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Finding a Better Approach to Diagnosing Abnormal Uterine Bleeding

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Despite advances in diagnostic medicine, the evaluation of abnormal uterine bleeding (AUB) remains a challenge for physicians. One-third of patients who visit a gynecologist are there because of abnormal bleeding, and AUB is believed to account for more than 70% of gynecologic consults in perimenopausal and postmenopausal women.¹ In younger women between the ages of 19 and 39 years, abnormal bleeding most frequently occurs as a result of pregnancy or benign structural lesions like polyps or myomas. Anovulatory cycles are also common in younger women, as are polycystic ovarian syndrome, and

abnormalities of hormonal contraception. Occasionally AUB can be the result of endometrial hyperplasia. In women between age 40 years to menopause, AUB is much more of a concern, and it is often due to anovulatory bleeding that is a normal physiologic response to declining ovarian function.

CooperSurgical recently introduced Endosee® Office Hysteroscopy to help in the differential diagnosis of AUB. This new approach to gynecologic diagnosis is having a transformative effect on the management of patients with a variety of gynecologic disorders. Unlike blind endometrial biopsy, Endosee Office Hysteroscopy gives clinicians direct visualization of the endometrial cavity, which can have a significant impact on the diagnostic process. The Endosee device can be utilized at the point of care, does not require any significant preparation or a special room, and can

DISCLOSURES

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FIGURE 1 Endosee Office Hysteroscopy

be performed almost as quickly as an endometrial biopsy. By way of contrast, traditional office hysteroscopy requires sterile equipment and associated processing, is time consuming, as well as costly. As such, traditional office hysteroscopy is not a satisfactory point of care option.

Endosee Office Hysteroscopy (**FIGURE 1**) solves many of the problems that occur with traditional hysteroscopy. Because it can be performed in any examination room, there is no need for a dedicated hysteroscopy suite, and it offers point of care visualization of the uterine cavity at the time of the endometrial evaluation.

The immediacy of the test results is one of the most appealing features of Endosee. In the past, it was often necessary to see a patient during more than one visit to obtain definitive results, which led to a delayed diagnosis. In addition, when hysteroscopy is done in the operating room (OR), scheduling problems often complicate matters. OR time is always limited, and it is impossible to schedule every patient with AUB for hysteroscopy in the OR at the most convenient time. Every gynecologist has also had the frustration of taking a patient to the OR for a surgical procedure only to find the previous transvaginal ultrasound (TVUS) showed a false positive. With Endosee, clinicians can avoid the OR if the case does not need surgery based on the available workup, or schedule appropriately for the OR for those cases that do require surgical intervention. This relieves the stress of the OR staff when unplanned myomectomies, polypectomies, endometrial resections, or lysis of adhesions are required.

In addition to offering clinicians immediate access to critically important diagnostic information, it is also possible to perform both an endometrial biopsy and hysteroscopy in the same visit when Endosee Office Hysteroscopy has been employed. That means clinicians can send the patient where she needs to go, whether it is home or to the OR.

In many situations, it is possible to eliminate the blind biopsy altogether. Because the Endosee procedure allows clinicians to visualize the endometrial cavity, there is often no need to take a

tissue sample. If the hysteroscopy reveals a large polyp or fibroid, for example, one can schedule its removal in the OR based on that quick view. That eliminates the discomfort the patient would have had to experience from a biopsy.

The Endosee device is revolutionary because it is a point of care option. It allows physicians to perform a hysteroscopy with the patient in stirrups, just as one would do when performing a Pipelle® endometrial biopsy. In fact, it is not much different or more difficult to perform an Endosee hysteroscopy than it is to do an endometrial biopsy. It requires little preparation and is almost as quick as a biopsy. In anesthesia-sensitive patients, the Endosee also reduces the associated risks, which means the patient avoids potential cardiac complications and other anesthesia-related risks.

The Endosee device includes a sterile, single-use flexible cannula that is less than 5 mm in diameter. It also contains a camera and light source at the distal end of the device, thus avoiding the necessity of cleaning or sterilizing. The accompanying handset contains a small LCD screen and the handset is lightweight and reusable. Visualizing a patient's uterine cavity with the Endosee hysteroscope takes no more than 90 seconds.

The Limitations of Blind Endometrial Biopsy

Endosee Office Hysteroscopy joins several other diagnostic tools available to the gynecologist. To investigate the value of these diagnostic procedures, my colleagues and I analyzed data from

433 perimenopausal women with AUB, including metrorrhagia, menorrhagia, or both.² Instead of performing a sampling procedure, the patients were reexamined 4 to 6 days into their next menstrual cycle so that we could perform imaging when their endometrium was at its thinnest. Women who had an endometrial echo that was 5 mm or less (double layer) during endovaginal ultrasound imaging were diagnosed as having AUB. Women with an endometrial echo larger than 5 mm in whom it was not possible to visualize the endometrium were imaged by means of saline infusion sonohysterography (SIS). AUB was diagnosed in patients when SIS detected a symmetric single-layer endometrial thickness of less than 3 mm.²

Blind office biopsy without the assistance of imaging techniques like endovaginal ultrasound and SIS can easily miss many lesions.

This protocol revealed 341 patients (79%) who did not have evidence of anatomic abnormality based on endovaginal ultrasound, in which case there was no longer a need to perform additional testing.² Fifty-eight patients (13%) had focal polyps, which we removed hysteroscopically and which were confirmed by means of pathology. On the other hand, 22 patients (5%) had submucous myomas, and 10 (2.3%) had a symmetrically thickened endometrium, as detected by SIS. Our results confirmed that blind office biopsy without the assistance of imaging techniques like endovaginal ultrasound and SIS can easily miss many lesions. In this series, it would have overlooked polyps, submucous myomas, and focal hyperplasia in as many as 80 patients (18%).²

A more recent investigation by Soguktas and colleagues has also provided evidence to support the value of hysteroscopy in the diagnosis of AUB.³ In their investigation, TVUS, SIS, and diagnostic hysteroscopy (DH) were compared with a pathologic specimen of the endometrium used as a gold standard in this patient population. This prospective cohort study involved the examination of 89

premenopausal women between the ages of 36 and 48 years. All 89 women were initially imaged with TVUS, followed up with SIS and DH, and then compared with the pathologic findings. The Turkish researchers found that DH generated the most accurate results, and that DH and SIS were more accurate than TVUS. For the diagnosis of polypoid lesions specifically, DH was found to be the most accurate, followed by SIS and then TVUS. The other advantage of DH was that it allowed clinicians to immediately treat patients with AUB during the same session.³

Pathophysiology and Differential Diagnosis of AUB

The imaging procedures available to clinicians are all designed to diagnose a variety of benign and malignant disorders. Let's review the most common causes of AUB as outlined by the American College of Obstetricians and Gynecologists (ACOG) in its Practice Bulletin on diagnosing the condition.¹ They include:

- endometrial polyps
- adenomyosis
- uterine leiomyoma
- endometrial hyperplasia or carcinoma.

Other possible causes include acquired and inherited coagulopathies (eg, von Willebrand disease) and ovulatory dysfunction. The latter includes a range of disorders from amenorrhea to irregular menstruation. The ACOG bulletin points out that these can include endocrine disorders like polycystic ovary syndrome. Among the possible mechanisms of action for ovulatory AUB: abnormal prostaglandin synthesis and receptor upregulation, increased fibrinolytic activity, and increased tissue plasminogen activator activity.

ACOG uses the PALM-COEIN classification to divide these various types of uterine bleeding disorders into 2 categories.¹ Disorders in the PALM family have a structural etiology and include polyps, adenomyosis, leiomyoma, and malignancy and hyperplasia. Disorders that fall into the non-structural etiology family include coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified.

Taking into account the patient's age will also help clinicians reach an accurate diagnosis.

Between the ages of 13 and 18 years, AUB is frequently the result of anovulation, which in turn occurs because an adolescent's hypothalamic–pituitary–ovarian axis is still immature. But also keep in mind that AUB in this age group can be precipitated by hormonal contraceptives, pelvic infection, pregnancy, and tumors, among other conditions. In patients between the ages of 19 and 39 years, you can expect to see AUB brought on by polyps, myomas, pregnancy, polycystic ovary syndrome, oral contraceptives and other hormonal contraception, and endometrial hyperplasia. Once a woman reaches age 40 years or approaches menopause, AUB may be a normal response to an age-related drop in ovarian response. However, hyperplasia, carcinoma, endometrial atrophy, and myomas are also possibilities.

Comparing Imaging Approaches to AUB Diagnosis

Guido et al have demonstrated that blind endometrial biopsy is very accurate in diagnosing endometrial cancer when an adequate specimen is obtained and when the endometrial process is global. Richard Guido and his colleagues reached this conclusion by studying a group of patients with existing endometrial cancer who were undergoing a hysterectomy, with each patient having the biopsy performed before having the surgery.⁴ The patient population was composed of women who had been referred to gynecologic oncologists at Magee-Women's Hospital in Pittsburgh, and who had been previously diagnosed with endometrial cancer; their mean age was 61 years.

Using the Pipelle endometrial suction curette, the investigators were able to obtain a biopsy capable of being analyzed in 63 of 65 patients (97%).⁴ They found that the biopsy was able to detect the malignancy in 54 out of 65 patients, yielding a sensitivity (SD) of 83% (5%). Eleven patients had false negative results, 5 of whom had tumors located within an endometrial polyp alone, while 3 of the 11 patients had less than 5% of the surface of the endometrium affected by the cancer, making these cancers more difficult to detect. Details on the histo-

pathologic findings of the specimens in these 11 patients were revealing. The endometrial surface area affected was 5% or less in 3 patients, between 6% and 25% in 4 patients, and 26% to 50% in 4 patients. Their research suggests that a cancer that occupies less than 50% of the surface area of the endometrial cavity can be missed by a blind endometrial biopsy.⁴

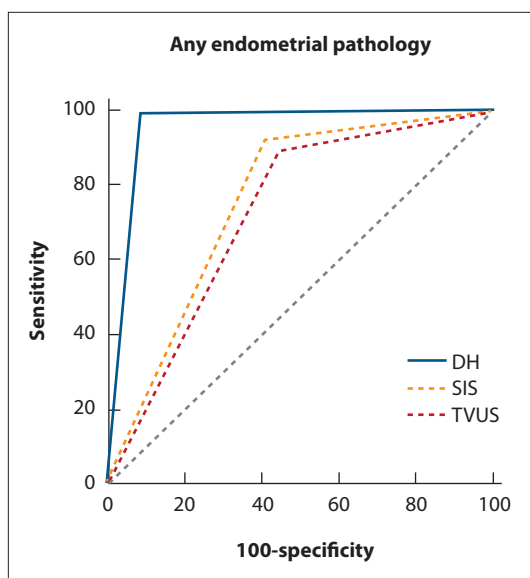
Clinicians can still begin with a biopsy, but unless the results are malignant or indicate complex atypical hyperplasia, the endometrial evaluation is not complete.

Similarly ACOG Practice Bulletin No. 128, *Diagnosis of Abnormal Uterine Bleeding in Reproductive-Aged Women*, states that an office endometrial biopsy is valuable as the first-line procedure of tissue sampling in the evaluation of patients with AUB, but it concurred with the findings from Guido et al and concluded that if a cancer occupies less than 50% of the surface area, it can be missed by a blind endometrial biopsy sample.¹ The Practice Bulletin further stipulated that a positive biopsy result is more likely to reveal the presence of disease than a negative biopsy is to rule out the disease.

In other words, a negative blind biopsy is not a stopping point in the diagnostic process. Clinicians can still begin with a biopsy, but unless the results are malignant or indicate complex atypical hyperplasia, the endometrial evaluation is not complete. The Bulletin went on to state that the primary imaging test of the uterus for the evaluation of AUB is TVUS.¹ If TVUS is not adequate, and if further evaluation of the cavity becomes necessary, hysteroscopy, preferable in an office setting, or SIS is recommended.

However, while TVUS has merit, its benefits need to be put into proper perspective, which is what a study by Grimbizis and colleagues accomplished.⁵ In a comparison of TVUS, SIS, and DH, Grimbizis et al evaluated 105 patients from

FIGURE 2 Diagnostic Hysteroscopy vs Transvaginal Ultrasound and Saline Infusion Sonohysterography



Abbreviations: DH, diagnostic hysteroscopy; SIS, saline infusion sonohysterography; TVUS, transvaginal ultrasound. Reprinted from *Fertility and Sterility*, Volume 94, issue 7, Grimbizis F, Tsolakidis D, Mikos T, et al, A prospective comparison of transvaginal ultrasound, saline infusion sonohysterography, and diagnostic hysteroscopy in the evaluation of endometrial pathology, pages 2720-2725, ©2010, with permission from Elsevier.

an ambulatory clinic who reported symptoms of menorrhagia, postmenopausal bleeding, and infertility; the study included 55 premenopausal patients with AUB, 28 infertility patients, and 22 postmenopausal women with vaginal bleeding. This was a prospective, blind, controlled investigation that was conducted from 2004 to 2006 by the Department of Obstetrics and Gynecology at Aristotle University of Thessaloniki in Greece. Their analysis found that DH outperformed TVUS and SIS (FIGURE 2). The researchers also found that hysteroscopy was a more precise procedure for the diagnosis of intracavitary masses, when compared to TVUS and SIS. In addition, the researchers found that SIS was more accurate than TVUS for diagnosing polyps and myomas.⁵

Grimbizis et al pointed out that their conclusions are consistent with other published work in the field.⁵ Kelekci et al, for instance, also compared TVUS to SIS and DH and found sensitivities of 56%, 81%, and 85%, respectively; specificity was 72%, 100%, and 100%, respectively for the exclusion of any endometrial pathology.⁶

The Advantage of Office Hysteroscopy

Moawad et al have demonstrated that office hysteroscopy can help decrease the rate of diagnostic hysteroscopy performed in the operative room setting under anesthesia, thereby reducing health care costs.⁷ They reached that conclusion after studying 130 patients who underwent traditional office DH at 2 ambulatory clinics affiliated with the University of Florida College of Medicine in Gainesville.

The University of Florida Women's Health Center began using office-based DH to investigate uterine pathology in 2009 and has found it very accurate in detecting endometrial cavity abnormalities, as well as anomalies in the tubal ostia and endocervical canal. Previous research had suggested that the office approach was safer and less costly than having the procedure done in a hospital setting. To confirm these findings, the Women's Health Center embarked upon an analysis of procedures done between 2009 and 2012. One hundred and thirty patients had office hysteroscopy performed to evaluate AUB.⁷ Those with abnormal findings and patients who required anesthesia for various reasons were sent to the OR to better visualize the anomaly, remove the lesion, or perform a dilation and curettage.

They conducted the aforementioned investigation using a flexible hysteroscope in conjunction with normal saline solution to distend each patient's uterus.⁷ The office procedure did not require tenaculums, cervical dilation, or anesthesia because the hysteroscope was flexible, with a small diameter. The procedure caused minimal or no trauma to the cervix. In the final analysis, the investigation revealed that among 130 enrolled women who had AUB, 75 were able to avoid OR-based hysteroscopy and were diagnosed by means of the office procedure, leaving

55 who required another hysteroscopy in the OR. Moawad et al calculated that the change in venue represented an estimated savings of \$1498 for each patient.⁷

Despite these positive findings, traditional office hysteroscopy still has its drawbacks. The equipment is expensive, needs sterilization, requires a dedicated room, and is time consuming. All of these issues make traditional office hysteroscopy less than ideal as a diagnostic tool at the point of care. As mentioned earlier in this paper, Endosee Office Hysteroscopy is an effective alternative because it avoids the need for a dedicated sterile environment, can be performed quickly, and provides direct visualization of the endometrial cavity.

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