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Review Article

Management of Post-Menopausal Bleeding

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Abstract

Introduction: Post-menopausal bleeding (PMB) is defined as uterine bleeding that occurs after one year of menopause. Amenorrhoea accounts for 10% of incidence immediately after menopause. One of the other common reasons for post-menstrual bleeding is endometrial carcinoma which occurs in 10 - 15% of cases. Endometrial Cancer, unlike ovarian cancer, presents at an early stage can be treated with hysterectomy, provided timely and accurate diagnosis is made. It is important to notice that lesions such as endometrial polyps, fibroids (benign focal lesions) and vaginal atrophy are some common reasons for post-menstrual bleeding, which is prevalent in up to 40% of cases. Risk factors include obesity, polycystic ovary syndrome, unopposed estrogens, and nulliparity. Post-menopausal bleeding mostly has an intrauterine source, but vulva, vagina, cervix, fallopian tubes, or ovarian pathology and cervical stenosis may be some other reasons. The extragenital sites for bleeding are the urethra or bladder and the rectum or bowel. Therefore, a prompt clinical approach is mandatory to evaluate the cause of post-menopausal bleeding and to exclude it from carcinoma of the genital tract or other precancerous lesions of the endometrium.

Aim of the Study: The aim of the review is to understand the various possible causative factors for post-menopausal bleeding and its management.

Methodology: The revive is a comprehensive research of PUBMED from the year 2012 to 2021.

Conclusion: There may be multiple reasons for Post-menopausal bleeding, and 10% of them are due to endometrial carcinoma; therefore, post-menopausal bleeding must always be investigated to rule out the cause, the most common among that is atrophic vaginitis or endometritis. Tissue pathology for assessment of endometrium is essential, even if there is an obvious presence of atrophic vaginitis or polyp. Most of the causative factors can be treated well if diagnosed early and present lesser complication; the prognosis for carcinoma is also usually good since most patients present at an early stage of disease attributed to its early symptom of post-menopausal bleeding.

Keywords: *Post-Menopausal Vaginal Bleeding; Carcinoma; Management; Hysterectomy*

Introduction

Menopause is a natural phenomenon that, on average, occurs at the of fifty-one years age, when the ovaries stop making estrogen and the woman is no longer ovulatory. After menopause, the level of follicle-stimulating hormone (FSH) is elevated as the hypothalamic-pituitary-ovarian axis in the brain attempts to stimulate the process of ovulation despite the ovaries no longer being able to produce it. The absence of menses for twelve months labeled the woman as menopausal. However, if further vaginal bleeding occurs, then it is no longer considered normal. Hence post-menopausal bleeding should be considered important, and a prompt diagnosis should be made as there may be various conditions such as benign and malignant conditions that may lead to bleeding, and the most common among them is atrophy, but the most concerning etiology are malignant endometrial cancer. Since most malignancies are diagnosed at early stages, therefore, exhibit a better prognosis [1].

Etiology

Abnormal genital bleeding with post-menopausal women is often described as "having a period" again despite not having had a menstrual cycle for a long period of time, and this is mostly attributed to the uterus. Post-menopause, there may be several sources of bleeding besides the uterus, such as from the vagina, perineum, vulva, or fallopian tubes. Bleeding can often be related to an ovarian pathology, or it may also be of non-gynecologic cause. Very often, bleeding from the bladder, urethra, or gastrointestinal tract (bowel, anus, rectum) could be mistaken for vaginal bleeding. Therefore, the etiology must be ruled out. The most common cause of post-menopausal bleeding is atrophy which can either be from the endometrium or the vaginal mucosa. Endometrial hyperplasia, submucous leiomyomas, and endometrial polyps are some other common etiology contributing to post-menopausal bleeding. The source for all this bleeding is uterine; therefore, it must be distinguished from non-gynecologic reasons for bleeding [2].

Some common causes of post-menopausal bleeding and frequency [3].

Cause of Bleeding	Frequency (%)
1. Endometrial or cervical polyps	2 - 12
2. Endometrial Hyperplasia	5 - 10
3. Endometrial Carcinoma	10
4. Exogenous Oestrogens	15 - 25
5. Atrophic Endometritis and Vaginitis	60 - 80
Others (Vaginal trauma, uterine sarcoma, urethral caruncle, cervical cancer, anticoagulants, etc.	

Epidemiology

Approximately about 4 - 11% of post-menopausal women reported having vaginal bleeding, Among which 5% accounts for gynecologic office visits. Endometrial Cancer is the most common malignancy of gynecologic origin in the United States, which accounts for 1 - 14% of post-menopausal bleeding secondary to endometrial cancer. The death rate from uterine cancer was 11,000 in the year 2017, and over 61,000 new cases were reported. In most of these cases, approximately 92% are endometrial in origin, and vaginal bleeding was a constant sign in more than 90% of cases among women after menopause and with endometrial cancer [4].

Pathophysiology

After menopause, the absence of estrogen causes atrophy of the endometrium and vagina. The collapsed and atrophic surfaces of the endometrium contain no fluid. As a result, it prevents friction inside the cavity and leads to the development of micro-erosions of

the epithelium and further chronic inflammation. The chronic state of the endometrium is prone to light bleeding or spotting. Upon ultrasound (pelvic), would show normal-appearing but small uterus and ovaries and a thin endometrial stripe after menopause. On the contrary, premalignant or malignant conditions of the endometrium arise after unopposed estrogen. The abnormal endometrial changes can be due to chronic anovulation (such as in polycystic ovarian syndrome), systemic estrogen-only therapy, obesity, and estrogen-secreting tumors. An infrequent, insufficient shedding of the endometrium is often maybe a result of anovulation. Apart from this, many women have genetic predispositions for endometrial cancer, which includes Cowden disease and Lynch syndrome [5].

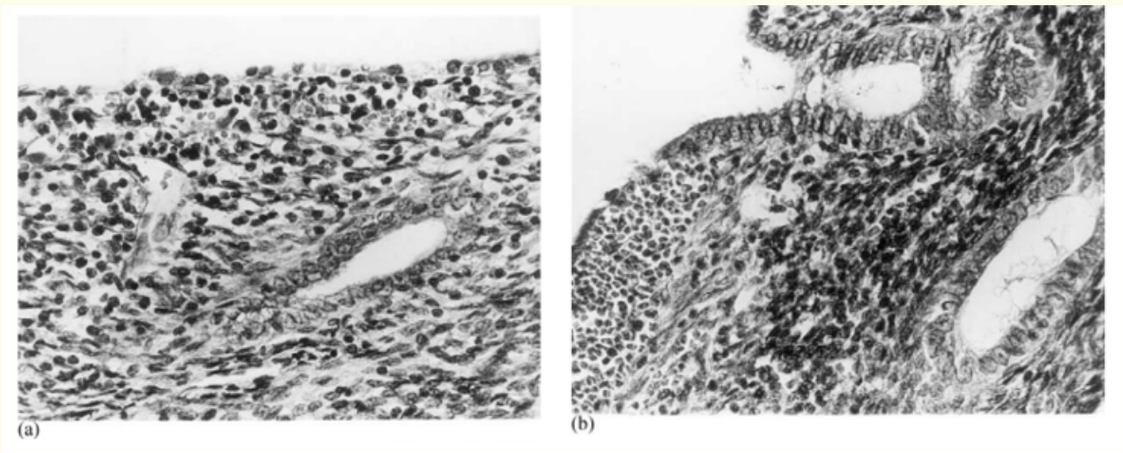

Figure 1: *Showing (a) Atrophic endometrium. Very thin mucosa with atrophic gland, denuded surface, inflammatory cell infiltrates, and ruptured capillary (b) Atrophic endometrium-extravasated red blood cells (left) under the very thin, fragile, partly ruptured surface epithelium. Scattered inflammatory cells are seen in the stroma [5].*

Histopathologically the normal proliferative endometrium contains regularly spaced glands that lie within stroma at a gland to stroma ratio of 1:1, while the Atrophic endometrial cells are smaller and more cuboidal than the normal endometrium in which the glands become cystic, appear large and round with few or no mitotic cells [1].

History of Present Illness:	The history of present illness deals with the nature of the patient's prior menses and current bleeding pattern, both of which are essential. Any previous history of heavy or abnormal uterine bleeding may indicate that there may be either structural abnormalities, such as leiomyomas, or endometrial abnormalities like hyperplasia, polyps, or malignancy. Questions should be asked regarding when the patient notices her first post-menopausal bleeding, whether in the clothing or on a pad, after intercourse, etc., as these provide some important clues for the contributing etiology of the bleeding. The number of bleeding days, the constancy or intermittent nature of bleeding, and the heaviness of bleeding are also essential.
Past Medical History:	The past medical history may be helpful to determine the possible cause as any history of obesity, polycystic ovarian syndrome or other anovulation, diabetes mellitus, and the use of medicines (tamoxifen) all give a clue of hyperplasia or malignancy if the cervical etiology is concerned then its essential to ask whether the patients recently have had Pap test, normal or abnormal. The Pap test revealing atypical glandular cells may indicate endometrial pathology. Apart from this, any history of radiation exposure should also be elicited.
Social History:	The condition Cervicitis should be considered by asking the nature of the bleeding (whether it's postcoital) or due to a history of infections or partner infidelity. The risk of bladder cancer increases with cigarette smoking (hematuria may be mistaken for vaginal bleeding) but decreases the risk of endometrial cancer.
Family History:	A family history of similar post-menopausal bleeding, breast, gynecologic, urologic, gastrointestinal cancers may also be elicited.
Medications:	Medications history is an important aspect since Post-menopausal hormone therapy, according to a different regimen, may lead to bleeding. The use of certain herbal supplements may stimulate the endometrial lining. The use of anticoagulants may also lead to vaginal bleeding [13-15].
Physical Exam:	A physical exam includes a thorough evaluation of the internal and external anatomy of the genital tract. The bleeding sites should be identified. Lesions and lacerations should be checked on the urethra, anus, vulva, vagina, or cervix. The shape, size, and tenderness of the uterus should be checked. The findings of uterus atrophy classically include pale, dry vaginal epithelium that is shiny and smooth and lacking rugae. Any other signs of inflammation (erythema or redness, petechiae), friability, discharge, visible blood vessels through the thin epithelium, or bleeding.

History and physical

The management starts with a detailed history to possibly rule out the causative factor of post-menopausal bleeding. They start from the establishment of menopausal status. Various questions should be asked regarding the last menstrual period, or surgical history (in patients with menopausal secondary to oophorectomy) must be determined. The history regarding testing of follicle-stimulating hormone (FSH) level to help establish the diagnosis of menopause [1,6].

Investigation and evaluation

After a comprehensive history and detailed physical examination, evaluation becomes is essential to rule out various possibilities and diagnose or exclude malignancy or hyperplasia.

Transgingival ultrasound: For initial 'noninvasive' evaluation of post-menopausal bleeding, the American College of Obstetricians and Gynecologists recommend a transvaginal ultrasound. The thickness of the endometrium is measured in an anterior-posterior fashion, at the area of endometrial echo of maximal thickness, on a long-axis view of the uterus. An endometrium thickness equal to or less than 4 mm is not suggestive of endometrial carcinoma in 99% of cases. However, it cannot definitively detect the presence or absence of malignancy. This may also be helpful in the diagnosis of leiomyomas, adnexa, and the assessment of uterine polyps, etc. Transvaginal ultrasound may also be helpful in deciding the endometrial sampling that is a finding on which the endometrial sampling is indicated is endometrial lining greater than 4 mm and the presence of diffuse or focal increased in echogenicity or heterogeneity [7].

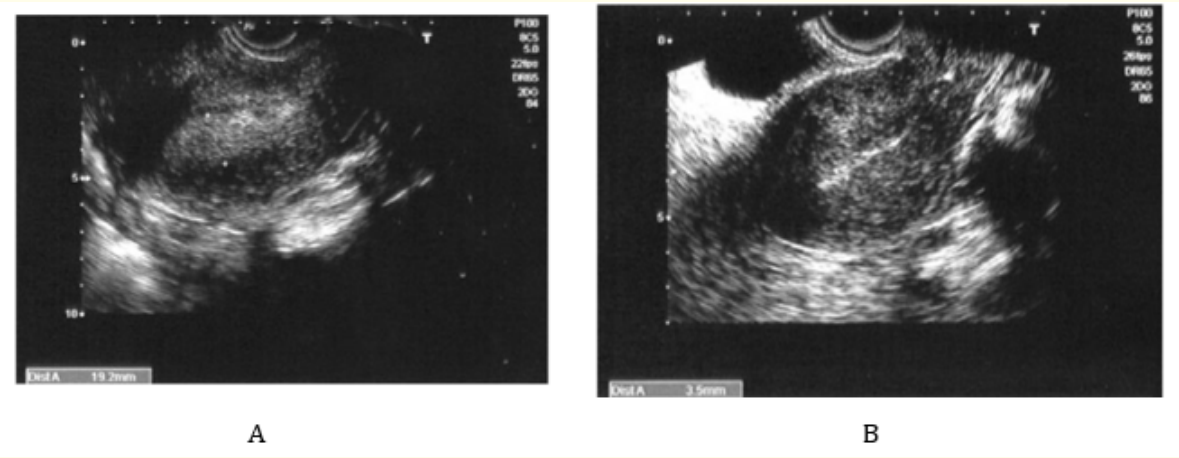

Figure 2: *(A) Showing thickened endometrium (endometrial thickness=19.2 mm) on transvaginal sonography in a woman with post-menopausal bleeding and (B) Thin endometrium (endometrial thickness=3.5 mm) on transvaginal sonography in a woman with post-menopausal bleeding [8].*

Endometrial sampling: Endometrial sampling is an invasive diagnostic technique that should be performed in patients with persistent or recurrent bleeding, despite the presence of thin endometrial echo. It is advisable to begin the diagnostic with endometrial sampling rather than ultrasound in patients who are at higher risk of malignancy. It has been suggested that the chances of missing endometrial cancer are 1 among 339 patients for whom the 4 mm endometrial thickness as a threshold has been detected in ultrasound. Besides that, the diagnostic accuracy of endometrial sampling correlates positively with the amount of tissue that is collected for the sampling [7,9].

There are various methods of endometrial sampling. Dilation and curettage methods have been used for years and are efficient in diagnosing endometrial cancer in 90% of cases. Metal curettes or flexible plastic samplers are used to perform an endometrial biopsy. In endometrial sampling, it is common to have findings that are insufficient for diagnosis and have a failure rate of up to 54% sampling. In such cases where sampling was first performed and showed the inadequate result, a follow-up ultrasound may be indicated, and if that further shows a thin endometrium and bleeding have stopped, then no further evaluation is required. A thickened endometrial echo may be due to intracavitary lesions such as endometrial polyps and not malignancy or hyperplasia [10].

If the ultrasound shows such lesions along with the history indicating such lesions polyps, then additional imaging may be recommended to identify such intracavitary lesions. In such cases, the use of Saline-infusion ultrasonography or hysterosalpingogram may be useful. A blind sample may miss the focal lesions or intrauterine pathology, and mass lesions may deflect flexible endometrial devices. An additional evaluation of hysteroscopy with dilation and curettage or directed biopsy is considered in patients with insufficient sampling or persistent vaginal bleeding (in those where focal lesions may have been missed) [11].

Management

The etiology dictates the management of post-menopausal bleeding as follow [11-14]:

1. **Atrophy:** In the case of atrophy, the bleeding is usually self-limited and requires no treatment. Lubricants may be used for vulvar and vaginal atrophy during intercourse; oral hormonal receptor modulator (ospemifene) and topical hormones (estrogen, DHEA) are also helpful.

2. **Polyp:** The bleeding may be resolved after the removal of the polyp. Endometrial polyps are benign in nature, but in 5% of cases, they can contain hyperplasia or malignancy. Therefore, it is wise to go for complete hysteroscopic removal. Removal is highly recommended in patients with symptoms or who are at risk of malignancy, such as those who exhibit larger polyps, obesity, diabetes, and use of tamoxifen)

3. **Submucous leiomyoma:** Submucous Leiomyoma are fibroids that can be removed hysteroscopically or laparoscopically, or they can be ablated with various devices. Some of these lesions are amenable to embolization of the uterine artery. If the minimally-invasive techniques fail and definitive management should be made with hysterectomy.

4. **Cervicitis:** Cervical infections are common, and the prescribed antibiotics are recommended, as indicated by the organism. In endometritis, doxycycline can be considered as a drug of choice since it may have anti-inflammatory effects too.

5. **Cervical cancer:** Cervical cancer is one of the common malignancies among women, and treatment is based on the stage of cancer which may vary from surgery to radiation therapy.

6. **Endometrial hyperplasia or malignancy:** This condition can be managed either medically or surgically, depending on the severity of hyperplasia. According to the WHO scheme, it can be classified on the basis of nuclear atypia and glandular complexity and endometrial intraepithelial neoplasia (EIN), which is the preferred scheme (either benign, premalignant, or malignant). Benign Endometrial Hyperplasia is kept on observation since it may resolve, and Endometrial Intraepithelial Neoplasia may require a hysterectomy (total abdominal, vaginal, and minimally invasive total). In such cases, supracervical hysterectomy, endometrial ablation, and morcellation should never be performed. Medical management such as the use of Medroxyprogesterone acetate Depot medroxyprogesterone acetate Megestrol acetate Micronized vaginal progesterone Levonorgestrel intrauterine device is recommended for patients who decline surgery or desire fertility [11].

7. **Endometrial adenocarcinoma:** Hysterectomy is recommended option for adenocarcinoma with comprehensive staging, which consists of a total hysterectomy, pelvic and para-aortic lymphadenectomy, bilateral salpingo-oophorectomy, and collecting pelvic

washings for cytology. Staging is an important to factor since it is helpful in determining the extent of disease and survival rate and also allows for appropriate diagnosis, prognosis, and any adjuvant therapy appropriately. Mostly the definitive management is recommended since an accurate prognosis cannot be determined without full staging. Some patients choose the fertility-sparing treatment that includes medical management. This conservative medical management is indicated when there is a strong desire for fertility-sparing, the patient understands and accepts the complication and outcomes, whether pregnancy-related or cancer-related, presence of Well-differentiated endometrioid endometrial carcinoma (grade 1) with no extrauterine involvement and myometrial invasion and no contraindications to medical management [15].

FIGO staging for endometrial cancer and prognosis are as follow [16].

FIGO Stage	Extent of disease	5 year survival
Stage I	IA: tumor limited to the endometrium IB: invasion to less than half of the myometrium IC: invasion to greater than half the myometrium	85%
Stage II	IIA: endocervical gland involvement only IIB: cervical stromal invasion	70%
Stage III	IIIA: tumor invades serosa of the uterus and/or adnexae, and/or positive peritoneal cytology IIIB: vaginal metastases IIIC: metastases to pelvic and/or para-aortic lymph nodes	40 - 60%
Stage IV	IVA: tumor invades bladder and/or bowel mucosa IVB: distant metastases including intra-abdominal spread or inguinal lymph nodes	10 - 20%

Urethral caruncle: Topical estrogen is used for the treatment of the caruncle, and its removal may be indicated. Acute cystitis is treated with antibiotics. The specialist referral should be done to rule out the origin of bleeding from renal etiologies or bladder masses/ malignancy [11].

Medications: If phytoestrogens cause stimulation of the endometrial lining, they should be stopped, and further endometrial evaluation should be made. For those who are under post-menopausal hormone replacement, the regimen is adjusted. Since post-menopausal hormone therapy may lead to uterine abnormalities, they should be treated as indicated. The progestins may control bleeding if the causative factor is anticoagulants therapy until the completion of course [11].

The following algorithm is followed for post-menopausal bleeding [8].

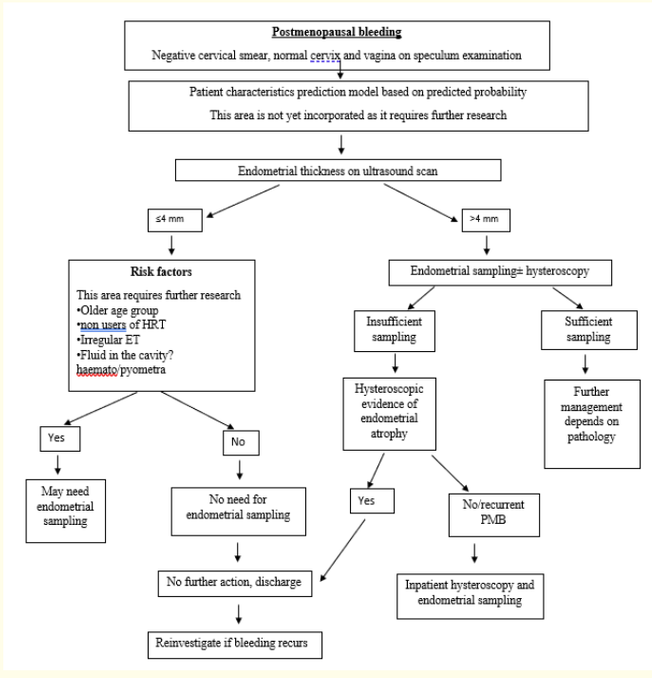

Figure 3

Conclusion

There are various etiologies associated with post-menopausal bleeding, and each exhibits its unique modern management. There are well-developed and evidence-based strategies on how best to investigate women with post-menopausal bleeding. The physician should seek the best outcome according to diagnosis, malignancy, staging, treatment option, and patient compliance.

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