Pathology of postmenopausal bleeding

Definition:

Postmenopausal state is considered established after one year of amenorrhea. Any vaginal bleeding following one year amenorrhea or more from the date of last menstrual period is called postmenopausal bleeding ***(Newell and Overton, 2012)***.

Any woman who is still menstruating after 55 years should be viewed with suspicion and postmenopausal blood stained discharge has equal significance to that of postmenopausal bleeding ***(McGregor, 2001).***

Postmenopausal bleeding must be considered as a symptom and not a diagnosis ***(Schuiling and Elikis, 2013)***. Postmenopausal bleeding should be considered cancer until proven otherwise, despite the fact that abnormal pathology is found in only 15% of endometrial biopsies ***(McGregor, 2001).***

For this reason any amount of bleeding from the genital tract should be etiologically, anatomically and pathologically explained so that the exact diagnosis can be reached in any case of postmenopausal bleeding ***(Bronz et al., 2000).***

Causes of postmenopausal bleeding include endometrial atrophy (approximately 75% of cases), endometrial polyps, submucosal fibroids, endometrial hyperplasia, endometrial carcinoma (approximately 10%), and estrogen withdrawal ***(Nalaboff et al., 2001).***

Imaging should take place immediately after bleeding has stopped, when the endometrium is presumed to be thinnest and any disease entity will be most prominent.

Endometrial thickness less than 4–5 mm at transvaginal US generally excludes cancer ***(Nalaboff et al., 2001).***

Etiology:

There are a variety of causes for postmenopausal bleeding the most important of them is the indiscriminate use of estrogens.

However, the most significant is malignant diseases. The likelihood of malignancy increases with the length of the duration from the menopause ***(Pratap Kumar, 2008).***

Among all women with postmenopausal bleeding uterine malignancy is the cause in 15-25% according to most studies.

The likelihood of a patient with postmenopausal bleeding having a malignancy increases with age, approximately 15% at 50-59 increasing to 35% at 60-69 and 42% at 70-79 years.

According to ***Pratap Kumar, (2008)*** the possible causes of postmenopausal bleeding may be listed as under the following headings:

A) Genital causes:

I- Estrogen evoked postmenopausal bleeding:

Both of endogenous or exogenous estrogen.

II- Uterine causes:

1- **Malignant:** carcinoma and sarcoma.

2- **Benign:** endometrial hyperplasia, endometrial polyp, and endometritis of specific causes as tuberculous endometritis, atrophic endometrium and rarely uterine myoma.

Uterine prolapse may cause postmenopausal bleeding by one of two mechanisms:

- Atrophic ulcers in a case of complete procidentia.
- Postmenopausal atrophic change of the vagina.

III- Cervical causes: including carcinoma, endocervical polyps and atrophic cervicitis.

IV- Vaginal causes: Atrophic vaginitis and rarely primary vaginal cancer.

V- Vulval causes: rare causes. They include vulvitis, vulval cancer, urethral carbuncle and urethral carcinoma. Due to atrophic changes of the vulval skin and especially in presence of diabetes. Vulvitis can occur in postmenopausal woman causing itching, ulceration and bleeding

VI- Ovarian and tubal causes: ovarian tumours and tubal cancer may cause postmenopausal bleeding ***(Pratap Kumar, 2008).***

Ovarian tumours which may be associated with postmenopausal bleeding are:

- **Non functioning ovarian tumours**
- **Feminizing ovarian tumours which may be:**

- Benign as theca cell tumour or ovarian tumours with functioning stroma as Brenner's tumour and adenofibroma.
- Malignant as granulosa cell tumour

The mechanisms by which these tumours cause bleeding may be:

Non functioning ovarian tumours:

- Metastasis in the endometrium.
- Metastasis in Douglas pouch which ulcerate in the vaginal mucosa.

Feminizing ovarian tumours:

- Presence of estrogen causes endometrial hyperplasia.
- In advanced cases, hyperplasia leads to endometrial carcinoma

B) Extra-genital causes:

1. **Systemic causes:** Thyroid, hepatic, or renal disease: as thrombophilic disorder requiring anticoagulation ***(Dighe, 2009).***
2. **Coagulopathy (acquired or inborn):** Von Willebrand disease, idiopathic thrombocytopenic purpura, thalassemia major, Fanconi anemia, or prothrombin deficiency ***(Dighe, 2009).***
3. **Nutrition and insulin resistance:** Nutrients support the cycle of hormonal balance ***(Dighe, 2009).***

4. **Weight loss**: Post-menopausal bleeding may also occur with a drastic weight loss and reduction in body fat. What's happening here is that estrogen stored in fat tissue becomes liberated into the bloodstream as a woman loses weight. Bleeding may also occur with weight loss as estrone (E1, one of three main types of estrogen naturally occurring in the body), which relies largely on fat as its source, is reduced as weight loss occurs, resulting in a shift in the relationship between **estrogen and progesterone.** This rebalancing of hormones, among other health reasons, is why we say **gradual weight loss** is usually best ***(Dighe, 2009).***

5. **Emotional stress:** Bleeding after menopause can also occur during a particularly stressful or emotional event or due to an unexpected spurt of hormones ***(Dighe, 2009).***

6. **Urinary tract causes:-** Hematuria due to infection or other urinary lesions (Mucosal atrophy, Mucosal prolapse Infection, Calculi, Malignancy)may produce spotting that is confused with that originating in the uterus ***(Dighe, 2009).***

7. **Gastrointestinal tract causes:-** Bleeding from hemorrhoids or anal fissures may be difficult to differentiate from vaginal bleeding ***(Pratap Kumar; 2008).***

Exogenous Estrogens

Women who are taking hormonal replacement therapy during menopause may be using a variety of hormonal regimens that can result in bleeding ***(Paula, 2002).***

Unopposed estrogen treatment of menopause is associated with eight folds increased incidence of endometrial cancer ***(Furness et al., 2012).***

Patient compliance has been a significant issue with hormonal replacement therapy. Missed doses of medication and failure to take medication in the prescribed fashion can lead to irregular bleeding or spotting that is benign in origin but results in patient dissatisfaction ***(Kenemans et al. 2001)***. The primary problems that women report with hormonal replacement therapy include vaginal bleeding and weight gain. The use of a continuous low dose combined regimen has the advantage that, for many women, bleeding will ultimately cease after a period of several months during which irregular and unpredictable bleeding may occur. The risk of endometrial hyperplasia or neoplasia with this regimen appears to be low ***(Shoupe, 2001)***.

I) Endometrial causes:

Endometrial Cancer

Endometrial adenocarcinoma is the most common invasive gynecologic malignancy, but thanks to early detection and treatment, it is not a leading cause of cancer deaths ***(Nalaboff et al., 2001).***

Risk factors:

Endometrial carcinoma most often occurs in 6th and 7th decades of life, at an average of 60 years; 75% of cases occur in women older than 50 years of age. Its risk factors are nulliparity, late menopause, obesity, diabetes mellitus, unopposed estrogen therapy, tamoxifen therapy and atypical endometrial hyperplasia.

In postmenopausal women with vaginal bleeding, the risk of (pre)malignancy of the endometrium is low in women under 50 years of age, increases considerably until 55 years of age, and rises only modestly with further advancing age ***(Opmeer et al., 2007).***

According to the observations of ***(Magyar et al., 2007).*** hormone replacement therapy does not increase the risk of endometrial carcinoma. Combined preparations decrease the frequency of hyperplasia and consequently the chance of occurrence of adenocarcinoma.

Types:

The differences noted in the epidemiology, presentation, and behavior of endometrial carcinoma suggest that there may be two different forms of the disease: an estrogen- related neoplasm that occurs in younger, perimenopausal women and tends to be low grade and a second, more virulent form, unrelated to estrogenic stimulation, that occurs in order postmenopausal women ***(Ryan et al., 2005).***

For purposes of this discussion/the former is designated type I (estrogen related) and the latter type II (non -estrogen - related) **(Table 1)** ***(Ryan et al., 2005).***

Table 1: Endometrial carcinoma: two types

	Estrogen dependent type	***Non-Estrogen dependent type***
• ***Unopposed estrogen***	*Present*	*Absent*
• ***Menopausal status***	*Pre & perimenopausal*	*Postmenopausal*
• ***Hyperplasia***	*Present*	*Absent*
• ***Race***	*White*	*Black*
• ***Grade***	*Low*	*High*
• ***Myometrial invasion***	*Minimal*	*Deep*
• ***Specific subtypes***	*Endometrioid*	*Serous*
• ***Behavior***	*Stable*	*Progressive*

Histopathological Classification: ***(Berek and Novak, 2012)***

- **Endometrioid adenocarcinoma:**
  - Villoglandular or papillary
  - Secretory
  - With squamous differentiation
- **Mucinous carcinoma**
- **Papillary serous carcinoma**
- **Clear cell carcinoma**
- **Squamous carcinoma**
- **Undifferentiated carcinoma**
- **Mixed carcinoma**

Clinically:

About 90% of women with endometrial carcinoma have vaginal bleeding or discharge as their only presenting compliant.

Bleeding may not occur due to cervical stenosis especially in older patients and may be associated with hematometra or pyometra causing purulent vaginal discharge. This is associated with poor prognosis.

Pelvic pressure and discomfort are indicatives of uterine enlargement or extrauterine spread ***(Ryan et al., 2005).***

Most women with endometrial cancer will be diagnosed with early stage disease when the prognosis is excellent as postmenopausal bleeding is an early warning sign that leads women to seek medical advice ***(Brand, 2007).*** 5% of women with endometrial carcinoma are asymptomatic and it is usually detected as a result of investigation of

abnormal laboratory test or evaluation of an abnormal finding on a pelvic U/S or CT scan ***(Marchetti et al., 2005).***

The recurrence rate after a first episode of postmenopausal bleeding managed expectantly is low and cannot be predicted by patient characteristics. Patients with recurrent bleeding should be evaluated, as they bear a considerable risk of carcinoma ***(Van Doorn et al. 2008).***

❖ **Staging of endometrium cancer:** ***(Goldstein, 2009)***

- **Stage I**

  Limited to endometrium =A
  <50% myometrial invasion=B
  >50% myometrial invasion=C

- **Stage II**

  Invasion of the cervix

- **Stage III**

  Pelvic and paraaortic nodes
  Extension inside the pelvis

- **Stage IV**

  Extension outside pelvis.
  A-Rectum/Bladder
  B- Distant metastases

Atrophic (senile) endometritis

The endometrium of the postmenopausal women is normally atrophic due to the low levels of circulating estrogen. So atrophic endometritis is the most common endometrial finding in women with postmenopausal bleeding (accounting for 60% - 80% of such bleeding). Women with endometrial atrophy have usually been menopausal for about 10 years. Microscopically, atrophic endometrium is thin and composed of variably sized glands with compact but reduced stroma ***(Paula, 2002).***

The infected epithelium exudes pus which tends to collect in the uterus to form a pyometra. Sometimes in response to pyometra, the endometrium undergoes squamous metaplasia ***(Todorović et al., 2002).***

On ultrasound, the endometrium is less than 5 mm thick and endometrial biopsy usually yields only scant tissue ***(Tsikouras et al., 2007)***.

Endometrial hyperplasia

Endometrial hyperplasia is an abnormal proliferation of endometrial stroma and glands and represents a spectrum of endometrial changes ranging from glandular atypia to frank neoplasia ***(Nalaboff et al., 2001).***

A definitive diagnosis can be made only with biopsy, and imaging cannot reliably allow differentiation between hyperplasia and carcinoma. Up to one-third of endometrial carcinoma is believed to be preceded by hyperplasia ***(Nalaboff et al., 2001).***

All types of endometrial hyperplasia (cystic, adenomatous, atypical) can cause diffusely smooth or, less commonly, focal hyperechoic endometrial thickening ***(Nalaboff et al., 2001).***

It represents a spectrum of morphologic and biologic alternations of endometrial glands and stroma ranging from an exaggerated physiologic state to carcinoma insitu. It usually evolves with a background of proliferative endometrium as a result of protracted estrogen stimulation in absence of progestin influence ***(Lurain, 2002).***

Complication:

The risk of endometrial hyperplasia progressing to carcinoma is related to presence and severity of cytologic atypia and the premalignant potential of hyperplasia and it is influenced by age, underlying ovarian disease, endocrinopathy, obesity and exogenous hormone exposure ***(Hunter et al. 1994).***

Endometrial polyp

Endometrial polyps are a common cause of postmenopausal bleeding and are most frequently seen in patients receiving tamoxifen.

Although endometrial polyps may be visualized at transvaginal US as nonspecific endometrial thickening, they are frequently identified as focal masses within the endometrial canal ***(Nalaboff et al., 2001).***

Origin: Endometrial polyps are common. They originate as focal hyperplasia of the basalis and develop into benign localized overgrowths of endometrial tissue covered by epithelium and containing a variable amount of glands, stroma and blood vessel ***(Kurman and Mazur, 1994).***

Pathological findings: Macroscopically, polyps of the endometrium are often multiple, can be broad based or pedunculated, and range in size from millimeters to several centimeters in diameter.

Its surface may be ulcerated, often at the tip ***(Kim et al., 2004).***

Clinical features: Polyps occur relatively frequently after the menopause. The prevalence of polyps in the general population is about 24%. The most common clinical presentation is abnormal bleeding. A polyp should always be considered if abnormal bleeding persists after curettage because polyps on a delicate, pliable stalk may be easily missed by the curette ***(Kurman and Mazur, 1994).***

Complications: There was a low prevalence of premalignant and malignant lesions in endometrial polyps. Older women and those with postmenopausal bleeding had a greater prevalence of malignancy ***(Antunes et al., 2007).***

Polyps are believed to be a risk factor for endometrial cancer because hyperplastic and neoplastic lesions can be found in their context ***(Savelli et al., 2003).***

The incidence of carcinoma arising in a polyp is thought to be less than 1%. The patients, whether symptomatic or not should be evaluated by hysteroscopic resection of the polyps. Asymptomatic premenopausal patients with polyps smaller than 1.5 cm can be observed ***(Ben-Arie et al. 2004)***.

Submucosal fibroids:

Uterine leiomyomas are benign soft-tissue tumors that occur in patients of all ages. Although their size and frequency increases with age, they may grow until menopause and then involute and are a cause of premenopausal uterine bleeding ***(Nalaboff et al., 2001).***

II) Cervical causes:

- **Cervical carcinoma**

Cancer cervix is a largely preventable disease. Long lead-time precancerous lesions that. Gradually progress to invasive disease.

However invasive disease when develops carries significant morbidity ***(Brant et al., 2012).***

The most common cause of its development is the human pappiloma virus. It shows different patterns of growth: Exophytic, nodular, infiltrating, ulcerating ***(Brant et al., 2012).***

US is used to assess tumor size and local regional spread. Early lesions are difficult to detect. Later it appears as ill defined hypoechoic lesions ***(Brant et al., 2012).***

Table 2: Staging System for Carcinoma of the Uterine Cervix (FIGO 1995) ***(Goldstein, 2009)***

Stage	**Characteristics**
IA	Invasive cancer identified only microscopically. (Depth of invasion less than 5 mm, width less than 7 mm)
IB	Clinical lesion confined to the cervix or preclinical lesion greater than stage IA.
IIA	Extension to the vagina (not the lower third), with no parametrial Extension
IIB	Parametrial invasion (but not to pelvic sidewall)
IIIA	Tumor involves lower third of the vagina, with no extension to pelvic sidewall
IIIB	Tumor extends to the pelvic sidewall or causes hydronephrosis or nonfunctioning kidney
IVA	Tumor invades mucosa of bladder or rectum and/or extends beyond the true pelvis
IVB	Distant metastases

III) Vaginal causes:

- **Atrophic vaginitis:**

It is an inflammation of the lining mucosa of the vagina due to low estrogen levels that occurs after menopause. It is presented as postcoital bleeding or spotting. Women who experience bleeding after menopause may attempt to minimize the extent of the problem; they may describe only "spotting" or "pink or brownish discharge". So, any complaint of bleeding or spotting should be evaluated with endometrial sampling ***(Paula, 2002).***

While postmenopausal bleeding is most commonly caused by atrophic vaginitis, bleeding should be investigated to rule out endometrial and cervical carcinoma ***(Telner* and Jakubovicz*, 2007).***

IV) Ovarian causes:

- **Ovarian tumors:**

Whether benign or malignant, are predominantly cystic. The tumors most commonly encountered are the epithelial tumors;serous and mucinous. Cystadenoma, cystadenocarcinoma, and benign cystic teratoma. US is used to differentiate functional ovarian cysts from ovarian tumors and to provide findings used to assess the risk of malignancy ***(Brant et al., 2012).***

- **Epithelial tumors:-**

Arise from the epithelial covering of the ovary. As a group, they account for 65% to 75% of all ovarian neoplasms. Most present as predominantly cystic masses. Pathologic differentiation of benign and malignant forms is sometimes difficult, resulting in some being classified as "borderline" malignant or tumor of "low malignant potential."

Bilateral tumors are common and more frequent with malignant types ***(Brant et al., 2012).***

A) Serous cystadenoma and cystadenocarcinoma comprise 30% of all ovarian neoplasms and 40% of all ovarian malignancies. Serous cystadenomas are thin-walled, usually unilocular, cysts with anechoic fluid. Serous cystadenocarcinoma are multiloculated, with thick walls, thick septa, and papillary projections into fluid that may be echogenic. Blood flow is usually documented within septa and papillary projections ***(Paula, 2002)***.

B) Mucinous cystadenoma and cystadenocarcinoma comprise 20% of ovarian neoplasms. About 85% are benign.

Mucinous tumors may be huge, filling the pelvis and extending high into the abdomen. Most have multiple septations. and contain fluid that is echogenic because of the presence of mucin.

Rupture spreads mucin-secreting cells throughout the peritoneal cavity and may result in pseudomyxoma peritonei ***(Brant et al., 2012).***

- **Endometrioid tumors:-**

Are nearly always malignant. Most are cystic masses with papillary projections ***(Brant et al., 2012).***

Other epithelial cell tumor types include clear cell carcinoma (unilocular cyst with a mural nodule); Brenner tumor (solid, benign); and undifferentiated epithelial tumor (aggressive, ill-defined, cystic or solid) ***(Bronz et al., 2000).***

Stromal tumors:

Include Sertoli-Leydig cell tumors (which may cause masculinization and are malignant in 10% to 20% of cases), Thecoma (which produces estrogen), and fibromas (which are associated with ascites and pleural effusions, i.e., Meigs syndrome). US reveals a solid hypoechoic mass that often causes striking sound attenuation.

Pedunculated leiomyomas have a similar appearance. Physical connection to and vascular supply from the uterus differentiates leiomyomas from solid stromal tumors.

Metastases to the ovary:

Occur most commonly with GI and breast carcinomas. A Krukenberg tumor is a metastasis to the ovary from a mucinproducing tumor of the GI tract. Most metastases to the ovary are bilateral and solid. Cystic metastases may be indistinguishable from a primary ovarian tumor ***(Brant et al., 2012).***

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