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Do Polyps Matter?

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Abstract: *Introduction***:** Endometrial polyps (EP) are common within the gynaecological practice. The aims of this study are to evaluate the risk of premalignant and malignant changes in EP and to determine the predictors of histological outcomes of these lesions.

Methods: This is a retrospective study conducted over a 12-year period between January 2000 and 2012. Data were retrieved from patients' and theatre records. The histopathology reports of all cases were retrieved. All cases with confirmed EP at hysteroscopy were identified.

Results: There were a total of 397 cases. Age range was between 24 and 89 years, median age at presentation was 54 years. Histology outcomes were classified into benign, premalignant (hyperplasia with atypia) and malignant. Age greater 60 years was strongly associated with abnormal histology *i.e.* premalignant and malignant changes in polyps (OR 2.174 [CI 1.645-2.874], p<0.001) Menopausal status showed a strong link with abnormal histology (OR 1.599 [CI 1.388- 1.842], p<0.001). These patients were about one and a half times more likely to have abnormal histology in the event of a polyp. The results are similar with premalignant histology (OR 1.610 [CI 1.394- 1.860], p<0.001).

Results for patients presenting with postmenopausal bleeding were also positive. They were more likely to have abnormal histology compared to patients with other symptoms (OR1.776 [CI 1.516-2.079], p<0.001). Postmenopausal bleeding is also strongly associated with premalignancy (OR 1.782 [CI 1.515- 2.096], p<0.001). The use of hormone replacement therapy (HRT) or tamoxifen was not associated with abnormal histology (p= 0.114 and p=0.668 respectively) or premalignancy (p= 0.138 and p= 0.764 respectively).

Polyps greater than 15mm were not associated with abnormal histology (OR 1.313 [CI 0.932-1.850], p= 0.143) or premalignancy (OR 1.292 [CI 0.896-1.864], p= 0.196).

Conclusion: There is a strong link between patients' age and menopausal status with abnormal or premalignant histology. Postmenopausal bleeding is also an important predictor of abnormal or premalignant changes at histology.

Keywords: Endometrial polyp, Abnormal histology, Premalignancy, Tamoxifen, Hormone replacement therapy, Postmenopausal.

INTRODUCTION

Endometrial polyp (EP) is a common presentation within the gynaecological practice. It is the most frequent endometrial finding in menopausal women [1]. It is usually benign [2] but may be associated with malignancy [3]. Women commonly present with abnormal uterine bleeding but a few are asymptomatic, discovered at routine ultrasound investigations for other reasons including infertility [2, 4-5]. Its prevalence is 7.8% within the population, increasing with age [6]. They are diagnosed in 5.8% of pre and 11.8% of postmenopausal women [6]. Lieng *et al.* [7] in their systematic review described a pooled prevalence of 0.8% and 3.1% of premalignant and malignant tissue changes respectively within polyps. The prevalence of malignancy varies significantly with age and menopausal status [7-12], with the postmenopausal group of patients presenting with abnormal uterine bleed having the highest risk of premalignant and malignant tissue changes [7-8,13]. Lee *et al.* [14] in their meta-analysis reported a prevalence of 5.42% and 1.7% for premalignant and malignant polyps respectively for postmenopausal women in general [14]. There are conflicting reports on the sizes of polyps that might be relevant as a predictor of malignancy. Some studies have shown sizes of greater than 15mm [11] and 18mm as significant factors for premalignant and malignant changes [15]. Endometrial polyps represent the most common endometrial pathology associated with postmenopausal tamoxifen use [16]. The use of tamoxifen predisposes patient to the development of EPs [16-17] and polyps tend to be larger for those taking tamoxifen compared to those that are not [18]. Kennedy and colleagues described the histological features as characteristically multiple and fibrotic, with a high rate showing malignant change [17].

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The aims of this study are to evaluate the risk of premalignant and malignant changes in EPs and to determine predicators of histological outcomes of these lesions.

MATERIALS AND METHODS

This is a retrospective study conducted over a 12-year period between 2000 and 2012 at Singleton hospital, a major district hospital in South Wales, United Kingdom. Data were retrieved from patients' and theatre records. The histopathology reports in all cases were retrieved. All cases with confirmed EP at hysteroscopy were identified. These include all pre and postmenopausal women who had endometrial polyps confirmed at hysteroscopy within the study period. Data analysed include the age, polyp size, and menopausal status. Data were also retrieved on use of hormone replacement therapy (HRT), current use of tamoxifen and histology results. Women were considered menopausal if they reported amenorrhea of at least 12 months after the age of 45 years. Abnormal uterine bleeding was defined as vaginal bleeding in post-menopausal women not receiving HRT or as irregular vaginal bleeding in women still actively menstruating or being treated with HRT. Histology results were classified as benign, pre-malignant, and malignant. Cases with simple and complex hyperplasia without atypia were classified as benign. 'Pre-malignant' refers to hyperplastic endometrium with atypia while 'malignant' were patients diagnosed with endometrial cancer In the analysis, abnormal histology refers to number of cases with malignant changes plus number of polyps with premalignant changes at histological examination. Results are presented as mean+/- S.D. Data were analysed using IBM SPSS Statistics 20 to determine Chi square and risk ratio. The level of statistical significance at which the null hypothesis was rejected was chosen at 0.05.

RESULTS

There were 397 cases of polyps confirmed at hysteroscopy. The age range was between 24 and 89 years with a median age of 54 years. 56% of patients were postmenopausal; and 88% of all the cases were done as day case procedures. 12 patients had been on tamoxifen at the time of presentation, while 17 patients were on HRT. The Table **1** below describes the symptoms patients presented with and the histological outcomes.

Postmenopausal bleeding accounted for about 53% of the cases. 8 patients had endometrial polyps confirmed at hysteroscopy as part of their investigations for infertility. There was one patient with EP confirmed at hysteroscopy for recurrent vaginal discharge.

Patients' symptoms at presentation varied particularly with age; patients presenting with postmenopausal bleeding were 53% of the entire cohort and dysfunctional uterine bleeding made up 37% of the cases. The prevalence of malignant EP in premenopausal women was 0.6%, increasing to 2.1% in postmenopausal women.

Age greater than 60 years had a very significant association with abnormal histology *i.e*. premalignant and malignant changes in polyps (OR 2.174 [CI 1.645-2.874.], p<0.001). Patients older than 60 years of age were twice as likely to have polyp with atypical hyperplasia compared to women below 60 years *i.e*. premalignant changes (OR 2.147 [CI 1.600- 2.882], p<0.001).

Menopausal status showed a strong link with abnormal histology (OR 1.599 [CI 1.388- 1.842], p<0.001). Postmenopausal women were about one and a half times more likely to have abnormal histology of endometrial polyp compared with premenopausal women. The results were similar for premalignant histology (OR 1.610 [CI 1.394- 1.860], p<0.001).

Results for patients presenting with postmenopausal bleeding were also significant. Patients presenting with postmenopausal bleeding were more likely to have abnormal histology compared to patients with other symptoms (OR 1.776 [CI- 1.516- 2.079], p=0.001). Postmenopausal bleeding is also strongly associated with premalignancy (OR 1.782 [CI- 1.515-2.096], p<0.001).

There were 33 patients who were asymptomatic. They had polyps' diagnosed following radiological assessment for other symptoms. EP diagnosed in patients without symptoms are not associated with abnormal histology (OR 0.458 [CI 0.113- 1.855], p=0.252) or with premalignancy (OR 0.522 [CI 0.129-2.105], p= 0.343). 30 out of the 33 asymptomatic patients were postmenopausal. The probability that an asymptomatic menopausal patient with EP will have an abnormal or premalignant histology is negligible (OR 0.507 [CI 0.125- 2.063], p=0.326; OR 0.578, [CI 0.143-2.342], p=0.430) respectively).

The use of HRT was not a predictor of abnormality. There was no association with abnormal histology or premalignancy (p=0.114 and p= 0.138 respectively).

Table 1:

		Histology			Total
		Benign	Pre-Malignant	Malignant	
Symptoms	Asymptomatic	31	2	0	33
	Post menopausal bleeding	168	37	5	210
	Dysfunctional uterine bleeding	140	4	1	145
	As part of investigations for infertility	8	0	0	8
	Recurrent vaginal discharge	1	0	0	1
Total		348	43	6	397

Tamoxifen use was not associated with either abnormal histology (OR 0.646 [CI 0.085- 4.892], p=0.668) or premalignancy (OR 0.736 [CI 0.097- 5.560], p= 0.764).

Polyps were also classified into two groups of <15mm and >15mm. Polyps greater than 15mm were unlikely to be associated with abnormal histology (OR 1.313 [CI- 0.932- 1.850], p= 0.143) or premalignancy (OR 1.292 [CI- 0.896- 1.864], p= 0.196). Polyps were further grouped into intervals of 10mm (Tables **2** and **3**). Data were analysed to determine if there was an association with increasing sizes of the polyp and abnormal histology/premalignancy. There was no association between increasing polyp size and abnormal histology see (Table **2**) or premalignancy (Table **3**).

Table 2: This Table Illustrates the Association between Increasing Polyps' Size and Abnormal Histology

Polyp Size	p-Value	Rate Ratio (RR)	Confidence Interval (CI)
≤ 10mm	Reference		
11-20mm	0.614	0.956	0.804-1.138
21-30mm	0.784	0.971	0.785-1.201
31-40mm	0.986	0.997	0.714-1.393
41-50mm	0.842	1.049	0.654-1.685
≥ 50mm	0.990	0.997	0.629-1.581

DISCUSSION

EP remains a common presentation in gynaecological practice. There is variation in the management of EP especially when they are incidental findings while investigating for other conditions. This is a study of women with EP over a period of 12 years. Approximately 12% of diagnosed cases had premalignant and malignant changes confined to polyps. About 11% of cases had hyperplasia with atypia while 1.5% of patients had carcinoma confined to EP. Our study analysed size of polyp in two ways: (i) absolute sizes *i.e*. <15mm or >15mm and (ii) at intervals of 10mm. There is no previous study in the literature that has analysed the size of EP in this way. There was no association with abnormal histology or premalignancy in either sub-group.

Table 3: This Table Illustrates the Association between Increasing Polyps' Size and Premalignancy

Polyp Size	p-Value	Rate Ratio (RR)	Confidence Interval (CI)
≤ 10mm	Reference		
11-20mm	0.739	0.971	0.815-1.156
21-30mm	0.822	0.976	0.788-1.208
31-40mm	0.974	0.994	0.712-1.389
41-50mm	0.850	1.047	0.652-1.680
≥ 50mm	0.981	0.994	0.627-1.577

Age was a significant predictor of abnormal histology. Older women have a higher chance of abnormal histology. 25% of patients over the age of 60 years were diagnosed with premalignant and malignant changes at histology. Patients over 60 years were twice as likely to have abnormal or premalignant changes at histology compared with patients below 60 years. This is similar to many previous studies [7-9,11]. Antunes and colleagues claimed that postmenopausal women over 60 years were 5 times more likely to have premalignant and malignant changes in EP [9].

Menopausal status is a strong predictor of abnormal histology. In their meta-analysis, Lee and associates identified this as predictor for malignancy [14]. Our study showed that postmenopausal women were almost twice as likely to have premalignant/malignant polyp as premenopausal women. Our study also showed that increasing age is a predictor of abnormal histology, which is similar to findings by previous studies in the literature [7-9,11].

Postmenopausal bleeding is also a relevant predictor, with women presenting with the symptom twice as likely to have premalignant or malignant changes at histology compared to women with other symptoms

Table 4: This Table is a Summary of Relevant Results from the Study (See Below)

	p-Values	Odd's Ratio	Confidence Interval
Age >60 years	<0.001	2.174	1.645- 2.874
Menopausal status	<0.001	1.599	1.388- 1.842
Post menopausal bleeding	0.001	1.776	1.516- 2.079)
Hormone replacement therapy, Tamoxifen, Polyp size	NS		

NS - not significant.

There was no association between tamoxifen or use of hormone replacement therapy (HRT) and premalignant or malignant changes in polyps. These findings differ from that other of other studies [19-20]. This discrepancy may be due to the relatively small numbers of patients on tamoxifen and HRT in our study.

Patients that are asymptomatic are unlikely to have premalignant or malignant changes of EP. The diameter of the polyp was not significant in the prediction of abnormal histology. Ferrazzi and colleagues, in their series, revealed that polyps greater than 18mm were likely to be associated with abnormal histology [15]. The difference in findings might be due to relatively small number of asymptomatic cases in our study compared to their study.

In conclusion, patients over the age of 60 years, menopausal status and postmenopausal bleeding are predictors of abnormal histology in endometrial polyps. This is the first study in the literature to evaluate increasing polyp size relative to abnormal histology and premalignancy. Our study shows that there is no association between these parameters. Patients and clinicians should be aware of these findings when making decisions on the clinical management of EP.

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