Cancer or Something Else?

Post-Menopausal Bleeding

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Post-menopausal bleeding is a problem seen frequently in both family practice and in gynecology. Fortunately, in about 98% of all cases, a benign process will be found as the underlying cause. However, as bleeding is the most common presenting symptom of endometrial carcinoma, this diagnosis must always be considered as the source of any postmenopausal bleeding, until proven otherwise.

Endometrial carcinoma

Endometrial carcinoma is the most common gynecologic malignancy, with 1% to 2% of women affected during their lifetimes. Approximately 75% of cases are Stage I, or confined to the uterus at diagnosis. At this stage, endometrial carcinoma is among the most curable of the solid tumors, with survival rates of up to 95%.[1]

Abnormal uterine bleeding

Abnormal uterine bleeding in the years leading up to menopause is a common problem, affecting up to 80% of women at some point during this time. While the principles of investigation are similar, the focus in this discussion will be on the post-menopausal patient, as this is the age group in which endometrial carcinoma is most commonly seen. A woman is considered to be post-menopausal when at least 12 months have passed since the last normal menstrual period. After this length of time, it is unlikely that uterine bleeding is physiologic, but it is important to recognize that sufficient ovarian activity (to produce estrogen)

Louise's case

Louise, 52, is a gravida 2 para 2 (G2 P2) who presents with a history of three episodes of vaginal bleeding in the previous six weeks.

She began using hormone therapy (HT) at age 50 because of nuisance symptoms and takes 1 mg of 17 ß-estradiol q.d. and 100 mg of micronized progesterone q.d. She stated that her last normal menstrual period was "a while ago."

She is in generally good health and is on no other medications.

Examination

On examination, she appeared well and was of ideal weight for her height. She was normotensive. The only positive findings were a cervical polyp and mild vaginal mucosal atrophy.

Louise had an endometrial biopsy at the office and her cervical polyp was removed.

The uterine cavity was easily entered and scant. Atrophic-appearing tissue was recovered. The pathology showed minute quantities of inactive endometrium, insufficient for diagnosis.

Having the risk factor of age > 45 years to 50 years, Louise opted to undergo (under general anesthetic) hysteroscopy along with dilation and curettage (D&C) as an outpatient. The procedure was technically easy and satisfactory.

For more on Louise, turn to page 80.

surges and rogue ovulation may occur even years after apparent menopause. In these cases, patients will often note and report premenstrual types of symptoms prior to the bleeding.

The perimenopausal use of oral contraceptives for cycle regulation and the use of cyclical hormone therapy (HT) for the control of nuisance symptoms may make it difficult to know if a patient is truly menopausal—because of the induction of regular withdrawal bleeding. An elevated serum follicle stimulating hormone (FSH) on the sixth day or seventh day of the medication-free interval may help to establish whether a patient is menopausal, but this is not absolutely diagnostic. In some patients, FSH levels may continue to be suppressed by medication, even after this length of time. If the diagnosis remains in doubt, it is safer to proceed on the assumption that the patient *is* menopausal and to investigate the bleeding.

Differential diagnosis

Occasionally, it may be difficult for the patient, or physician and sometimes for even both, to distinguish whether bleeding is actually vaginal, as opposed to urethral or rectal. Urinary tract pathologies that may masquerade as vaginal bleeding include:

- transitional mucosal atrophy,
- prolapse,
- lower urinary tract infection,
- calculi and
- malignancy.

Other causes of bleeding that may be difficult to differentiate from post-menopausal bleeding are:

- hemorrhoids,
- anal fissure,
- rectal mucosal prolapse and
- malignancy.

Louise's case cont'd...

Results

The endometrium appeared atrophic and there were no focal lesions. Curettings confirmed benign atrophic epithelium. However, Louise reported another episode of vaginal bleeding three months later.

Louise had a further bleeding episode four months following her hysteroscopy and D&C. Returing to the office for treatment, she indicated that she was not prepared to stop using HT, as she had debilitating menopausal symptoms in the three weeks in which she stopped using HT prior to the hysteroscopy and D&C.

If there is doubt as to the origin of the bleeding, a tampon test may be helpful to confirm if the origin is in the genital tract.

Vulvar and vaginal cancers

Vulvar and vaginal cancers are among the more uncommon malignancies of the genital tract, as is cervical cancer in screened populations. All may present with bleeding as a first symptom. Epithelial ovarian carcinoma, the most common ovarian malignancy, is not a known cause of post-menopausal bleeding. Very rarely, a hormonally active ovarian neoplasm, such as a granulosa cell tumor, may present with abnormal uterine bleeding.

Premalignant diseases

Premalignant diseases of the lower genital tract (*i.e.*, vulvar, vaginal and cervical intraepithelial neoplasia) are not causes of abnormal bleeding. Intense pruritus is a common symptom of vulvar intraepithelial neoplasia and therefore, may be associated with bleeding due to excoriation from scratching. In contrast, endometrial hyperplasia is

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a cause of bleeding. Endometrial hyperplasia without atypia has a low malignant potential, with 1% to 3% of cases progressing to carcinoma; when cytologic atypia is present, the risk of progression to invasive disease is up to 45%.[2]

Mucosal atrophy

Mucosal atrophy, which is a universal event in post-menopausal women not using HT, may develop within months of cessation of menses and is frequently associated with focal surface erosion of the epithelium, leading to bleeding. Atrophy may involve the mucosa of the entire genital tract, including the endometrium.

Benign dermatoses of the vulva

Benign dermatoses of the vulva, such as lichen sclerosus and lichen simplex, are common in the post-menopausal age group and may present with bleeding if there is marked tissue atrophy, ulceration or excoriation due to pruritus. Vulvar lesions are often very difficult to diagnose on purely clinical grounds and a biopsy is strongly recommended in most cases.

Infections

Infections of the endocervix or vagina may present with bleeding, either as a primary manifestation of inflammation, or as a result of scratching where pruritus is a symptom.

Vaginal mucosal prolapse

Vaginal mucosal prolapse, particularly where there is prolonged contact with air or clothing, can lead to damaged mucosa which bleeds.

Table 1
Risk factors for endometrial carcinoma

Factor	Estimated relative risk
• Unopposed estrogen use (> 5 years)	4 to 20
• Diabetes	3 to 7
• Weight > 90 kg	2 to 6
• Family history of endometrial carcinoma	1.5 to 6
• Use of tamoxifen	3 to 5
• Family history of colon carcinoma	2 to 5
• Age ≥ 45 years to 50 years	2 to 4
• Infertility	2 to 3.5
• Nulliparity	2.5 to 3
• Hypertension	1.5 to 2.5
• History of menstrual irregularities	2.5
• History of polycystic ovarian syndrome with oligomenorrhea or amenorrhea	1 to > 5

Cervical polyps

Cervical polyps are among the most common benign genital tract pathology which cause bleeding because of their friability and vascularity. Approximately one in 200 cervical polyps harbours cervical intraepithelial neoplasia and even those that are completely benign may give rise to atypical cells that may interfere with the interpretation of cervical cytology. They are safe, easy and virtually painless to remove in the office setting.

Endometrial polyps

Endometrial polyps are also a cause of post-menopausal bleeding and have a prevalence of about 10%. Between 1% and 3% of endometrial polyps in the post-menopausal patient are malignant.[3] Fibroids should not cause post-menopausal bleeding unless they are submucosal. Among users of endogenous hormones, iatrogenic bleeding is the most common etiology. Combined HT does not increase the risk of endometrial carcinoma in users compared to non-users, but it is not protective either.

Endometrial carcinoma risk factors

Patient factors reported to be associated with a significantly higher probability of developing endometrial carcinoma are shown Table 1 with their estimated relative risks.[4-6] Patients who are thought to have a benign cause for post-menopausal bleeding, but continue to bleed despite appropriate therapy, should also be considered at particularly high-risk and have further investigations carried out.

Investigation

Sampling of the endometrium is indicated in all patients with post-menopausal bleeding, unless an endometrial source can be excluded with confidence. Office endometrial biopsy, dilation or curettage (D&C) with or without hysteroscopy are equally acceptable options.[7] Stenosis of the internal cervical os is a common finding in postmenopausal women and may make office endometrial biopsy technically more difficult. The use of 200 mg to 800 mg of vaginal misoprostol, eight hours to 12 hours prior to the planned instrumentation, safely promotes cervical priming and increases success rates.[8] Misoprostol does not have a formal indication for use as a cervical priming agent in Canada at this time.

Abnormal uterine bleeding in the years leading up to menopause is a common problem, affecting up to 80% of women at some point during this time.

D&C or transvaginal ultrasound

Patients will occasionally refuse office biopsy, usually because of fear of pain. Such patients should be offered D&C with general anesthetic or conscious sedation on an outpatient basis. If this is refused, transvaginal ultrasound, with attention to the endometrial echo, would be appropriate as an initial investigation.[7]

In cases where the uterine cavity cannot be entered, or where tissue recovery is not satisfactory for diagnosis, follow up with D&C with or without hysteroscopy is indicated as a next step in most cases. Patients who do not have any of the risk factors for endometrial carcinoma may be offered a transvaginal ultrasound for assessment of the endometrial echo as an alternative

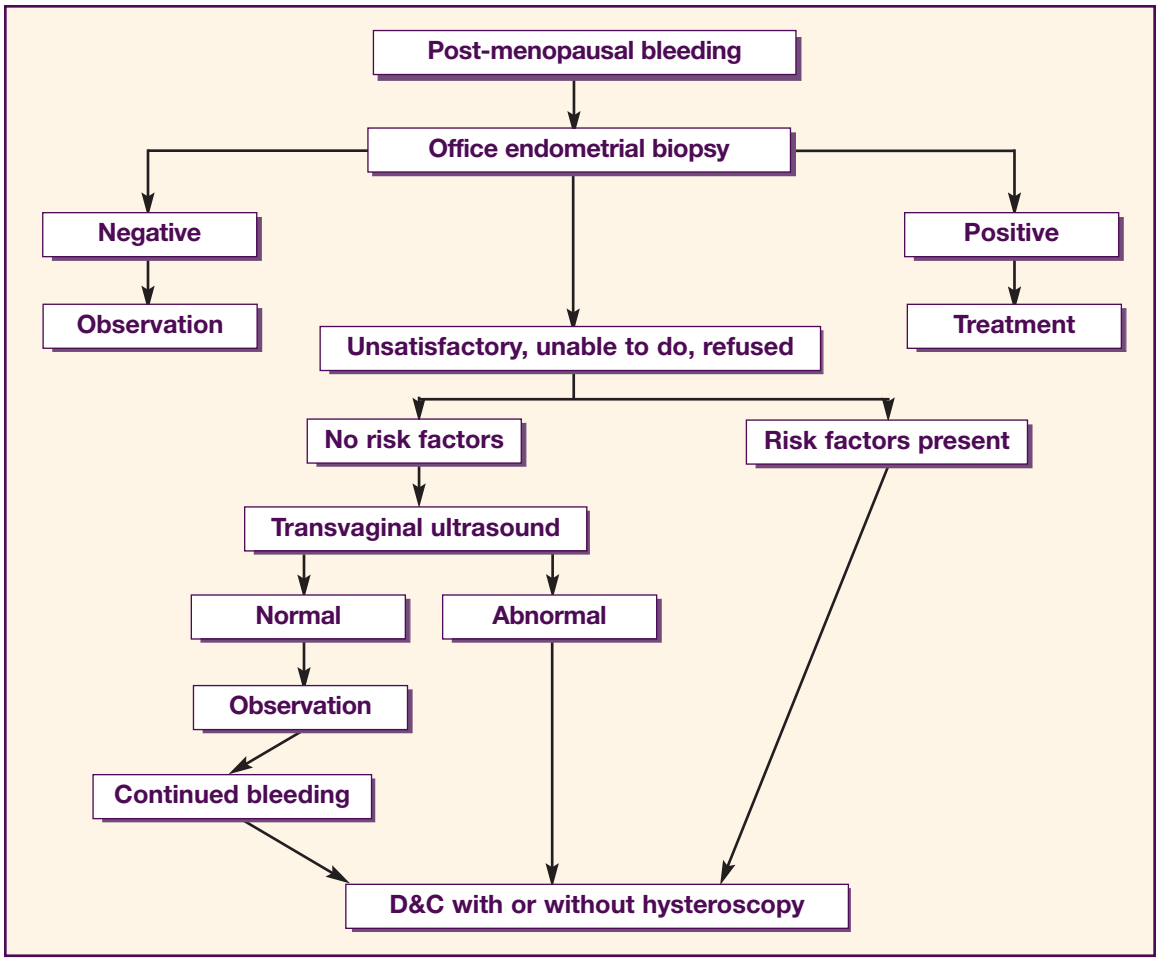

Figure 1. An algorithm for the investigation of post-menopausal bleeding.

investigation. Thickening or focal irregularity should be considered a sign of malignancy.[7] An endometrial thickness of < 4 mm appears to be associated with approximately a one in 300 probability of an occult endometrial carcinoma and observation is an option in such patients, provided that the bleeding does not continue. The 4 mm cut-off applies to all patients, whether they are using HT or not. Patients who have an abnormal endometrial echo require D&C; a hysteroscopy may be done concomitantly.

Sonohysterography

Sonohysterography may allow for a more detailed evaluation of focal endometrial lesions, but is currently not universally available throughout Canada.

At present, there are no guidelines or evidence that would dictate how or when to re-investigate patients who continue to have post-menopausal bleeding, despite a negative evaluation. Given the natural history of endometrial carcinoma, which evolves through a premalignant state over time, a year may be a reasonable interval.[9] However, it is important to have ruled out other possible causes of continued bleeding.

A situation that arises from time to time is the incidental finding of an abnormally thick endometrial echo on ultrasound in a post-menopausal patient who does not have bleeding.

There are no guidelines to help in the management of this problem, as evidence is lacking. It may be reasonable to investigate, with endometrial biopsy, patients who have a focal lesion of the endometrium on ultrasound or who are at particularly high-risk of endometrial carcinoma.[9] An algorithm for the investigation of postmenopausal bleeding is shown in Figure 1.

Specific management challenges

Management of post-menopausal bleeding is dictated by the findings on tissue sampling. Polyps and small submucosal fibroids (< 4 cm in diameter) can be removed under hysteroscopic guidance.

Endometrial hyperplasia

Endometrial hyperplasia, without atypia, has a small potential to progress to malignancy and should be treated for three months with a pro gestin-only therapy. One hundred mg to 200 mg of micronized progesterone q.d., or 5 mg to 10 mg of medroxyprogesterone acetate q.d., will reverse most cases of endometrial hyperplasia. Confirmatory biopsy at the end of this time is indicated.

Endometrial hyperplasia with cytologic atypia is a direct precursor of carcinoma and patients with this diagnosis should be referred to a gynecologist for subsequent management.

Endometrial atrophy

The patient known to have marked endometrial atrophy, who continues to have bleeding, may benefit from a four week course of an unopposed estrogen, such as 0.5 mg to 1 mg of 17 ß-estradiol q.d, or 0.3 mg to 0.6 mg of conjugated estrogens, q.d. Progestin opposition is not required for such a short course of treatment with an estrogen.

Possibly the greatest management challenge in post-menopausal bleeding is the patient who uses HT and continues to bleed after a negative evaluation.

Management options

In many cases, it is difficult to explain why some of these patients continue to bleed and in part, poorly understood individual idiosyncrasies appear to be an underlying factor. Because of this, non-empirical treatment, such as changing the specific HT formulation, is one of few management options. Progestin appears to be the component of combined HT most associated with iatrogenic bleeding. Some specific or directed management strategies are described below:

1. If pathology showed highly atrophic or inactive endometrium, it may be appropriate to increase the estrogen component of HT to try to promote some degree of proliferation, which can lead to a more stable endometrium. Conversely, if the biopsy showed proliferative or disorganized endometrium (without atypia), this would tend to suggest an estrogen excess effect; treatment in such cases could include decreasing the estrogen dose, or increasing the progestin dose.
2. Transdermal estrogen and progestin are associated with a more steady state of hormone delivery and less first-pass effects than with oral HT. Some patients are exquisitely sensitive to the slight fluctuations in hormone levels that occur with the use of oral HT and may bleed, even if the doses are taken on time. A transdermal agent may also be a good option for the patient who has bleeding which clearly correlates with late or missed doses of HT.

Take-home message

- Post-menopausal bleeding should be regarded as a symptom of endometrial carcinoma until proven otherwise
- Endometrial carcinoma is among the most curable solid tumors with a survival rate of > 95% for early disease
- Vaginal misoprostol can be used for cervical priming to increase success rates and todecrease patient discomfort related to endometrial biopsy
- In some patients, ongoing bleeding may be due to the effects of HT, some of which are idiosyncratic and poorly understood

Cyclical HT tends to be associated with less unscheduled bleeding than long-term continuous HT. The trade-off is regular withdrawal bleeding, which some patients may find more acceptable and less concerning than unscheduled bleeding. Good control of bleeding does not necessarily require withdrawal from HT on a monthly basis; in many patients, a three month cycle with 12 days to 14 days of progestin exposure gives highly satisfactory clinical results, with no increase in the development of endometrial neoplasia.

Unopposed estrogen is associated with less iatrogenic bleeding than HT, but does place the patient at an increased risk of endometrial carcinoma in the long term. In highly symptomatic patients, where lack of estrogen is a major quality of life issue, consideration may be given to unopposed estrogen therapy, with the informed consent of the patient and her commitment to undergo a yearly endometrial biopsy for surveillance.[10]

There have been reports of endometrial ablation as a therapy for unusually refractory iatrogenic bleeding on HT, but the evidence for long term outcome and safety is anecdotal at this time.

Summary

Women with post-menopausal bleeding require investigation to establish the cause and in particular, to rule out endometrial carcinoma. Consequently, endometrial sampling, either by office biopsy or D&C, is indicated in all cases.

Transvaginal ultrasound has a limited role in the investigation of those patients in whom tissue sampling is not technically possible, unsatisfactory or refused.

Specific management depends on the cause of the bleeding, which in most cases will be due to a benign process. Patients who have post-menopausal bleeding and a continued need for HT present a special problem, but there are management strategies that can be helpful in these cases.

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