Clinical Evaluation of Abnormal Uterine Bleeding

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Introduction

Abnormal uterine bleeding is one of the most common problems a woman faces in her reproductive life span, and it accounts for 20 % of visits to the gynecologic clinic. Abnormal uterine bleeding (AUB) is defined as "bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration" and accounts for 25 % of all gynecologic procedures [1]. All clinicians dealing with a case of abnormal uterine bleeding face the basic challenge of excluding genital tract malignancy by formulating a well-organized and logical approach for evaluation of the symptom. Abnormal uterine bleeding is caused by the disruption of normal physiology, anatomical changes in the endometrium, or endometrial malignancy; therefore, the role of detailed history and clinical examination of the pelvis, besides endometrial sampling and imaging studies, forms the backbone of evaluating this condition.

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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 AUB in non-gravid women of reproductive age. 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 [2]. According to the proposed classification system, nonspecific terms like dysfunctional uterine bleeding should be abandoned to favor a more specific etiology like ovulatory dysfunction.

In order to identify the underlying etiology, evaluation of the women presenting with AUB must be undertaken in a comprehensive manner which not only justifies the suspected clinical situation but also suits available resources of a given setup. The clinician must always be suspicious of endometrial cancer and hyperplasia especially in perimenopausal and postmenopausal age group and must establish the diagnosis based on visual and histopathologic assessment of the endometrium. The various diagnostic techniques advocated are transvaginal ultrasound (TVS), saline infusion sonohysterography (SIS), hysteroscopy, MRI, and endometrial sampling. Finally, the management should be devised for each patient regardless of age, incorporating all risk factors for malignant disease [3].

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Evaluation of Abnormal Uterine Bleeding

There can be multiple identifiable factors that can contribute to abnormal uterine bleeding in a woman. Besides systemic, iatrogenic, and hormonal age-related causes, endometrial pathologies (endometrial polyps, submucous myomas, endometrial hyperplasia, and endometrial carcinomas) should always be suspected and thoroughly investigated. Up to 8 years before menopause, women may have intermittent anovulation resulting in recurrent irregular cycles, and the presence of recurrent anovulation causes increased risk of endometrial cancer [4]. About 14 % of premenopausal women with recurrent anovulatory cycles develop endometrial carcinoma or its precursor, hyperplasia with atypia [5]. About 10–20 % of endometrial cancers are diagnosed in premenopausal women, and women at highest risk of cancer have advanced age, obesity, nulliparity, infertility, diabetes mellitus, family history of colon cancer, long-term use of unopposed estrogen therapy, or a history of tamoxifen use [6]. There is a need for a protocol of diagnostic modalities which give us high sensitivity and specificity as well as high negative predictive value for evaluation of women with AUB.

Guidelines and Rationale for Investigation

General Assessment

The role of detailed history taking and a thorough general and pelvic examination cannot be overemphasized. A clinician must always rule out pregnancy in any women of reproductive age group before proceeding further. History should elicit the duration and severity of symptoms, any associated vaginal discharge, and postcoital bleeding. History of any chronic medical condition like hypertension or diabetes should be taken along with history of any drug intake (e.g., tamoxifen in breast cancer patients, hormone therapy in postmenopausal females). Family history of cancer such as in cases of hereditary non-polyposis colorectal cancer should be sought as such women are at risk of developing endometrial cancer (lifetime risk being 60 %). Initial basic investigation must include a complete blood count to assess degree of anemia, and after confirming that bleeding is from uterus, one must proceed in a systematic fashion to ascertain the exact cause of abnormal uterine bleeding.

Anovulatory bleeding is characterized by abnormal duration, frequency, or volume of bleeding over baseline occurring at irregular intervals and often interspersed with periods of amenorrhea. All reproductive age and perimenopausal females with suspected recurrent anovulatory cycles must undergo evaluation for anovulation which includes endometrial sampling.

Endometrial Sampling

Histopathologic evaluation of the endometrium can efficiently exclude endometrial hyperplasia or malignancy but is not required for all patients of AUB. The treating clinician must select women based on a combination of factors which when present increase the risk of endometrial hyperplasia or endometrial carcinoma. Several reports and guidelines use age, personal, and genetic risk factors along with TVS screening for endometrial echo complex thickness to determine which patients should undergo endometrial sampling [5, 7, 8]. Although age over 35 years is nowadays considered as the lower limit for biopsy in women with abnormal bleeding but regardless of age, persistent AUB that is unexplained or not adequately treated requires endometrial sampling, if possible, in association with hysteroscopic evaluation of the endometrial cavity [2, 3]. Several techniques can be used to perform endometrial sampling, but most importantly, one must ensure to obtain an adequate sample before declaring that a woman is at low risk of malignant neoplasm [9].

Office endometrial aspiration is a relatively inexpensive, convenient, and safe procedure which is now preferred over a blind endometrial curettage. It is performed using a small flexible suction cannula (Pipelle device) which suctions the shedded endometrial cells especially the malignant ones which are relatively more fragile, and hence, even a focal malignant lesion is likely to be picked up. In premenopausal women, endometrial biopsy (EB) using Pipelle is 82.3 % sensitive for detecting

endometrial hyperplasia with atypia and 91 % sensitive for detecting endometrial carcinoma, while the specificity is 98 % for both. In postmenopausal women the sensitivity is as high as 99.6 %, thus making it the best device for endometrial sampling, and inadequate sampling has been reported only in 10–12 % of cases [10]. Inadequate samples must be re-evaluated with TVS and hysteroscopy to avoid missing an endometrial cancer and must not be construed as negative for malignancy.

ACOG recommends that women with postmenopausal bleeding must be assessed to exclude malignancy with either endometrial biopsy or TVS; the initial assessment does not require performance of both the tests. If on TVS, endometrial thickness (ET) is ≤4 mm, EB is not required, but endometrial thickness of >4 mm or inability to adequately visualize the endometrium must trigger alternative evaluation including office hysteroscopy or EB [11].

Imaging Studies

Transvaginal Ultrasonography (TVS)

To evaluate the structural abnormalities of the uterine cavity, TVS has been utilized as the first-line screening tool in evaluating AUB. The benefits of TVS lie in its effectiveness in assessing the complete pelvis, its ease of application, patient acceptability, and immediate results. On TVS, endometrial thickness is measured as the maximum anteroposterior thickness of the endometrial echo on a long axis view of the uterus. If TVS shows ET of less than 5 mm, the probability of the woman having endometrial cancer is 1.7 % and it is 0.8 % when the cut-off is taken as 4 mm. In perimenopausal and postmenopausal women with AUB, endometrial sampling is generally considered unnecessary when the endometrial thickness is less than 4 mm since the risk of endometrial hyperplasia or cancer is extremely low. Endometrial biopsy is indicated when the clinical history is suggestive of long-term estrogen exposure even when the ET is normal on ultrasound (5–12 mm), and biopsy must be considered when ET is greater than 12 mm even when the clinical suspicion of disease is low [12]. Transvaginal ultrasound detects intracavitary abnormalities like uterine tumors, polyps, and endometrial and myometrial abnormalities with a sensitivity of 60–92 % and a specificity of 62–93 % in perimenopausal women [13, 14]. Since TVS is not 100 % sensitive for diagnosing endometrial polyps and other small lesions, examination with other imaging techniques like saline infusion sonohysterography (SIS) or hysteroscopy should be considered [15]. Another limitation of ultrasound is that it cannot always reliably distinguish between benign proliferation, hyperplasia, polyps, and cancer, and in 5–10 % of women with postmenopausal bleeding, the endometrium cannot be identified on USG, these women need further evaluation with more sensitive techniques [16].

Doppler Studies

It is usually considered that benign lesions have high resistance vessels (mostly single feeding artery) and malignant lesions have low resistance vessels (mostly multiple feeding vessels with broad base); based on this principle, Doppler studies may be considered useful in differentiating between the two, but studies have shown that Doppler does not improve the detection of premalignant and malignant lesions of the endometrium [17].

Saline Infusion Sonohysterography

Saline infusion sonohysterography (SIS) or sonohysteroscopy is the technique of contrast enhancement of transvaginal scan which further increases the sensitivity and negative predictive value of sonographic evaluation. The procedure involves instillation of 5–10 ml of saline in the uterine cavity using 5–8 F Foley's catheter followed by TVS. Once the cavity is distended by anechoic saline, lesions like endometrial polyps, submucous fibroid, and lesions distorting endometrial contour are better identified. In a study by Mathew et al., SIS has been shown to have a better sensitivity in evaluating endometrial cavity as compared to TVS alone (91.4 % vs. 72.4 %). Negative predictive value of SIS was found to be 94.1 % as compared to 74 % for TVS [18]. The combination of sonohysterography and endometrial biopsy offers a high sensitivity and negative predictive value for detection of endometrial and uterine pathologies,

especially in women with focal endometrial lesions [19]. Although it is feasible to conclude that SIS can be used as an effective screening tool prior to hysteroscopy in evaluating women with abnormal uterine bleeding, increased cost and limited availability as compared to TVS must also be considered. Further studies have also compared the role of 3-D sonohysterography and hysteroscopy in detecting intrauterine lesions and concluded that 3-D sonohysterography is comparable to hysteroscopy for investigating intrauterine lesions in perimenopausal and postmenopausal females with AUB [20].

Magnetic Resonance Imaging

MRI has no established role in the initial evaluation of women with AUB but may be useful in evaluating females with difficult vaginal access where TVS, SIS, and hysteroscopy are not the feasible options. MRI can reliably distinguish between adenomyosis and leiomyomata and can also demonstrate the proximity of these lesions to the uterine cavity, but cost-effectiveness for this purpose needs to be justified. In case of diagnosed endometrial cancer, MRI helps in identifying the site and size of endometrial tumor along with the degree of myometrial invasion and lymph node metastasis and is described in detail in Chap. 8.

Hysteroscopy

Hysteroscopy helps in direct visualization of the endometrial cavity and, hence, is now considered to be the gold standard for diagnosis and treatment of intrauterine pathologies. It helps in assessing the endometrium and taking directed biopsy from the suspected lesion in the same sitting. Earlier, the major concern with hysteroscopy used to be the need for general anesthesia, which increased the applied cost and also delayed the diagnosis of endometrial cancer in women with hypertension and diabetes. The advent of modern hysteroscopes with an outer diameter of 2–3 mm now permits diagnostic and minor operative procedures in office setting with minimal anesthesia. Hysteroscopy being an invasive procedure may be associated with complications like uterine perforation, infection, and excessive bleeding, but adequate training minimizes the incidence of such complications. Hysteroscopy is more expensive than TVS and it does not evaluate the myometrium or ovaries but the sensitivity and specificity is better for diagnosing intracavitary abnormalities, i.e., 94 % and 99 %, respectively, with an overall success rate of 96.9 % [21].

For better diagnostic accuracy, ideally, hysteroscopy 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. Lasmar et al. studied the importance of hysteroscopic view in provisionally diagnosing endometrial hyperplasia and cancer in patients with AUB. They found that in 97 out of 103 (94.2 %), hysteroscopic evaluation with suspected cancer findings had histological diagnosis of cancer or hyperplasia, and hence, they concluded that there is good validity of hysteroscopic diagnosis for endometrial hyperplasia and cancer but histological study is mandatory in patients with AUB [22]. Hysteroscopy-guided biopsy is now considered gold standard procedure for evaluating women with postmenopausal bleeding and in whom ET is >4 mm. Women with ET <4 mm and persistent postmenopausal bleeding should also undergo hysteroscopic evaluation of the endometrium and directed biopsy. Blind biopsy with curettage may not be reliable for evaluation of endometrial pathology especially in women with thin endometrium and focal endometrial lesions; in these women too hysteroscopic evaluation of the endometrial cavity becomes necessary for diagnosis. Theoretical risk of spill of cancer cells into peritoneal cavity exists but studies have shown no impact on prognosis.

Women on Tamoxifen Therapy

Tamoxifen is a nonsteroidal selective estrogen receptor modulator (SERM) used in breast cancer patients for its anti-estrogenic effects, but it also has some estrogenic effects on the endometrium. It is associated with endometrial proliferation, hyperplasia, and polyps and is known to increase the relative risk of endometrial cancer by two to three times than the age-matched controls [23]. This risk further increases with advanc-

ing age of the patient and duration of use, leading to poorer prognosis due to less favorable histology and higher stage; hence, we need follow a strict protocol for evaluating these women when they present with AUB [24]. The following are the ACOG recommendations for evaluating patients on tamoxifen [25]:

(a) Postmenopausal women taking tamoxifen should be monitored closely for symptoms of endometrial hyperplasia and cancer.
(b) Premenopausal women taking tamoxifen have no increased risk for uterine cancer and as such require no additional monitoring beyond routine gynecologic care.
(c) Women should be informed the risk and should be asked to promptly report any abnormal discharge or bleeding.
(d) Any abnormal bleeding, discharge, or spotting should be investigated.
(e) Emerging evidence indicates the presence of low- and high-risk groups for development of atypical hyperplasia with tamoxifen in postmenopausal women based on the presence of benign endometrial polyps. Hence, there may be a role of pretreatment screening with TVS, SIS, or office hysteroscopy before initiating therapy.
(f) Routine surveillance, except in high-risk groups, does not increase the chances of early detection of endometrial cancer in women using tamoxifen.

Conclusions

Abnormal uterine bleeding is one of the leading gynecologic complaints in women of perimenopausal and postmenopausal age group. Until recently, there has been confusion in not only the nomenclature of abnormal bleeding patterns but also in investigation protocols of women with AUB. FIGO has now proposed a new classification for AUB named PALM-COEIN which mainly highlights the various and most common etiologies causing abnormal uterine bleeding [2]. The new classification helps in standardizing the investigation algorithm for AUB and helps in adapting a more comprehensive and practical approach for such patients universally.

Women presenting with abnormal uterine bleeding irrespective of age should be diligently investigated, keeping in mind the high-risk factors for endometrial hyperplasia and cancer. Previously, blind endometrial curettage was used to evaluate the endometrium, but current practice recommends endometrial aspiration biopsy and, preferably, hysteroscopy-guided biopsy wherever indicated and feasible. Imaging studies like TVS are commonly used as a first-line investigation as it is readily available, noninvasive, and easily acceptable with added advantage of evaluating the myometrium and adnexa, over hysteroscopy. SIS has its role in evaluating endometrial polyps and submucous fibroids with better detection rate over TVS.

MRI has a role in preoperative evaluation of patients with endometrial cancer, for planning appropriate surgery. Hysteroscopy and directed biopsy is the "gold standard" approach for most accurate evaluation of the endometrium and diagnosing endometrial cancer. It is a one-step 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 >12 mm in premenopausal AUB) as it combines diagnosis of the endometrial lesion, directed biopsy, and treatment, all with minimal anesthesia and least complications.

Key Points

1. Abnormal uterine bleeding accounts for 20 % of patients seeking gynecologic referral and 25 % of all gynecologic procedures.
2. Any perimenopausal woman with AUB who is >35 years old, postmenopausal women with bleeding, or younger women with high-risk factors should be thoroughly investigated for endometrial hyperplasia/cancer.
3. TVS is accepted as the first screening test to look for endometrial, myometrial, or adnexal pathologies of AUB. Further

evaluation is required in case of normal ultrasound findings, inconclusive results, thickened endometrium, or ET >4 mm in case of postmenopausal females.
4. SIS has a better sensitivity and negative predictive value for imaging small endometrial polyps and submucosal fibroids.
5. An endometrial aspiration biopsy is to be done for histopathologic evaluation wherever indicated.
6. Hysteroscopy-directed biopsy is the gold standard technique for diagnosing endometrial pathologies like endometrial hyperplasia, cancer, and focal lesion.
7. Hysteroscopy being a single-step approach for diagnosis and treatment of endometrial pathologies might be preferred in cases of postmenopausal bleeding where detecting endometrial cancer as soon as possible is crucial.
8. Routine surveillance, except in high-risk group, does not increase the chances of early detection of endometrial cancer in women on tamoxifen.

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