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Review Article

Strategies for managing postmenopausal bleeding: a clinician's perspective

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ABSTRACT

Postmenopausal bleeding (PMB) poses a diagnostic challenge due to the varied presentation of endometrial pathologies ranging from benign endometrial atrophy to the possibility of endometrial carcinoma. Although the incidence varies with patient characteristics, it warrants thorough evaluation. Risk factors such as obesity and hormone use should guide assessment. Bleeding may originate from various gynecological and non-gynecological sites, demanding meticulous history-taking and examination. Transvaginal sonography (TVS) is typically the initial step, yet its accuracy in excluding carcinoma remains debated. Invasive procedures like hysteroscopy and endometrial sampling offer higher accuracy but are more intrusive. The optimal diagnostic strategy remains uncertain, necessitating focused research for enhanced accuracy. TVS-guided assessment with an endometrial thickness (ET) threshold of >4 mm prompts evaluation and endometrial sampling. Progestogen therapy mitigates endometrial cancer risk associated with estrogen use, with atypia-hyperplasia necessitating vigilant monitoring and possible hysterectomy. Patient counselling on treatment options is crucial. In summary, PMB warrants a systematic approach integrating imaging, histological assessment, and tailored therapy guided by risk factors, final diagnosis and patient preferences.

Keywords: PMB, Endometrial cancer, Endometrial hyperplasia, ET

INTRODUCTION

The total absence of menstrual cycles characterises menopause. When a woman has no more ovarian follicles in reserve, she enters menopause, which is officially identified when she has had amenorrhoea for a year. In India, the average age of menopause is 46.2 years, compared to 51 years in Western countries, according to a survey conducted by the Indian menopausal society.[1] About two-thirds of all gynecologic office visits in postmenopausal women are related to bleeding, which is referred to as " PMB " and is deemed abnormal. Several conditions are included in the differential diagnosis of PMB.

Even though atrophy of the lower reproductive tract is the most common cause of PMB, vaginal bleeding was detected in 90% of postmenopausal women diagnosed with endometrial cancer. Between 4 and 11 percent of postmenopausal patients experience PMB, which contributes to about 5 percent of office gynaecology visits.[2-6] The chance of bleeding appears to decrease with time, and the occurrence appears to be inversely correlated with the amount of time since menopause. As with most cancers, early detection and treatment result in a much better prognosis.

Therefore, thorough clinical examination and diagnostic investigations, such as endometrial biopsy and imaging,

should be conducted as soon as possible and thoroughly for any postmenopausal woman with vaginal bleeding.

EPIDEMIOLOGY

Up to 10% of postmenopausal women report having vaginal bleeding, which is the presenting symptom for around two-thirds of these women's gynecologic office visits.[3,7] Age may, however, cause a decline in PMB incidence. About 40% of women report bleeding annually at the start of menopause, but three years later, PMB drops to 4% annually.[2]

According to data from 2020, endometrial cancer is the second most common and fourth globally among gynaecological cancers in terms of cause of mortality. The global incidence reported for 2020 was 417,367, representing 2.2% of newly diagnosed cancer cases that year, ranking it as the sixth most frequent disease worldwide. Endometrial cancer accounted for approximately 97,370 deaths in 2020 or 1% of all cancer-related deaths. Age-standardized incidence is 8.7, and mortality is 1.8/1 lakh population. Endometrial cancer incidence is higher in developed nations.[8] In India, however, endometrial cancer incidence is relatively low compared to developed nations, with a reported incidence of 16,413 cases in 2020, mortality of 6385 cases, and a cumulative risk of diagnosis of 0.75.[9]

PMB is a presenting symptom in more than 90% of postmenopausal women with endometrial cancer.[6] Less than 1% of PMB in women under 50 is related to endometrial cancer. However, in women over 80, the incidence of PMB related to endometrial cancer rises to 24%.[10] The rising prevalence of endometrial cancer risk factors, including obesity and late menopause, is the main cause of the rising incidence of endometrial cancer worldwide. It is projected that by 2030, there will be twice as many endometrial cancer diagnoses.[11]

ETIOLOGY

Women wrongly link bleeding to menstrual bleeding even when they haven't had a period in over a year, leading to the common assumption that PMB is related to the uterus. Nevertheless, the urethra, vulva, vagina, cervix, or rectum could potentially be the source of the bleeding. Genitourinary atrophy is the most common cause of PMB, accounting for 60% of cases.[12] PMB can also have non-gynecologic causes (such as the urethra, bladder, or GI tract) that are misdiagnosed as vaginal bleeding.[13] Postmenopausal haemorrhage frequently has the following underlying reasons:[5,6,13,14] Vaginal or endometrial atrophy; urogenital infections (such as endometrial tuberculosis, vaginitis, cystitis, or cervicitis); endometrial polyps; uterine leiomyomas; genital tract cancers; vaginal foreign bodies; genitourinary atrophy; endometrial hyperplasia with or without atypia and medications (such as oestrogen, tamoxifen, and anticoagulants).

PATHOPHYSIOLOGY

Atrophic endometrium is the most frequent cause of postmenopausal haemorrhage. Genitourinary atrophy is caused by the hypoestrogenic environment that follows menopause. The uterine cavity is deflated and the atrophic endometrial lining has little to no fluid to reduce friction, which results in epithelial microerosions and chronic inflammation. Light bleeding or vaginal spotting may be symptoms of chronic endometritis caused by atrophy. Pelvic ultrasound in these patients usually shows small ovaries, a small uterus, and a thin endometrial stripe that seems normal overall.[15]

Premalignant or malignant endometrial diseases frequently arise from unopposed oestrogen exposure. Abnormal alterations in the endometrium can be caused by obesity, systemic estrogen-only therapy, and tumours that secrete oestrogen. Certain women are genetically predisposed to endometrial cancer, such as those with Cowden disease and Lynch syndrome. Few studies have shown that those who carry BRCA gene mutations, particularly those who have a BRCA1 mutation, may be somewhat more likely to the develop endometrial cancer.[16]

HISTORY AND PHYSICAL EXAMINATION

To determine the patient's menopausal status and evaluate both underlying etiologies, a thorough history is crucial when examining PMB. A crucial part of PMB examination is ruling out malignant etiology, mainly endometrial cancer.[11] A complete history should be obtained by clinicians, incorporating the following common components:

HISTORY OF PRESENT ILLNESS

Clinicians should get a history of the type of bleeding a patient is experiencing at the moment and any accompanying symptoms to assess the differential diagnosis for PMB and clinically confirm the patient's menopausal state. Abnormal bleeding patterns in the uterus, such as heavy monthly flow, may be a sign of cancer, hyperplasia, or structural abnormalities such as leiomyomas or polyps.[17]

The onset, length, heaviness, and triggering events (such as bleeding after sexual activity or wiping) of PMB are crucial in defining the symptoms of vaginal bleeding. Investigating related symptoms such as fever, dysuria, pelvic pain, vasomotor symptoms, dyspareunia, and vaginal dryness is also recommended.[18,19]

Past medical history

Obesity, diabetes, thyroid disorders, coagulopathies, pelvic infections, and polycystic ovarian syndrome are possible causes of irregular bleeding.[20]

Gynecologic history

When determining a person's postmenopausal status, a detailed examination of their menstrual history-including their most recent menstrual period-is essential. Endometrial cancer risk increases with early menarche and late menopause. HPV and PAP test results from the past should be reviewed.[17]

Surgical history

Potential causes of vaginal bleeding and menopausal amenorrhoea can be identified by clinicians based on past surgical treatments. Current pelvic treatments may cause bleeding following surgery, and surgically induced menopause (e.g., oophorectomy, hysterectomy) might help determine a patient's menopausal status.[17]

Social history

Smokers are more likely to develop bladder cancer, experience mesh erosion, and experience hematuria, which can result in bleeding.

Family history

Inherited mutations (such as Lynch or Cowden syndrome) that can predispose people to endometrial cancer should also be evaluated, as should a family history of breast, gynecologic, urologic, or gastrointestinal cancers.

Medication

Additionally, clinicians should ask patients about their medication history because certain herbal supplements, anticoagulants, tamoxifen, hormone replacement therapy, and other medications can alter the uterine lining and cause PMB.[21-23]

PHYSICAL EXAMINATION

The genital tract's internal and external anatomy must be carefully assessed during a physical examination. Bleeding sites, genital lesions, lacerations, urethral prolapse, and symptoms of genitourinary atrophy-which usually include pale, dry vaginal epithelium with loss of rugae-should all be seen using a speculum exam. It is possible to identify inflammation by erythema, petechiae, friability, and discharge. Additionally, by performing a bimanual exam, doctors can palpate for enlarged lymph nodes, pelvic masses, and abdominal distention.[11]

EVALUATION

When evaluating low-risk women who present with PMB, the American college of obstetricians and gynaecologists (ACOG) advises either transvaginal ultrasound or endometrial biopsy as the first step; doing both tests at the same time is not necessary. On the other hand, in those with recurrent PMB or endometrial cancer risk factors, endometrial biopsy is advised as the initial test.[6] To evaluate for problems resulting from significant vaginal bleeding and to help rule out alternative diagnoses, laboratory testing may be taken into consideration (Figure 1).[24]

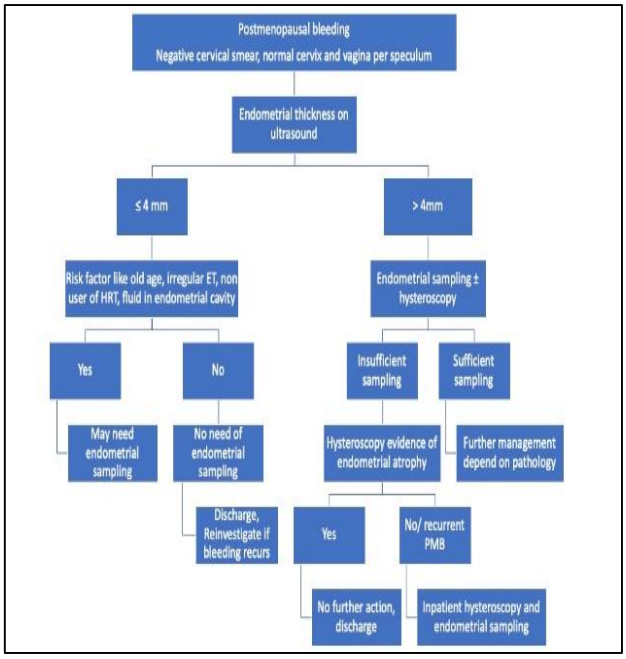

Figure 1: Approach to management of patients with PMB.

ENDOMETRIAL BIOPSY

Since an endometrial sample offers tissue for histologic diagnosis, which is essential for finding malignancies, it is the first-line diagnostic for evaluating PMB in any patient.

Persistent or recurrent bleeding PMB despite a thin endometrial stripe on ultrasonography. Transvaginal ultrasound measurements of the endometrial lining thickness in a PMB woman that are greater than 4 mm. Insufficient endometrial visualisation in imaging investigations. Risk factors (such as obesity, smoking, and exposure to unopposed oestrogen) for endometrial cancer.

Endometrial sampling is also advised by ACOG for women over 45 who experience abnormal uterine bleeding.[20] The two main techniques used for endometrial sampling are outpatient disposable thin plastic devices that are placed into the endometrial cavity through the endocervical incision without the need for anaesthesia and dilatation and curettage (D and C).[25,26] Since the diagnostic sensitivity for endometrial cancer is around 90%, clinicians have been doing D and Cs with or without hysteroscopy for years to analyse the histology of cancer.[27,28] Studies have shown that the diagnostic

accuracy of office endometrial biopsies performed using flexible plastic samplers is comparable.

Follow-up ultrasonography may be done for inadequate sampling that was done initially; if this results in a thin endometrial stripe on a later transvaginal ultrasound and vaginal bleeding does not continue, additional testing is not required.[6]

IMAGING STUDIES

When a patient has no indications for a histologic evaluation, transvaginal imaging to determine ET can potentially be employed as a first-line method to examine PMB. The thickest part of the endometrial stripe visible in a long-axis uterine image should be measured anterior to posterior, according to the method ACOG advises.[6] A negative predictive value of >99% is associated with endometrial cancer in cases when the endometrial stripe thickness is ≤4 mm.[29] When endometrial stripe thickness is <4 mm, there is about a 0.3% chance of endometrial cancer. Studies have shown that just 1 in 339 endometrial tumours are missed when using this 4 mm threshold.[6]

Other pathologic pelvic aetiologies (such as leiomyomas or adnexal masses) may also be detected by ultrasound imaging. If the endometrial stripe is not visible, further testing involving endometrial sampling is necessary. Clinicians should do an endometrial biopsy for persistent or recurrent PMB, even for patients with an endometrial lining <4 mm, as endometrial imaging is not diagnostic and ET does not necessarily rule out cancer.[6] Mass lesions have the potential to deflect flexible disposable devices, and blind endometrial sampling without hysteroscopy may miss isolated lesions or intrauterine pathology, such as polyps.

Therefore, patients with insufficient sampling or recurrent vaginal bleeding, in whom focused lesions may have gone unnoticed, should have further imaging examination considered; directed biopsy or hysteroscopy with dilatation and curettage may be necessary.[6]

It is occasionally possible to better characterise urogenital disease seen on ultrasound by using pelvic CT and MRI.[5] The gold standard, however, is hysteroscopy with dilatation and curettage since it allows for the simultaneous performance of therapeutic excision for certain PMB etiologies (such as endometrial polyps) and diagnostic samples.

HYSTEROSCOPY WITH ENDOMETRIAL SAMPLING

Hysteroscopy is still the gold standard technique for examining the endometrial cavity since it allows for the simultaneous treatment of anomalies such as polyps, the visualisation of macroscopically focused abnormalities, and directed biopsies. Outpatient hysteroscopy seems to be as accurate and well-received by patients.[30]

Hysteroscopy indications include: Insufficient tissue retrieved with an office-based device, failed endometrial biopsy, suspected polyp on imaging or biopsy material and recurrent PMB after a negative first assessment

Hysteroscopy should wait to be scheduled until after the office-based biopsy histology results are available, as the outcome may eliminate the need for further investigation. It is best to schedule hysteroscopy under general anaesthesia if outpatient hysteroscopy is unsatisfactory or ineffective. Biopsies should be performed in conjunction with hysteroscopic endometrial examination.

Hysteroscopy, which has an overall sensitivity and specificity of 86.4% and 99.2%, respectively, is a very accurate method of diagnosing endometrial cancer when the uterine cavity is sufficiently visualised.[31]

Laboratory studies

When evaluating patients with PMB, coagulation assays (such as prothrombin time and partial thromboplastin time) should be performed to rule out certain differential diagnoses and check for secondary anaemia caused by irregular bleeding.[24] It is recommended to perform pregnancy tests and vaginal cultures to detect sexually transmitted illnesses.

HISTOPATHOLOGY

Postmenopausal endometrial histological findings

Microscopic analysis reveals numerous consequences of the hypoestrogenic environment on the postmenopausal endometrium. A normal premenopausal proliferative endometrium has around a 1:1 gland-to-stroma ratio and evenly spaced, organised glands surrounded by simple epithelial cells in the stroma. The postmenopausal endometrium's normal histologic results exhibit widely dispersed glands that range in size from tiny to cystically dilated. The histologic findings of pathologic endometrial abnormalities differ based on the underlying aetiology.

While smooth muscle fibres are a defining feature of uterine fibroids, the histology of endometrial polyps frequently demonstrates cellular immaturity with cystic hyperplasia. In postmenopausal women, these diseases have an increased risk of the malignant transformation.[32,33]

Endometrial hyperplasia

A disorganised proliferation of glands, an elevated gland-to-stroma ratio, and extensive crowding of endometrial glands are characteristic histologic findings of endometrial hyperplasia. Endometrial intraepithelial neoplasia (EIN) is premalignant disease that is characterised by aberrant gland nuclei and gland crowding.[5]

Endometrial cancer

Endometrial cancer is one of the most concerning causes of PMB; it is usually categorised as type I or II according to its histologic appearance, grade, and hormone receptors.[34]

Endometrial cancer type 1

The majority of uterine malignancies, around 90%, are classified as grade I or II endometrioid adenocarcinomas, which affect the endometrial glands. This is the most prevalent histologic form of endometrial carcinomas. From a histological perspective, solid patches, glands resembling mazes, or significant cribriforming are seen. The majority of endometrioid adenocarcinomas are limited to the uterus and are of low grade.[35]

Endometrial cancer type 2

These are sarcoma, carcinosarcoma, clear cell carcinoma, and papillary serous histologies; they are rare, high-grade, poorly differentiated, and more aggressive uterine cancers. Compared to type I tumours, type 2 endometrial cancers (Table 1) had a poorer prognosis and a higher of extrauterine disease at diagnosis.[35]

Table 1: Comparison of type 1 and type 2 endometrial carcinoma.

Characteristic features	Type 1 endometrial cancer	Type 2 endometrial cancer
Unopposed estrogen	Present	Absent
Menopausal status	Perimenopausal	Postmenopausal
Tumor grade	Low	High
Myometrial invasion	Minimal	Deep
Histopathological type	Endometroid type	Serous and clear cell type
Behaviour	Indolent	Aggressive
Genetic factors	PTEN, KRAS mutation	P53 mutation

TREATMENT

The underlying etiology generally guides treatment for PMB. When deciding on management, additional clinical variables are taken into account, such as patient preferences and comorbidities and the PMB characteristics.[36]

Genitourinary atrophy

Usually, bleeding stops on its own and doesn't need to be treated. Nonhormonal vaginal lubricants and moisturisers can be used to relieve vaginal dryness and preserve sexual activity. The recommended pharmacologic treatment for genitourinary atrophy is topical oestrogen, which can effectively correct the symptoms of vaginal and vulvar atrophy. If other treatments fail to produce results, alternative options such as hormonal replacement therapy and hormonal receptor modulators (such as ospemifene) may be explored.[18]

Endometrial polyp

Malignant endometrial polyps make up 1% of all cases and are most frequently found in postmenopausal women.[32] Endometrial polyps account for thirty percent of PMB patients; nevertheless, polyps may not cause any symptoms at all. Moreover, neither the quantity nor the size of polyps influences the severity of PMB. When a woman has no symptoms but is at a higher risk of the developing cancer, she should consider surgical excision (i.e., large polyps, tamoxifen use, obesity, or the diabetes mellitus). Since the physician may perform simultaneous guided biopsies as well as the polyp excision, hysteroscopic polypectomy is the recommended course of the action.[32]

Uterine leiomyoma

Leiomyomas, also known as fibroids, are usually benign, regress throughout menopause, and if patient is asymptomatic, treatment may not be necessary. Malignant fibroids are rare and mostly affect postmenopausal women. Sometimes peripheral conversion of adipose reserves to oestrogen can cause benign leiomyomas to proliferate/even cause symptoms in post-menopausal individuals, specially in obese women.[37]

If uterine fibroids are discovered in women with PMB and their assessment is otherwise normal, medication therapy (such as aromatase inhibitors and selective oestrogen receptor modulators) or surgical therapy (such as myomectomy and hysterectomy) may be explored.

Though symptomatic postmenopausal women are more susceptible to leiomyosarcomas, which cannot be conclusively ruled out with laboratory or imaging testing, doctors should thoroughly advise patients and decide care through shared decision-making.[37,38]

Genitourinary infection

The results of vaginal cultures are used to guide treatment for genital infections and STDs.[20,39] Clinicians may treat endometritis patients with oral doxycycline.

Cervical, vaginal, and vulvar carcinomas

Depending on the stage, surgery and chemotherapy-radiotherapy are the most common treatment methods for these PMB etiologies.[40,41]

Endometrial hyperplasia or malignancy

There are two types of endometrial hyperplasia: EIN (Atypical hyperplasia) and endometrial hyperplasia without atypia. Both surgical and nonsurgical therapies are used to manage hyperplasia; the choice of treatment depends on several clinical criteria.

Endometrial intraepithelial neoplasia

Patient preferences are one of the many clinical criteria that determine the therapy plan. The ideal course of treatment for postmenopausal women is minimally invasive hysterectomy combined with bilateral salpingectomy, as fertility conservation is typically not desired in this population.

Patients who are not good candidates for surgery or who are refusing surgery have the option of receiving medical management. Patients should be advised that many women with endometrial cancer also have EIN. If medical treatment is selected, repeat endometrial sampling should be performed every three to six months for a minimum of one year to evaluate therapeutic response. Among the nonsurgical treatments are:[5] Levonorgestrel 52 mg intrauterine device; micronized vaginal progesterone 100 to 200 mg daily; medroxyprogesterone acetate oral 10 to 20 mg daily, megestrol 80 mg twice a day; depot medroxyprogesterone acetate 150 mg intramuscularly every three months; and levonorgestrel 52 mg intrauterine device;

Endometrial adenocarcinoma

The standard of therapy is definitive treatment with a hysterectomy and thorough staging. Staging determines prognosis and suitable adjuvant therapy.[5]

Hematuria

Asymptomatic Microscopic hematuria might result from genitourinary atrophy. In asymptomatic low-risk women, ACOG only advises examination if urine microscopy reveals more than 25 red blood cells per high-power field. The right antibiotics should be used to treat acute cystitis based on clinical observations and diagnostic investigations that support this diagnosis.[42]

Gastrointestinal bleeding

Haemorrhoids and diverticulitis, two gastrointestinal etiologies that might be confused for vaginal bleeding, are among the differential diagnosis for PMB. Antibiotics, anti-inflammatory drugs, or surgery may be used as a form of management. Referral to a gastrointestinal specialist for further assessment and treatment may be necessary if bleeding is severe or recurrent.[43]

Medication

For the first two to three months following commencement, postmenopausal hormone replacement therapy often results in PMB, which most women resolve on their own. After the initial few months of treatment, physicians should assess women with persistent or recurrent PMB for endometrial pathology. Progestin therapy may reduce vaginal bleeding caused by anticoagulants until the anticoagulants can be stopped. Patients receiving lifelong anticoagulation may require a discussion on longer-term solutions.[4]

DIFFERENTIAL DIAGNOSIS

When assessing patients with PMB, clinicians need to take into account the multiple differential diagnoses that can present similarly to PMB and originate from either gynecologic or nongynecologic regions (such as the urethra, bladder, or GI tract). When assessing PMB, common conditions like these should also be taken into account:[5,6] Urogenital infections, such as cervicitis, endometritis, vaginitis, or cystitis, intestinal leiomyomas, cancers of the reproductive tract, foreign bodies vaginally, radiation effects on nearby organs (e.g., hemorrhagic cystitis, proctitis, necrosis), conditions relating to the digestive tract (e.g., diverticulitis, colitis, haemorrhoids, cancer).

PROGNOSIS

Since the most prevalent etiologies are benign and curable, PMB has a good prognosis. Furthermore, with a 90% 5-year survival rate, endometrial cancer-the most prevalent malignant PMB etiology-has a far better prognosis than other cancers. Approximately 43% of individuals with endometrial hyperplasia who had hysterectomy also had undetected endometrial cancer.[5]

COMPLICATIONS

About 10% of postmenopausal women experience secondary anaemia, the main consequence of PMB. Additional difficulties that could arise are usually linked to the primary cause. For example, uterine fibroids may induce pelvic discomfort, and genitourinary atrophy can lower quality of life by reducing sexual intimacy and self-esteem.[37] Treatment for PMB etiologies, such as megestrol-based pharmacologic therapy for endometrial hyperplasia, may potentially have side effects, such as nausea, weight gain, venous thrombosis, and persistent vaginal bleeding.[5]

CONCLUSION

Ultrasound measurement of ET is valuable for assessing postmenopausal women with bleeding. Endometrial biopsy is warranted for symptomatic women with thickened endometrium or persistent bleeding. Incidental findings in asymptomatic women, like polyps, may not

necessitate removal unless factors warrant consideration. Management of incidental increased ET should be individualized based on risk factors and clinical findings. Routine screening of asymptomatic postmenopausal women for endometrial cancer lacks evidence of efficacy or cost-effectiveness and is not recommended.

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REFERENCES

1. Ahuja M. Age of menopause and determinants of menopause age: A PAN India survey by IMS. J Midlife Health. 2016;7(3):126-31.
2. Carugno J. Clinical management of vaginal bleeding in postmenopausal women. Climacteric. 2020;23(4):343-9.
3. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of Endometrial Cancer Risk with Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018;178(9):1210-22.
4. Santoro N, Roeca C, Peters BA, Neal-Perry G. The Menopause Transition: Signs, Symptoms, and Management Options. J Clin Endocrinol Metab. 2021;106(1):1-15.
5. Ring KL, Mills AM, Modesitt SC. Endometrial Hyperplasia. Obstet Gynecol. 2022;140(6):1061-75.
6. ACOG Committee Opinion No. 734: The Role of Transvaginal Ultrasonography in Evaluating the Endometrium of Women with Postmenopausal Bleeding. Obstet Gynecol. 2018;131(5):e124-9.
7. Jo HC, Baek JC, Park JE, Park JK, Cho IA, Choi WJ, et al. Clinicopathologic Characteristics and Causes of Postmenopausal Bleeding in Older Patients. Ann Geriatr Med Res. 2018;22(4):18993.
8. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
9. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women: Burden and trends. Cancer Epidemiol Biomarkers Prev. 2017;26:444-57.
10. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022;399(10333):1412-28.
11. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, Oaknin A. Endometrial cancer. Nat Rev Dis Primers. 2021;7(1):88.
12. Smith PP, O'Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: a prospective cohort study. J Minim Invasive Gynecol. 2014;21(5):799-803.
13. Swain M, Kulkarni AD. Endometrium at Menopause: The Pathologist's View. J Midlife Health. 2021;12(4):310-5.
14. Carugno J. Clinical management of vaginal bleeding in postmenopausal women. Climacteric. 2020;23(4):343-9.
15. Ferenczy A. Pathophysiology of endometrial bleeding. Maturitas. 2003;45(1):1-14.
16. Matanes E, Volodarsky-Perel A, Eisenberg N, Rottenstreich M, Yasmeen A, Mitric C, et al. Endometrial Cancer in Germline BRCA Mutation Carriers: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2021;28(5):947-56.
17. Klein DA, Paradise SL, Reeder RM. Amenorrhea: A Systematic Approach to Diagnosis and Management. Am Fam Physician. 2019;100(1):39-48.
18. Nappi RE, Martini E, Cucinella L, Martella S, Tiranini L, Inzoli A, et al. Addressing Vulvovaginal Atrophy (VVA)/Genitourinary Syndrome of Menopause (GSM) for Healthy Aging in Women. Front Endocrinol (Lausanne). 2019;10:561.
19. Gibson CJ, Huang AJ, McCaw B, Subak LL, Thom DH, Van Den Eeden SK. Associations of Intimate Partner Violence, Sexual Assault, and posttraumatic stress disorder with Menopause Symptoms Among Midlife and Older Women. JAMA Intern Med. 2019;179(1):80-7.
20. Committee on Practice Bulletins-Gynecology. Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. Obstet Gynecol. 2012;120(1):197-206.
21. Van Hunsel FP, Kampschöer P. Postmenopausal bleeding and dietary supplements: a possible causal relationship with hop- and soy-containing preparations. Ned Tijdschr Geneeskd. 2012;156(41):A5095.
22. Chandrareddy A, Muneyyirci-Delale O, McFarlane SI, Murad OM. Adverse effects of phytoestrogens on reproductive health: a report of three cases. Complement Ther Clin Pract. 2008;14(2):132-5.
23. Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril. 2004;82(1):145-8.
24. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and Management of Endometrial Cancer. Am Fam Physician. 2016;93(6):468-74.
25. Sorosky JI. Endometrial cancer. Obstet Gynecol. 2012;120(2 Pt 1):383-97.
26. Terzic MM, Aimagambetova G, Terzic S, Norton M, Bapayeva G, Garzon S. Current role of Pipelle endometrial sampling in early diagnosis of endometrial cancer. Transl Cancer Res. 2020;9(12):7716-24.
27. Kaan M. Arguments and counter-arguments about the orthodontic treatment of missing incisors. Literature review. Fogorv Sz. 2010;103(3):83-8.
28. Sany O, Singh K, Jha S. Correlation between preoperative endometrial sampling and final

endometrial cancer histology. Eur J Gynaecol Oncol. 2012;33(2):142-4.
29. Manchanda R, Thapa S. An overview of the main intrauterine pathologies in the postmenopausal period. Climacteric. 2020;23(4):384-7.
30. Kremer C, Duffy S, Moroney M. Patient satisfaction with outpatient hysteroscopy versus day case hysteroscopy: randomised controlled trial. BMJ. 2000;320(7230):279-82.
31. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of Hysteroscopy in the Diagnosis of Endometrial Cancer and Hyperplasia. JAMA. 2002;288(13):1610.
32. Nijkang NP, Anderson L, Markham R, Manconi F. Endometrial polyps: Pathogenesis, sequelae and treatment. SAGE Open Med. 2019;7:2050312119848247.
33. Wen KC, Horng HC, Wang PH, Chen YJ, Yen MS, Ng HT, et al. Uterine sarcoma Part I-Uterine leiomyosarcoma: The Topic Advisory Group systematic review. Taiwan J Obstet Gynecol. 2016;55(4):463-71.
34. Parkash V, Fadare O, Tornos C, McCluggage WG. Committee Opinion No. 631: Endometrial Intraepithelial Neoplasia. Obstet Gynecol. 2015;126(4):897.
35. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin. 2019;69(4):258-79.
36. Wouk N, Helton M. Abnormal Uterine Bleeding in Premenopausal Women. Am Fam Physician. 2019;99(7):435-43.
37. Ulin M, Ali M, Chaudhry ZT, Al-Hendy A, Yang Q. Uterine fibroids in menopause and perimenopause. Menopause. 2020;27(2):238-42.
38. Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine Sarcoma: Analysis of 13,089 Cases Based on Surveillance, Epidemiology, and End Results Database. Int J Gynecol Cancer. 2016;26(6):1098-104.
39. Di Caprio R, Lembo S, Di Costanzo L, Balato A, Monfrecola G. Anti-inflammatory properties of low and high doxycycline doses: an *in vitro* study. Mediators Inflamm. 2015;2015:329418.
40. Jhingran A. Updates in the treatment of vaginal cancer. Int J Gynecol Cancer. 2022;32(3):344-51.
41. Small W, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: A global health crisis. Cancer. 2017;123(13):2404-12.
42. Committee Opinion No.703: Asymptomatic Microscopic Hematuria in Women. Obstet Gynecol. 2017;129(6):e168-72.
43. Dichman ML, Rosenstock SJ, Shabanzadeh DM. Antibiotics for uncomplicated diverticulitis. Cochrane Database Syst Rev. 2022;6(6):CD009092.

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