% of patients, D and C alone may miss an existing endometrial pathology. It is associated with uterine perforation in 0.6-1.3% of cases, infection 0.3-0.5% and unexpected hemorrhage in 0.4% of cases.[27,28]

Office endometrial biopsy results in adequate samples 87-97% time,[29,30] and detects 67-96% of endometrial carcinomas.[29,30] Although the choice of sampling device may affect the accuracy, no existing method will sample the entire endometrium.[31] Hysteroscopically-directed sampling detects a higher percentage of abnormalities when compared directly with D and C as a diagnostic procedure.[32,33] Even if the uterine cavity appears normal at HYS, the endometrium should be sampled since HYS alone is not sufficient to exclude endometrial neoplasia and carcinoma.[34,35]

D and C, the former gold standard, and Vabra® are now recognized as other blind sampling techniques which often sample less than half of the endometrium and should no longer be performed, with limited exception.[36,37]

A vacuum device has higher pick-up rate compared to the traditional D and C (by contact scraping the walls of endometrial canal). Malignant cells are relatively more fragile and get detached more freely than normal endometrial cells and get sucked in a negative suction

device more readily, especially in case of a focal endometrial malignancy. A sono HYS guided or HYS guided approach allows more accurate detection of focal lesions.

When clinical symptoms, HYS findings and H and E, staining of endometrium suggest infection, a check for the presence of plasma cells is important to confirm a diagnosis of endometritis. Special immuno-histochemical stain for Syndecan 1, a proteoglycan present on the surface of plasma cells makes an accurate diagnosis of endometritis as the cause of AUB.[38]

Summary

Imaging, especially ultrasonography, plays a key role in screening and diagnostic triage. Transvaginal US is often the first imaging test undertaken for evaluation of the uterus in women with AUB. Endovaginal sonography is used to identify mural abnormalities, such as fibroids and adenomyosis, and to screen for thickened endometria, which require non-focal biopsy to detect cancer or hyperplasia.

SHG is a powerful tool for evaluating the endometrial cavity for focal abnormalities such as endometrial polyps or submucosal fibroids. The pre-menopausal assessment of the endometrium is relatively less accurate with ultrasound compared to the evaluation and predictability in postmenopausal bleeding episodes. A sono HYS -guided approach allows accurate detection of focal lesions. Data confirm that SIS is a safe, cost-effective, easy tool for endometrial investigation,[39,40] and may be included in any standard protocol flow-chart for the management of AUB.

HYS and directed biopsy is the 'gold standard' approach for most accurate evaluation of the endometrium to rule out andometrial Ca. The HYS procedure should be performed in early proliferative phase. A single stop approach, especially in high-risk women (Obesity, diabetes, family history of endometrial, ovarian or breast cancer) as well as in women with endometrial hyperplasia (>4 mm in postmenopausal bleeding and less so with >12 mm in pre-menopausal AUB) of combining the office HYS, directed biopsy in the presence of a focal lesion, and vacuum sampling of the endometrium, all without anesthesia is the most minimally invasive and yet accurate approach in current practice.

There is currently no evidence that any intrauterine diagnostic procedure using fluid may disseminate endometrial cancer cells into the peritoneum, thereby worsening the stage or lowering the vital prognosis of patients.

Histology constitutes the definitive diagnosis in all women with abnormal vaginal bleeding that is unresponsive to medical or hormonal therapy. Blind endometrial biopsies should no longer be performed as the sole diagnostic strategy in perimenopausal women with AUB.[28]

Endometritis as a cause of AUB should be kept in mind and evaluation and medical therapy can obviate a more aggressive therapy in such cases.

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