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DOI:
10.1080/13697137.2018.1461825

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Document Version
Peer reviewed version

Citation for published version (Harvard):
Ghoubara, A, Sundar, S & Ewies, AAA 2018, 'Endometrial pathology in recurrent postmenopausal bleeding: observational study of 385 women', *Climacteric*. https://doi.org/10.1080/13697137.2018.1461825

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Checked for eligibility on 11/06/18

This is an Accepted Manuscript of an article published by Taylor & Francis in Climacteric on 09/05/2018, available online: http://www.tandfonline.com/10.1080/13697137.2018.1461825

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Endometrial pathology in recurrent postmenopausal bleeding – observational study of 385 women

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Abstract

Objectives

Women with recurrent postmenopausal bleeding (PMB) are considered as being at higher risk for endometrial hyperplasia and cancer, and guidelines suggest offering hysterectomy in unexplained cases with repeated negative investigations. This study aims to determine the prevalence of endometrial pathology in women referred with recurrent PMB to help inform clinical practice.

Methods

Observational study, of prospectively collected data over 5-year period, including 1902 women referred to the PMB clinic. Women were classified into two groups; those with single referral episode: 1517 (79.8%), and women with multiple referrals because of recurrent PMB: 385 (20.2%).

Results

The prevalence of endometrial hyperplasia or cancer was 32 (8.3%) in women with multiple referrals and 159 (10.5%) in those with single referral (p=0.21). The prevalence of benign polyps was 80 (20.8%) and 214 (14.1%) in the two groups, respectively (p=0.002). On

comparing to single referral, the OR (95% CI) for women with multiple referrals because of recurrent PMB to have endometrial polyps was 1.6 (1.2-2.1).

Conclusion

Women with recurrent PMB had higher prevalence of endometrial polyps, rather than hyperplasia or cancer, when compared with those with single referral. Hysteroscopy may be warranted as the first line investigation, if PMB recurs, to enable polyp diagnosis.

Keywords

Endometrial cancer, endometrial hyperplasia, endometrial polyp, recurrent postmenopausal bleeding

Introduction

Recurrent postmenopausal bleeding (PMB) is considered as a risk factor for endometrial hyperplasia and cancer [1,2], and many gynecologists state: “beware of the weeping womb” [3]. The management of these women is inconsistent amongst gynecologists since there is no clear pathway or strong evidence to inform clinical practice. The guidelines of the British Society of Gynecological Cancer (BCGS) asserts: "In cases of recurrent unexplained PMB with repeated negative investigations, hysterectomy may be indicated and should be discussed with the patient – Grade D recommendation" [4]. On the other hand, a prospective series in the literature documented lower prevalence of endometrial hyperplasia or cancer and higher prevalence of endometrial polyps in women with multiple referrals with recurrent episodes of PMB (*n*=106) when compared with those with a single referral episode (*n*=1430) [5].

PMB is a common condition, affecting 7-15% of postmenopausal women [6], and the prevalence of endometrial cancer in these women ranged in various studies from 3% to 10% [7]. Most of published data did not discriminate between women with multiple referrals because of recurrent PMB and those with a single referral episode. Trans-vaginal ultrasound scan (TVS) is the established initial tool of investigation since several studies demonstrated its safety [1,8,9] and cost-effectiveness [10]. The prevalence of endometrial cancer is <1% when the endometrial thickness (ET) is ≤ 4mm, regular, and no fluid in the uterine cavity [11]. It is widely accepted under these circumstances to refrain from further investigations [12]. Above this cut-off, endometrial sampling is recommended because the risk of cancer is higher [9].

All investigations for PMB carry a false-negative rate for endometrial hyperplasia and cancer [2,8,13]. In contrast to the standardized approach to investigating initial episodes of PMB, management of recurrent PMB is ambiguous. There is a great deal of diversity amongst gynecologists despite it being a common clinical problem with estimated rates for recurrent PMB ranging between 4-33% [2,5,14]. Further, there is no clear evidence on when women with recurrent PMB should be reinvestigated with some investigators recommending 6-month interval [2,8,13], and others suggesting hysteroscopy as the first line investigation tool [1,8,13].

Given the lack of clarity regarding the prevalence of endometrial pathology, the time interval for reinvestigation, and the diagnostic algorithm in women with multiple referral episodes because of recurrent PMB, this study was conducted to determine the prevalence of endometrial hyperplasia, cancer or polyps in these women in comparison with those with a single referral episode. The aim was to produce data to help the development of clinical practice guidelines about the management work-up.

Materials and methods

The routine demographic and clinical data of the PMB clinic were prospectively collected in a specially designed Microsoft Access database, then extracted anonymously and compiled on an Excel spreadsheet. The database contained the details of 2005 consecutive women who were referred for PMB service at a Sandwell and West Birmingham Hospitals NHS Teaching Trust, UK between 1st January 2011 and 31st January 2015. The TVS and histopathology reports were accessed using the hospital Electronic Clinical Data Archive System, while hysteroscopic (diagnostic or therapeutic) procedure findings were retrieved from the case notes.

PMB was defined as an episode of vaginal bleeding occurring ≥ 12 months after cessation of menstruation in women aged ≥45 years. Recurrent PMB was defined as bleeding episodes that recurred, after negative investigations at first referral, necessitating a new referral to the PMB clinic by the family doctor. The recurrence interval is defined as the period between the date of referral for the first episode to the date of referral for the subsequent episode as per the family doctor's referral letter. Women with unscheduled bleeding while taking hormone replacement therapy (HRT) were also considered to have PMB since all of them in this cohort had been on treatment for >6 months [15]. Out of the 2005 women, we excluded (i) frail women not fit for investigations (*n*=10), (ii) women who were referred with incidental finding of increased ET without PMB (*n*=81), and (iii) women diagnosed with hyperplasia at the initial visit and managed with progestogen therapy and surveillance being not fit for hysterectomy (*n*=12). The remaining 1902 were included in the analysis.

All women attending the PMB clinic underwent pelvic examination and TVS. If the endometrium was regular, ≤ 4 mm in thickness, with no evidence of fluid, no further investigations were performed. An outpatient Pipelle® endometrial aspiration biopsy was performed in women with ET >4 mm, indistinct endometrium or in case of fluid in the cavity [9]. For women with first referral episode with PMB, hysteroscopy was performed when the sampling device could not be introduced into the uterine cavity, the sample was deemed inadequate by the histopathologist, or when focal lesion was seen on TVS [1,5,8,15]. However, hysteroscopy was performed in all women with recurrent PMB. All endometrial polyps in this series were confirmed on hysteroscopic examination.

Women were classified according to the presenting history into two cohorts: (i) women with single referral episode by family doctor with PMB during the study period, and (ii) women with multiple referral episodes because of recurrent PMB. We included in this second group women who had their first referral episode before or during the study period. Women were further categorized according to the investigation results into: (i) group 1 - benign finding (including endometrial polyps), and (ii) group 2 - endometrial hyperplasia or cancer. For the purposes of this study, endometrial hyperplasia and cancer were combined as a single category. This is because of the high rate of concurrent cancer (42.6%) [16,17] and progression to cancer (28%) [18] when endometrial atypical hyperplasia is found. Endometrial hyperplasia without cytologic atypia was also combined in the same group, despite the low progression rate of <5% over 20 years, considering the recent Guidelines of the Royal College of Obstetricians and Gynaecologists that recommended at least progestogenic therapy and surveillance i.e. these women should not be categorized as having negative investigations or benign pathology [15].

Data were collected as part of the routine investigations and treatment, and the project was considered as "service evaluation"; therefore, ethics approval was not deemed necessary. Service evaluation may not require ethical approval in the UK [19,20].

Statistical analysis

Statistical analyses were carried out using IBM® SPSS® Statistics for windows software version 20 (International Business Machines corporation, Armonk, NYC, USA). Continuous variable indices are presented as mean with standard deviation or as median with inter-quartile range (IQR) as distribution demands. The difference between groups in last menstrual period (LMP) and ET was sought by *t* test. Age and Body mass index (BMI) were not normally distributed; therefore, Mann-Whitney U test was used. Chi-squared test was used to test the difference in categorical variables; ethnic origin, hypertension, diabetes and HRT use. The strength of association between recurrent PMB and the outcome groups was measured by odds ratio (OR) with 95% confidence interval (95% CI). Univariate analysis and Multivariate logistic regression analysis (MVLRA) was used for further analysis of the recurrent PMB group to identify the predictors of endometrial hyperplasia, cancer and polyps.

Results

The number of women with multiple referrals with recurrent PMB was 385 (20.2%), while the number of those with a single referral episode was 1517 (79.8%). The median recurrence interval was 24 months (IQR=13-47). Women with multiple referrals because of recurrent PMB had significantly older age, longer duration since last menstrual period, higher BMI and higher prevalence of hypertension and diabetes. When the investigations revealed benign findings, the median (IQR) age of women with recurrent referrals *v* those with single referral was 62 (55-40) *v* 56 (52-65), $p<0.001$. However, there was insignificant age difference between women in the two groups when the diagnosis of non-atypical hyperplasia (p=0.091) or atypical hyperplasia or cancer was made (p=0.76). Women's demographic and clinical characteristics are summarized in table 1.

The total number of women diagnosed with endometrial hyperplasia or cancer was 191 (10%). The prevalence of endometrial hyperplasia or cancer was 32 (8.3%) in women with multiple referrals with recurrent PMB and 159 (10.5%) in those with a single referral episode. The difference was statistically insignificant. On comparing to single referral, the OR (95% CI) for women with multiple referrals with recurrent PMB to have endometrial hyperplasia or cancer was 0.77 (0.5-1.1), p=0.21. On excluding the 186 women with HRT, the result remained the same: OR (95% CI) = 0.76 (0.5-1.2), p=0.23.

On further analysis after splitting endometrial non-atypical hyperplasia from atypical hyperplasia and cancer, there was no significant difference between women with multiple referrals with recurrent PMB and those with single referral episode in the prevalence of endometrial non-atypical hyperplasia: OR (95% CI) = 2 (0.8-4.7), p=0.11. Women with

multiple referrals were found to have insignificantly lower prevalence of endometrial atypical hyperplasia and cancer: OR (95% CI) = 0.64 (0.4-1), p=0.06.

The prevalence of benign endometrial polyps with normal background endometrium was 80 (20.8%) and 214 (14.1%) in women with multiple referrals and those with a single referral episode, respectively. On comparing to single referral, the OR (95% CI) for women with multiple referrals because of recurrent PMB to have endometrial polyps was 1.6 (1.2-2.1), p=0.002. On excluding the 186 women with HRT, the result remained the same: OR (95% CI) = 1.55 (1.15-2.1), p=0.005.

On univariate analysis in women with multiple referrals episodes because of recurrent PMB, the median BMI was 30 (IQR=26-36) and 34 (IQR=30-40) in the benign group and in hyperplasia and cancer group, respectively (p=0.002). The mean ET was 5.8 mm (SD=5.1) and 14.1 mm (SD=7.2) in the benign group and in hyperplasia and cancer group, respectively (p<0.001). There was no significant difference in the other demographic and clinical variables between the two groups.

On multivariate logistic regression analysis in women with multiple referrals episodes because of recurrent PMB, the ET was the only independent predictor for the outcome of endometrial hyperplasia and cancer (adjusted OR=1.2, 95% CI = 1.1-.1.3, p<0.001). This means that for every 1mm increase in ET, there is a 20% (95% CI=10%-30%) increase in the odds of endometrial hyperplasia and cancer, considering the effect of other predictors. Neither age, number of years since last menstrual period, hypertension, BMI, diabetes independently predicted the outcome of endometrial hyperplasia and cancer.

Figure 1 represents a summary for the investigations performed at the first referral for the 385 women with multiple referrals with recurrent PMB. The recurrence interval is also presented. Of them, 42 (11%) women had their first episode investigated before 1st January 2011; the date when prospective collection of the PMB clinic data had started. The family doctors' referral letters for the subsequent episodes confirmed previous negative investigations although the details are lacking.

Discussion

To our knowledge, this is the largest series with prospectively collected data in the literature investigating recurrent PMB. In contrast to the traditional belief, we found that women with multiple referrals because of recurrent PMB have less prevalence of endometrial atypical hyperplasia and cancer when compared to those with a single referral episode. However; they have significantly higher prevalence of benign endometrial polyps similar to two other reports in the literature [5,21]. The same result was obtained on excluding HRT users from the analysis, which is also similar to previous reports [5,21]. The ET was the only independent predictor for endometrial hyperplasia or cancer in these women with 20% rise in the risk for every 1mm increase in ET, considering the effect of other predictors. Neither age, ethnic origin, BMI, number of years since last menstrual period, hypertension, diabetes or HRT use independently predicted the outcome of endometrial hyperplasia and cancer.

Similarly, a prospective study, comparing women with multiple referrals with recurrent PMB (*n*=106) *versus* those with a single referral episode (*n*=1832), found that the prevalence of endometrial hyperplasia or cancer was significantly less (6.6% v 14.4%, *p*= 0.04) and the prevalence of benign endometrial polyps was significantly higher (28% v 19%, *p*= 0.02) in women with recurrent PMB [5]. Another retrospective study, comparing women with multiple referrals with recurrent PMB (*n*=126) *versus* those with a single referral episode (*n*=1430), reported no difference in the prevalence of endometrial cancer between the two groups over 56 months period [2].

The prevalence of recurrent PMB varied in published reports between 4-33% [2,14], which may reflect the variations in the definition of recurrent PMB. There is no universal definition

in the literature, and some studies mixed women who were re-referred with recurrent PMB after negative initial investigations with women who suffered multiple episodes of bleeding before they got referred for the first time [1]. In our opinion, this is incorrect since women who are re-referred with recurrent PMB either have pathology missed during initial investigations or have risk factors to develop endometrial pathology. This should not be confused with late presentation or late referral which highlights issues around access to care rather than underlying risk of pathology. We have been pragmatic and considered as recurrent PMB those with multiple referrals after negative initial investigation since this group of women is the cause for concern in every day clinical practice.

Little is known about the interval for reinvestigation i.e. the time after which women should be reinvestigated if they got re-referred with recurrent PMB after negative initial investigations. We found that the median recurrence interval to be 24 months (IQR=13-47). No case of endometrial hyperplasia or cancer was diagnosed in the first 10 months after negative initial investigations. Similarly, Ronghe and Gaudoin, in a series of 1536 women with PMB of whom 126 (8%) had multiple referrals, reported a mean recurrence interval of 21 months (range: 2–62 months). All the six cases (except one missed at initial hysteroscopy, bicornuate uterus) of endometrial atypical hyperplasia or cancer presented with recurrent PMB after 6 months (range: 20–57 months) from the negative initial investigations. The authors recommended a 6-month interval to reinvestigate women with recurrent PMB [2]. Further, two studies from the same center, including 471 women with PMB of whom 47 (15%) had multiple referrals, reported median recurrence intervals of 49 weeks. The four cases of endometrial atypical hyperplasia or cancer presented with recurrent PMB 16-182 weeks after negative initial investigations. The PMB recurrence rate was not related to incorporation of hysteroscopy or polyp removal at the initial work-up [22]. The European

Menopause and Andropause Society (EMAS) clinical guidelines suggested that women with recurrent or persistent bleeding should be followed up e.g. after 6 months. A combination of TVS, hysteroscopy to directly visualize the uterine cavity, and biopsy was advised [23]. Similarly, the Scottish Intercollegiate Guidelines Network (SIGN) recommended in year 2002 that re-investigation of recurrent PMB should be considered after six months of initial negative investigations; [9] however, their guidelines on the management of PMB are currently under review for updating.

Some investigators suggested that the increase in prevalence of endometrial polyps in women with recurrent PMB may reflect the higher accuracy of hysteroscopy for detecting focal disease when used at the second presentation i.e. polyps are missed at first presentation when TVS is used as the first line investigation [24,25]. Nevertheless, our data suggest that polyps *de novo* may develop more frequently accounting for further bleeding symptoms. The prevalence of polyps is highest in the 108 women with recurrent PMB who had polyps resected at first presentation as demonstrated in figure 1. Of them, 50 (46.3%) were found to have polyps in the subsequent presentations, with median recurrence interval of 27 months (IQR=15-52).

The finding that benign endometrial polyps are more prevalent in women with recurrent PMB has potential implications for how best to manage these women. Although the vast majority of endometrial polyps are benign [26] and the consequences of diagnosis are deemed less serious than endometrial hyperplasia or cancer, they are frequently associated with abnormal uterine bleeding. Removal frequently resolves symptoms, preventing further referrals and alleviating women's anxiety [27]. Our data strongly supports the previous recommendation

that all women with recurrent PMB should undergo hysteroscopy as the first line investigation since it has high accuracy for enabling diagnosis of focal diseases [5]. The Canadian Society of Obstetricians and Gynecologists guidelines states that hysteroscopic examination should be considered in women with persistent or recurrent uterine bleeding with negative initial investigations irrespective of the menopausal status (II-2B) [28].

The strength of the present study is that the data were collected prospectively, consecutively, and in standardized fashion, minimizing bias from incomplete data. In addition, our findings are generalizable given the large sample size, and the fact that we used the widely accepted standard protocol in managing women with PMB as highlighted in the methodology.

Conclusion

Women with multiple referrals with recurrent PMB had higher prevalence of endometrial polyps, rather than hyperplasia or cancer, when compared with those with a single referral episode. Our data support the recommendation that hysteroscopy should be used as the first line investigation, if PMB recurs, since it has high sensitivity to enable accurate polyp diagnosis. It may be plausible not to re-refer these women for reinvestigations before 6 months from the negative initial investigations. Polyp resection or morcellation at the initial diagnosis may be recommended, and the practice should change to refrain from routinely offering hysterectomy to these women.

Author contributions

AG: Managed the data and revised the manuscript.

SS: Contributed to the study design and revised the manuscript.

AAAE: Designed the study and wrote the first draft of the manuscript.

Conflicts of interest

None of the authors has any conflicts of interest for this manuscript

Funding

No fund was obtained for this study but the research fellowship of AG was funded by Aswan University, Egypt and the Egyptian Cultural Bureau in London, UK.

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Tables legends

Figure 1: Summary of the investigations performed and the outcome at first referral for women with multiple referral with PMB (*n*=385)

Table 1: Women's demographic and clinical characteristics (*n*=1902)

Table 2: Investigation results (*n*=1902)

Table 1: Women's demographic and clinical characteristics (*n*=1902)

Variable	Recurrent PMB *n*=385 (20.2%)	Single PMB episode *n*=1517 (79.8%)	Total *n*=1902	*p*-Value
Age				
Group1	62 (55-70)	56 (52-65)		<0.001*
Group 2	66 (58-71)	63 (57-74)		0.95
Total	62 (56-70)	56 (52-66)		<0.001*
LMP	12 (7)	9 (7)		<0.001*
BMI	30 (26-36)	29 (25-35)		0.027*
HRT users	38 (9.8%)	148 (9.9%)	186 (9.8%)	0.9
Hypertension	189 (49.1%)	611 (40.3%)	800 (42.1%)	0.002*
Diabetes	88 (22.9%)	258 (17.1%)	346 (18.2%)	0.008*
Endometrial thickness	6.5 (5.8)	6.3 (5.5)		0.32

Group 1=Benign findings

Group 2=Endometrial hyperplasia or cancer

BMI=Body Mass Index

CI=Confidence interval

HRT=Hormone Replacement Therapy

LMP=Last menstrual period

$^{*}p<0.05$ is considered significant

Values of Age and BMI are expressed as median (inter-quartile range)

Value of LMP is expressed as mean (standard deviation)

Values of HRT, hypertension, DM, outcome groups and endometrial polyps are expressed as *n* (%)

Table 1: Investigations results (*n*= 1902)

Outcome	Recurrent PMB *n*=385 (20.2%4)	Single PMB Episode *n*=1517 (79.8%)	Total *n*=1902	*p* value	OR (95% CI)
Group 1	353 (91.7%)	1358 (89.5%)	1711 (90%)		
Endometrial polyp	80 (20.8%)	214 (14.1%)	294 (15.5%)	0.002*	1.6 (1.2-2.1)[a]
Other benign findings	273 (70.9%)	1144 (75.2%)	1417 (74.5%)		
Group 2	32 (8.3%)	159 (10.5%)	191 (10%)	0.21	0.77 (0.5-1.1)[b]

Group 1=Benign findings

Group 2=Endometrial hyperplasia or cancer

CI=Confidence interval

OR=Odds ratio

PMB=Postmenopausal bleeding

Group 1=Benign findings

Group 2=Endometrial hyperplasia or cancer

[*] $p<0.05$ is considered significant

[a]OR for the likelihood of recurrent PMB to have endometria polyp

[b]OR for the likelihood of recurrent PMB to have endometrial hyperplasia and cancer