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Case Report

Management of Proliferative Endometrium on Biopsy in Post-Menopausal Women

Sidharth Srinivas[1], Sachchidananda Maiti[2], Perunkulam Jothilakshmi[2]

[1]Manchester Medical School, University of Manchester, Manchester, United Kingdom

[2]Obstetrics & Gynaecology, The Pennine Acute NHS Hospitals, Crumpsall, United Kingdom

Email address:

sid.srinivas@nhs.net (S. Srinivas)

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Abstract: Post-menopausal bleeding (PMB) is usually caused by several endometrial conditions (hyperplasia and carcinoma) for which there are evidence-based treatments. However, there is little literature and no evidence-based treatments for a finding of proliferative endometrium without atypia on Pipelle endometrial biopsy in women presenting with PMB. Our aim is to explore management and treatment options for this subset of women. This is a retrospective, observational case series review of women presenting with PMB to a gynaecology rapid access clinic at a District General Hospital in Manchester, UK over a period of three weeks. Four women who were found to have a proliferative or secretory endometrium on endometrial Pipelle biopsy were chosen. Their history, examination findings, investigations, treatment and follow-up findings were then analysed. This case series has identified the management dilemma posed by patients with proliferative endometrium with no atypia on endometrial sampling. The four patients were followed-up with a repeat Pipelle endometrial biopsy six weeks after presentation to the specialist gynaecology unit. They were subsequently counselled or treated with oral progesterone therapy for six to eight weeks. The management options included the Mirena intrauterine system (IUS), oral progesterone therapy and discharging the patient back to primary care. There is no consensus on the importance of oral progesterone or the duration of follow up necessary to monitor for the development of endometrial hyperplasia or cancer in this subset of patients. Further research is needed to develop evidence-based, management guidelines for proliferative endometrium in women with PMB.

Keywords: Post-Menopausal Bleeding, Proliferative Endometrium Without Atypia, Progesterone Therapy

1. Introduction

Post-menopausal bleeding is an important and common presentation in gynaecology clinic. Urgent investigations are necessary to rule out endometrial cancer - the most common gynaecological malignancy in the United Kingdom [1]. Benign causes such as atrophic vaginitis, polyps and fibroids also have the potential to cause significant stress to the patient. A histological diagnosis of endometrial hyperplasia increases the risk of malignancy and treatment is required to induce regression. In contrast, a histological diagnosis of proliferative endometrium without atypical cells leaves clinicians without evidence-based treatment and uncertainty as to its potential for malignant transformation.

In this report we have analysed four cases of PMB whose investigations found proliferative endometrium on histology. This case series is of interest because there is paucity of literature evidence on proliferative endometrium in post-menopausal women presenting with a symptom of PMB, and as a result no evidence-based treatment. This report will identify areas of uncertainty in our understanding and management of these patients.

Methods

This is a retrospective, observational case series looking at women presenting with PMB to a gynaecology rapid access clinic (RAC) at a District General Hospital in Manchester over a period of 3 weeks in November 2014. Four patients found to have proliferative or secretory endometrium on endometrial sampling with a Pipelle device were chosen at random. The postmenopausal women in this case series were all referred urgently to secondary care after experiencing at

least one episode of bleeding. In this case series, women of all ages who have undergone natural menopause were included. Case notes were used to analyse each patient's history, examination findings, investigations, treatment and follow-up.

2. Case Series

Table 1. *Relevant aspects of the patient history.*

Patient	Age & Menopausal status	Reason for referral	Associated symptoms	Past medical history	Contraception, HRT & tamoxifen status	Cervical smear history
1	54, post-menopausal for 2 years	Two heavy episodes of bleeding for five days each	Abdominal discomfort	Nil	Nil	Normal & up-to-date
2	59, post-menopausal for 5 years	Ten days of heavy vaginal bleeding with clots	Lower abdominal discomfort and weight loss	Type 2 Diabetes mellitus, hypertension and gallstones	GP initiated Norethisterone for bleeding	Normal & up-to-date
3	52, post-menopausal 1 year	Irregularly thick endometrium on ultrasound in primary care	Intermittent bleeding with clots and flooding	Breast cancer, bi-lateral mastectomy and axillary node clearance	Mirena IUS and Tamoxifen one year ago	Normal & up-to-date
4	59, post-menopausal	Eight days of continuous light vaginal bleeding	Mild abdominal pain	Hypertension, hyperthyroidism, rasied body mass index	Nil	Unknown

Table 2. *Investigation results and treatment.*

Patient	Pelvic examination & TVUS	Hysteroscopy	Pipelle biopsy	Repeat pipelle biopsy	Treatment	Duration of follow-up
1	Normal & 1.3mm	Not performed	Proliferative endometrium with no atypia or malignancy	Secretory endometrium with no atypia or malignancy	MDPA 100mg BD for 6 to 8 weeks	6 weeks
2	Normal & 10mm	Normal apart from 2.5mm polypoidal polyp	Secretory endometrium with no atypia or malignancy	Proliferative endometrium with no atypia or malignancy	Mirena IUS counselling	6 weeks
3	Normal & 2mm	Not performed	Proliferative endometrium with no atypia or malignancy	Proliferative endometrium with no atypia or malignancy	Nil	8 weeks
4	Normal & 10mm	Normal apart from a small polyp	Proliferative endometrium with no atypia or malignancy	Proliferative endometrium with no atypia or malignancy	MDPA 100mg BD for 6 to 8 weeks	8 weeks

3. Discussion

3.1. Endometrial Changes During the Menopause

An endometrium that atrophies and loses it functional layer, with endometrial stroma that becomes fibrous and glands that show neither proliferative nor secretory activity - is the accepted picture of the post-menopausal endometrium [2]. This endometrial regression coincides with the cessation of menstruation, therefore when bleeding occurs pathology must be ruled out. The physiology of the post-menopausal endometrium and its role in pelvic pathology has attracted interest in recent decades, with particular focus on precursors to endometrial carcinoma. However, there is much less literature on the post-menopausal endometrium in comparison to the endometrium during reproductive life.

On the whole studies have shown that three-quarters of post-menopausal women appear to have atrophied endometrium with varying degrees of dilated cystic glands. A further 15% have endometrial polyps composed of cystic glands. Endometrium showing proliferation and hyperplasia account for the remaining 10% [3]. Endometrial atrophy is seen during the first year of menopause and its incidence stays constant through menopause. In contrast to cases of proliferation and hyperplasia which are seen primarily in the first 5 years after the menopause.

In 1954 McBride analysed post-menopausal endometrium in a large study; taking specimens using curettage from 1,521 patients at various periods after menopause. In 1,315 samples, little material but mucous was obtained, while the remaining 206 cases showed the following endometrial patterns: atrophy, single or diffuse cystic gland, hyperplasia, proliferation, secretory and fibro-adenomatous polyps. The results suggest that the incidence of proliferative or secretory endometrium is 6.3%. However, the author proposes that where no sample was obtained, the endometrium was either inactive or atrophied. Under this assumption, the incidence of proliferative or secretory endometrium is 0.8%. This leads us to believe that the true incidence of a proliferative or secretory endometrium lies in-between 6.3% and 0.9% [2].

A study investigating endometrial biopsies from peri- and post-menopausal women on continuous HRT found that the majority of endometrium are either atrophic (68.7%) or

proliferative (23.5%). While 0.6% showed simple hyperplasia without atypia, 0.5% had secretory endometrium and well-differentiated adenocarcinoma was found in 0.07% of cases [4]. This suggests that post-menopausal women receiving hormonal stimulation have a higher incidence of proliferative endometrium.

3.2. Causes of Post-Menopausal Bleeding

Post-menopausal bleeding refers to any vaginal bleeding in a post-menopausal woman that is not the expected cyclic bleeding that occurs with sequential hormone replacement therapy [5]. PMB warrants an urgent gynaecology referral as 10% of these patients have endometrial cancer [6]. An early diagnosis of endometrial cancer is important to reduce local and malignant spread and is associated with up to 90% survival [7]. Endometrial cancer often presents early with PMB, however atrophic vaginitis and benign lesions such as polyps and fibroids are common. A study found that up to 30% of cases of PMB reveal an underlying anatomical abnormality (see table 3).

Table 3. *The anatomical causes of post-menopausal bleeding.*

Endometrium	Cervix	Vagina	Ovary
Fibroids	Polyps	Atrophic vaginitis	Cancer
Hyperplasia	Cancer	Cancer	
Polyps			
Cancer			
Endometritis			

3.3. Investigation of Post-Menopausal Bleeding

In accordance with the National Institute of Clinical Excellence (NICE) guidelines three of the patients in our case series presenting with PMB, and not on HRT, were all referred to secondary care to rule out cancer [8]. These patients were all seen within 2 weeks at a gynaecology clinic - meeting the national target for urgent referrals.

Patients being treated with HRT are more complex as it can be difficult to differentiate between normal cyclical and irregular bleeding. Uterine bleeding or spotting when initiating HRT is common but should cease after 6 months [9]. However, NICE recommends an urgent referral for persistent or unexplained postmenopausal bleeding after cessation of HRT for 6 weeks.

The Scottish Intercollegiate Guidelines Network (SIGN) offers an algorithm for the investigation of PMB (see table 4). In keeping with these guidelines all four patients received a pelvic examination to look for any benign causes of bleeding such as cervical ectropion, polyps or to raise the suspicion of malignancy. A thorough history with identification of endometrial cancer risk factors such as a history of chronic anovulation, obesity, diabetes, oestrogen or tamoxifen use and genetic syndromes is valuable. In addition, a speculum examination allows experienced clinicians to diagnose vulval, vaginal and cervical lesions. A thorough history and examination may also raise suspicion of rare causes of vaginal bleeding such as clotting disorders and leukaemia.

As recommended by SIGN, TVUS was the first line investigation used for women presenting with PMB in our case series. Its evidence base, convenience, lack of complications makes it an ideal investigation to assess patients at a higher risk of cancer [10]. With thicker endometrium, the risk of pathology such as malignancy increases, warranting further investigation [11]. While women with thin endometrium can be reassured and re-called for further investigations only if bleeding persists [12]. Setting the endometrial thickness cut-off value balances the need to identify all sinister pathologies while minimising the overuse of resources. Setting the cut-off at 3mm ensures a high sensitivity (100%) but compromises on specificity (25.8%) of the investigation, resulting in excessive numbers of patients being investigated. Currently, 4mm is used in clinical practise as it is deemed to offer the optimum sensitivity (91.6%) and specificity (44.5%) [13].

Other forms of ultrasonography are available such as transvaginal doppler, three-dimensional, saline enhanced and measuring endometrial texture and margin analysis. However, studies have failed to show their advantages over TVUS and are not recommended nor used in routine clinical practise at present [14, 15]

Direct inspection and sampling of endometrial tissue is considered the gold standard and second line of investigation in this cohort of patient. Current practise and SIGN guidelines recommend the use of endometrial biopsy devices to further investigate patients deemed to be at a higher risk of endometrial cancer. Conventionally dilatation & curettage was used to investigate abnormal bleeding but evidence now supports the use of endometrial sampling devices such as the Pipelle device - used in all four patients in my case series. It has a detection rate of 99.6% for endometrial cancer in post-menopausal women, as-well as high sensitivity (81%) and specificity (98%) for identifying atypical hyperplasia [16]. In summary, a combination of TVUS and Pipelle endometrial biopsy offers sufficient diagnostic information to diagnose or rule out benign and malignant endometrial disease [17].

Patients being treated with tamoxifen have a three to six times higher incidence of endometrial cancer, and an urgent referral for such women complaining of PMB is recommended by NICE [18]. The risk of cancer and proliferation, due to the weak oestrogenic effect of tamoxifen, has been shown to rise with increasing dose and duration of treatment. Patient 3 in our case series, a 59-year-old woman on tamoxifen, was more extensively investigated by means of hysteroscopy in addition to a TVUS and Pipelle biopsy. This is in line with guidelines which suggest that hysteroscopy with biopsy is preferred to TVUS, as interpretation of ultrasonography is made difficult by endometrial thickening in patients taking tamoxifen.

Table 4. *Women presenting with post-menopausal bleeding (and not on tamoxifen) [6].*

HRT Status	**Current or use of sequential HRT within the last year**		**Never used HRT, not used HRT for over 1 year or using continuous combined HRT**	
TVUS result	≤5mm	>5mm	≤3mm	>3mm
Risk of endometrial cancer	0.1-0.2%	2-5%	0.6-0.8%	> 20-22%
Further action	No further investigation	Endometrial sampling	No further investigation	Endometrial sampling

3.4. Endometrial Hyperplasia

A diagnosis of endometrial hyperplasia (EH) is made in roughly 10% of women presenting with PMB [19]. The World Health Organisation (WHO) classifies endometrial hyperplasia into simple and complex types; each type is then further classified on the presence or absence of nuclear atypia. Women found to have atypia (see figure 2) on endometrial biopsy require further investigation as approximately 50% have concurrent endometrial carcinoma [20]. In addition, the risk of progressing to cancer is increased in the presence of atypia (27.5% at 9 years after diagnosis), but much lower for hyperplasia without atypia (4.6% at 9 years after diagnosis) [21]. Given the likelihood of future malignancy, hysterectomy with bilateral salpingo-oophorectomy is recommended in post-menopausal women with EH in the presence of atypia. In the absence of atypical cells, women can be managed with progestins and serial biopsies every 6 months to ensure response to treatment. Commonly used progestins include megestrol acetate and medroxyprogesterone acetate. Although the four patients in our case series do not have endometrial hyperplasia, it can be postulated that if atypical cells had been found, the risk of malignancy and the need for further investigates would have risen in patients with proliferative or secretory endometrium.

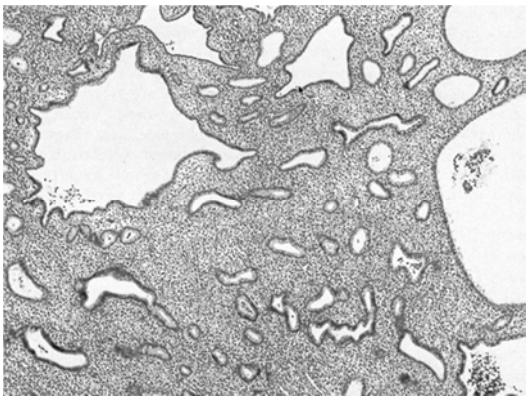

Figure 1. *An endometrial biopsy showing simple endometrial hyperplasia, with endometrial glands irregularly distributed and widely separated by hyperplastic stroma [22].*

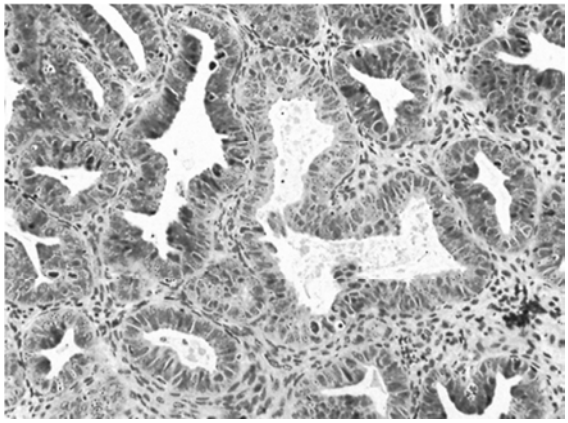

Figure 2. *An endometrial biopsy showing endometrial hyperplasia with atypical glandular cells [22].*

3.5. Pathogenesis of Proliferative Endometrium

My report has identified post-menopausal women whose biopsies mimicked endometrium found in a reproductive woman's monthly menstrual cycle. Increased mitotic activity of the stromal epithelium accompanied by cellular hyperplasia and increased extracellular matrix result in thickening of the endometrium during the proliferative phase of the endometrium (see figure 3). This proliferation is stimulated by oestrogen secreted by developing follicles during the menstrual cycle. Progesterone opposes the actions of oestrogen and its effects halt the proliferative phase of the endometrial cycle. Progesterone induces the secretory phase by stimulating endometrial glands and increasing vascularity (see figure 4). The thickness of the endometrium further increases as glands, stromal cells and blood vessels become engorged. In post-menopausal women it is thought low-levels of oestrogen and progesterone from extra-follicular sources stimulate the endometrium to proliferate. In addition, phytoestrogens such as oil seeds, soy products and tofu are plant substances that are structurally and functionally similar to estradiol. Despite studies suggesting phytoestrogens do not induce proliferation nor increase the risk of endometrial cancer, their long-term effects are relatively unknown [23]. Similarly, there is uncertainty surrounding over-the-counter

use of black cohosh - a herbal remedy with potential proliferative effects on the endometrium.

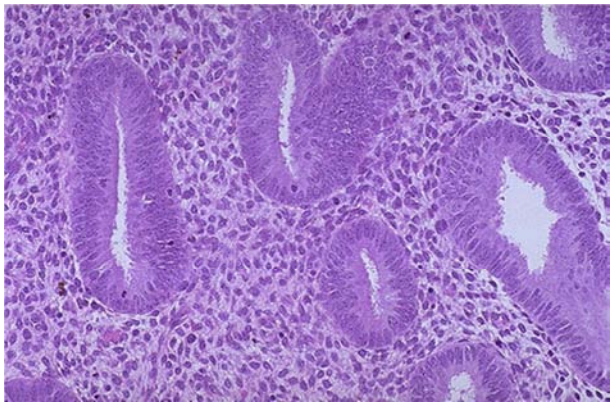

Figure 3. *The microscopic appearance of proliferative endometrium, with proliferation of tubular glands and dense stroma [24].*

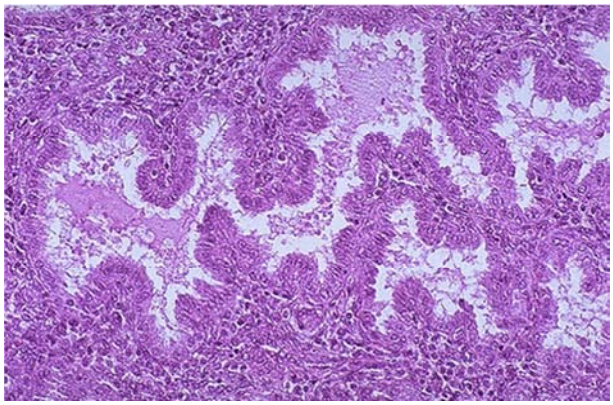

Figure 4. *The microscopic appearance of secretory endometrium and large tortuous glands filled with secretions [24].*

Studies have shown that proliferative endometrium is not uncommon and also suggest that cancers of the endometrium originate from a background of proliferative activity not inertia [25]. The likelihood of simple proliferative endometrium transforming into malignancy is however very low and significantly lower than the 0.3 to 1% risk of endometrial hyperplasia progressing to cancer [26]. However, risk factors include increased body mass index and age. Both of which are associated with peripheral aromatisation and common co-morbidities amongst patients with endometrial cancer.

3.6. Management of Proliferative Endometrium

There are no studies published to our knowledge looking at the management of endometrial proliferation without atypia in post-menopausal bleeding. As a result, there is at present no evidence-based treatment for such women. There is also no consensus on the recommended dose and duration of treatment with MDPA in this subset of patients. Furthermore, there is no agreement on the frequency of follow-up required to rule out more sinister endometrial proliferative pathologies.

There are a few schools of thought amongst gynaecologists about how best to manage these patients. As the risk of proliferative endometrium transforming into cancer is assumed to be very low, an option is to reassure the patient before discharging them back to primary care. On the other hand, a more conservative approach involves the use of systemic progesterone therapy to induce regression of the endometrium. Oral medroxyprogesterone acetate can be prescribed for a relatively short period (six to eight weeks in our case series) to induce endometrial regression. The benefits of progesterone therapy must be balanced carefully against its side effects such as the risk of deep vein thrombosis. A more long-term option being considered by some gynaecologists is the Mirena intrauterine system, a long-acting reversible form of contraception that thins the endometrium by releasing progesterone into the uterus. Both these forms of progesterone are also used in endometrial hyperplasia and have been shown to protect the endometrium from proliferation and malignant transformation [27]. Mirena IUS is licensed to provide endometrial protection for 4 years. The second patient in our case series was initiated on progesterone therapy after one Pipelle biopsy found proliferative endometrium, while the fourth patient was started on the same treatment after confirmation of histology with repeat Pipelle biopsy. As a result of the lack of evidence, it is uncertain whether a repeat biopsy is required to confirm the findings or a single biopsy is sufficient to treat. We also found that patients in our case series were being treated with oral medroxyprogesterone for 6 to 8 weeks but no study to our knowledge has looked at the ideal duration of treatment. A more radical approach to treat proliferative endometrium would be a hysterectomy for repeated episodes of PMB to eliminate any risk of transformation into endometrial carcinoma. However, the anaesthetic, operative risks and psychological impact make this the last resort. A follow-up and repeat Pipelle endometrial biopsy was arranged in 6 weeks time for three out of the four patients. However, there is no evidence on the frequency of follow-up or assessment for response to treatment. Furthermore, it is unclear whether risk factors such as high BMI and breast cancer should reduce the threshold for offering repeat Pipelle biopsy.

4. Conclusion

This report has identified the current trends in management of proliferative endometrium with oral medroxyprogesterone. Multiple areas of uncertainty such as duration of treatment and follow-up have been highlighted. More research into proliferative endometrium in PMB is needed in order to develop evidence-based treatment guidelines.

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