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ORIGINAL ARTICLE

Risk Factors Associated with the Malignant Changes of Symptomatic and Asymptomatic Endometrial Polyps in Premenopausal Women

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Abstract

Objective This study aimed to evaluate the prevalence of premalignant and malignant lesions of symptomatic and asymptomatic endometrial polyps among premenopausal women and to verify whether different clinical parameters, and polyp volume and number are associated with a more precise estimate of malignancy.

Methods One hundred and fifty women aged 29–52 years and with certain diagnosis of endometrial polyp were enrolled in a prospective observational study. The recruited patients underwent hysteroscopic polypectomy based on saline infusion sonohysterography and diagnostic hysteroscopy. Pathologic report was the main outcome.

Results Among women with endometrial polyps, 62 % had asymptomatic polyps. The prevalence of premalignant and malignant polyps comprised 4.6 % of cases (3.3 % hyperplasia with atypia and 1.3 % carcinomatous polyps). The presence of abnormal uterine bleeding was not a predictor of premalignant and malignant changes in the polyp. On logistic regression analysis, the premalignant and malignant lesions were influenced by polycystic ovary syndrome ($p < 0.001$; OR 4.61; CI 1.9–27), polyp volume >10 ml ($p < 0.001$; OR 5.83; CI 4.31–9.17), and multiple polyps ($p = 0.01$; OR 2.05; CI 1.09–3.76). Notably, the odds ratio of polyp volume >10 ml was 5.83. This additional risk confirms the importance of polyp volume in the detection of malignant transformation rather than associating bleeding in premenopausal women.

Conclusion Polycystic ovary syndrome, polyp volume greater than 10 ml, and increased polyp number represent the markers of risk for premalignant and malignant

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transformation of endometrial polyps in premenopausal women. Nonetheless, the majority of polyps are asymptomatic, and the risk of malignancy is very low. Therefore, for women with polyp volume ≤10 ml and no risk factors, a more expectant approach may be warranted in order to reduce surgical risks and costs.

Keywords Risk factors · Endometrial polyps · Malignancy · Polycystic ovary syndrome · Polyp diameter

Introduction

The etiology and pathogenesis of endometrial polyp remain unclear. Some investigators suggested that the endometrial polyp is formed as a consequence of abnormal expression of estrogen and progesterone receptors [1–3]. The prevalence of endometrial polyps depends on the population being studied and the uterine imaging technique. Using saline infusion sonohysterography (SIS), endometrial polyps could be found in 10 % of asymptomatic premenopausal women older than 30 [4]. Polyps occur in all age groups, but are most commonly found in women aged 40–49 years [5]. Their prevalence ranges are from 20 % in symptomatic premenopausal women to 40 % in the postmenopausal period [6, 7].

Some studies found malignancy arising from a polyp only in symptomatic menopausal women [8], whereas others found malignancy in premenopausal women and in asymptomatic postmenopausal women [9]. The polyps may be an incidental asymptomatic finding diagnosed during routine vaginal sonography or infertility investigations. Most women with symptomatic endometrial polyps present with abnormal uterine bleeding (AUB), and this has been recently classified as AUB-P for premenopausal women as endorsed by FIGO [10].

The presence of abnormal bleeding, during the perimenopause, was not found to be a risk factor for premalignancy or malignancy [8]. However, late menopause, obesity, arterial hypertension, and the use of tamoxifen therapy in women with breast cancer have been identified as risk factors [11].

Once a polyp has been identified, operative hysteroscopy is often the treatment of choice in the resection of endometrial polyps and the evaluation of the endometrial cavity, allowing complete removal of the lesion and biopsy of the suspicious areas in the adjacent endometrium [12]. The objectives of this study were to determine the incidence of premalignant and malignant lesions in symptomatic as well as asymptomatic endometrial polyps in premenopausal women and to assess whether different clinical parameters, and polyp volume and number are associated with malignant transformation.

Patients and Methods

The present prospective cohort study was conducted in Ouhd Hospital (a Taibah University Teaching Hospital). A series of premenopausal women with or without AUB admitted to the department of obstetrics and gynecology over 31 months, from May 2011 to August 2013, with endometrial polyp were evaluated for eligibility to participate in this study. Patients were excluded if they were older than 52 years, had reached menopause, had submucosal uterine leiomyomas, or had adenomyosis. The polyp was diagnosed incidentally without AUB on ultrasound scan that was done for other reasons (e.g., pain, rule-out pelvic mass, inadequate pelvic examination, infertility, or a screening examination performed by the referring clinician).

The diagnosis of endometrial polyp was made preoperatively by transvaginal ultrasound examination with SIS using 8F Foley catheter (Schering AG, Berlin). The sonographic volume of polyps was calculated with the formula for a prolate ellipsoid: $4/3 \times D1 \times D2 \times D3$ (where $D1$, $D2$, and $D3$ represent the three diameters of the polyp), and the volume was expressed in milliliters (ml) [13]. The diagnosis of endometrial polyp was confirmed during diagnostic hysteroscopy using a 5-mm sheath (Karl Storz GmbH & Co., Tutlingen, Germany). No anesthesia was needed during this procedure. When polyps were found in a patient, hysteroscopic polypectomy was performed in the same session using the monopolar cutting loop with a continuous flow operative hysteroscope (Karl Storz GmbH & Co., Tutlingen, Germany) equipped with a 7- or 9-mm operative sheath under general anesthesia. Sodium chloride was used as a distension medium, and fluid balance was carefully monitored. Moreover, the women who underwent hysterectomy due to recurrent or severe bleeding were included in our study after they had a definitive histologic diagnosis.

Baseline patient characteristics such as age, body mass index, history of hypertension, diabetes, AUB, and associated PCOS were recorded by accessing the clinical history of the participants and the validated questionnaire. The diagnosis of PCOS was based on the Rotterdam criteria [14].

The endometrial polyp number was noted during hysteroscopy. Polyps were removed in one piece or in pieces that were able to pass through the cervical canal. The specimens were placed in 10 % formaldehyde for histologic examination. A diagnosis of endometrial polyp was made on the basis of tissue in a polypoid shape that was covered by surface endometrium with the presence of fibrotic stroma that contained thick-walled blood vessels and endometrial glands that were variable in size and shape [13]. All the specimens were analyzed and categorized

according to the World Health Organization (WHO) criteria [15].

According to the final histopathologic assessment, 150 cases of endometrial polyp were included in our analysis. Histopathology results of symptomatic and asymptomatic endometrial polyps were compared. When multiple polyps were present, the polyp with the worst pathologic report was considered for the present study. All the participants gave consent according to the Helsinki declarations. The study protocol was approved by the Medical and Health Sciences Research Committee Involving Human Subjects of our Hospital, which conforms to the provisions of the Declaration of Helsinki.

The results were presented as mean and standard deviation (±SD) for numerical variables, while categorical variables were presented as number and percentage. Statistical significance for differences was analyzed using the Independent sample t test, Wilcoxon rank, sum (Mann–Whitney) test, Kruskal–Wallis test, and Chi-squared test, when appropriate. Further, logistic regression was performed as multivariate analysis to estimate the odds ratio (95 % CI) and to test whether the set of variables, significant with the univariate analysis, produced a good model for the prediction of the premalignant or malignant polyps. The statistical analyses were performed using SPSS 13 (SPSS Inc., Chicago, IL 60606, USA). In all the cases, statistical significance was accepted for p values <0.05.

Results

The mean age of 150 women participated in the study was 42.1 ± 5.6 (range 29–52 years). Obesity (BMI ≥30 kg/m^2) was found in 34.6 % of cases, whereas diabetes and hypertension were detected in 25.3 and 29.3 %, respectively. The incidence of PCOS was 14 %, and AUB was reported by 38 % of the study population (Table 1). Fourteen women underwent hysterectomy but were included in our analysis after they had a definitive histologic diagnosis.

The overall incidence of benign endometrial polyps was detected in 95.4 % of the patients; premalignant and malignant pathologies were detected in 4.6 % of patients (3.3 % hyperplasia with atypia and 1.3 % carcinomatous polyps). In addition, patients with symptomatic endometrial polyps were not at risk of premalignant and malignant changes of polyps compared with those without bleeding, and the difference failed to reach significance ($p = 0.067$) (Table 2).

The comparison between clinical parameters, polyp volume and number, and histopathologic findings were presented in Table 3. Premalignant and malignant polyps were statistically more frequent in older women ($p = 0.019$). Among the other clinical data considered, BMI ≥30 kg/m^2, associated PCOS, polyp volume >10 ml, and multiple polyp number were found to be significantly associated with premalignant and malignant changes of endometrial polyps ($p < 0.05$). The mean volume of premalignant and malignant polyps was 15.2 ± 2.6 ml (range 11.8–20.2 ml), compared with 9.9 ± 2.7 ml (range 0.4–13.8 ml), for the benign polyps. None of the other clinical variables considered (parity, diabetes mellitus, hypertension, and AUB) were statistically related to the histopathologic results.

Polycystic ovary syndrome, polyp volume >10 ml, and polyp number were eventually the only significant independent variables retained by multivariate analysis for the prediction of premalignant or malignant polyps ($p < 0.001$; OR 4.61; CI 1.9–27), ($p < 0.001$; OR 5.83; CI 4.31–9.17), and ($p = 0.01$; OR 2.05; CI 1.09–3.76), respectively. Notably, the odds ratio of polyp volume >10 ml was 5.83. This additional risk confirms the importance of polyp volume in the detection of malignant transformation rather than associating bleeding in premenopausal women (Table 4).

In asymptomatic patients, only 2 (1.3 %) uneventful uterine perforations during operative hysteroscopy were observed. Minor complications such as cervical tears occurred in 3 (2 %) and 1 (0.6 %) cases of asymptomatic and symptomatic women, respectively. No major complications were reported.

Table 1 Clinical characteristics of 150 women with endometrial polyps

Clinical variables	Number of patients	(%)
Age (years) mean (SD) (range)	42.1 ± 5.6 (29–52)	
Parity		
Nullipara	62	41.3
Multipara	88	58.7
BMI (kg/m^2)		
<25	43	28.7
25–29.9	55	36.7
≥30	52	34.6
Diabetes mellitus	38	25.3
Hypertension	44	29.3
PCOS	21	14
AUB		
Yes	57	38
No	93	62

PCOS polycystic ovary syndrome; *BMI* body mass index; *AUB* abnormal uterine bleeding

Table 2 Final histopathologic results of symptomatic and asymptomatic endometrial polyps

Histological diagnosis	Total	Symptomatic	Asymptomatic	*P* value**
Benign				
Endometrial polyp	97 (64.7)	36 (63.1)	61 (65.6)	0.129
Polyp with simple hyperplasia	36 (24)	12 (21.1)	24 (25.8)	
Polyp with complex hyperplasia	10 (6.7)	4 (7)	6 (6.4)	
Subtotal	143 (95.4)	52 (91.2)	91 (97.8)	
Premalignant/malignant				
Polyp with simple hyperplasia with atypia	2 (1.3)	1 (1.8)	1 (1.1)	0.067
Polyp with complex hyperplasia with atypia	3 (2.0)	2 (3.5)	1 (1.1)	
Endometrial carcinoma	2 (1.3)	2 (3.5)	0 (0.0)	
Subtotal	7 (4.6)	5 (8.8)	2 (2.2)	
Total number	150 (100)	57 (38)	93 (62)	

Values are given as number (percentage)

** *P* values between symptomatic and asymptomatic women obtained using Kruskal–Wallis test

Table 3 Clinical risk factors, and polyp volume and number associated with premalignant and malignant transformation of endometrial polyps

Factor	Benign polyps (%), $n = 143$	Premalignant/malignant polyps (%), $n = 7$	*P* value	95 % CI
Age (years) ± mean (SD) (range)	41.9 ± 5.7(29–52)	47.1 ± 4.2 (41–52)	0.019	9.58–0.885
Parity				
Nullipara	93.5	6.5	0.386	0.437–0.462
Multipara	96.6	3.4		
BMI				
<30 kg/m^2	97.9	2.1	0.037	0.43–0.52
≥30 kg/m^2	90.4	9.6		
Diabetes mellitus				
Yes	92.1	7.9	0.277	0.363–0.381
No	96.4	3.6		
Hypertension				
Yes	93.1	6.9	0.422	0.666–0.685
No	96.2	3.8		
PCOS				
Yes	80.9	19.1	0.001	0.005–0.010
No	97.6	2.4		
AUB				
Yes	91.2	8.8	0.063	0.102–0.114
No	97.8	2.2		
Mean polyp volume (ml)**	9.9 ± 2.7 (0.4–13.8)	15.2 ± 2.6(11.8–20.2)	<0.001	−7.65–3.41
Mean polyp volume (ml)				
≤10 ml	100	0.0	<0.001	−6.31–2.78
>10 ml	92.7	7.3		
Polyp number	1.3 ± 0.59	2.2 ± 0.95	<0.001	−1.39–0.449

Values are given as a percentage or mean ± SD unless otherwise indicated

PCOS polycystic ovary syndrome; *BMI* body mass index; *AUB* abnormal uterine bleeding

** In case of multiple polyps, the one with the worst pathologic report was considered

Table 4 Results of Logistic regression analysis

Variable	Odds ratio	95 % CI		*P* value
		Lower	Upper	
Age	0.12	0.94	1.05	0.121
BMI	1.55	0.78	3.10	0.261
PCOS	4.61	1.9	27	<0.001
Polyp volume >10 ml	5.83	4.31	9.17	<0.001
Polyp number	2.05	1.09	3.76	0.01

Discussion

Endometrial polyps represent the most common causes of menometrorrhagia resistant to the medical therapy in reproductive aged women or can cause abnormal bleeding in postmenopausal patients. However, more often polyps are asymptomatic and are incidentally found during routine gynecologic examination. Our study including 150 consecutive women aged 29–52 underwent hysteroscopic polypectomy and histologically verified as endometrial polyps aiming to assess the premalignant and malignant changes and to evaluate the associated risk factors in symptomatic and asymptomatic women.

A remarkable finding in our study was that polyps were more frequent in women without AUB compared to women with AUB; 62 % of women with polyps were asymptomatic. The incidentally discovered polyps were reported to be 20–46.2 % [13, 16]. On the other hand, Dreisler et al. [17] found that the prevalence of uterine polyps among women without AUB was up to 82 % when women with myomas were excluded from analysis. Accordingly, a causal relationship between endometrial polyps and AUB is questionable. The reported high values in our population may be attributed to the fact that more women are having imaging studies done in the pelvic region for different indications as pelvic pain and infertility, in addition to incidental finding on other imaging studies done for non-gynecologic purposes. Such patients often had no abnormal vaginal bleeding, but the suspicious ultrasound findings led to sonohysterography which diagnosed an endoluminal mass compatible with a polyp.

In this study, cases of atypical endometrial hyperplasia and endometrial carcinoma were grouped together because the frequency of coexistent endometrial cancer among patients with atypical endometrial hyperplasia ranged from 17 to 52 %. In addition, when hysterectomy was performed, it is well known that endometrial carcinoma is diagnosed in up to 42.6 % of women with premalignant endometrial polyps [18].

The overall incidence of premalignant and malignant pathology was detected in 4.6 % of patients (3.3 % hyperplasia with atypia and 1.3 % carcinomatous polyps). These findings seem to be similar to those reported in previous studies in which malignancy rate was described to vary between 0.8 and 8 % [12, 19–22]. One study reported a high prevalence of hyperplasia without cytologic atypia (25.7 %) and a prevalence of hyperplasia with atypia (3.1 %), and it added that polyps represent a wide spectrum of alterations that range from normal endometrium to cancer [12]. These differences in the prevalence rates observed may be due to different study designs, sample sizes, inclusion and exclusion criteria, and different methods used for removal of polyps, such as uterine curettage this blind method fails to extract the whole polyp and obtains only a mixed specimen of polyp and the adjacent endometrial mucosa. Hysteroscopic endometrial polyp removal appears to be superior to the current practice [23]. In addition, it gives the possibility of removing the entire polyp with its stalk, and the histological examination proved the presence of an endometrial carcinoma hidden in either stalk or center [24], so that the risk of malignancy of endometrial polyps can be estimated confidently.

The present study revealed that patients with symptomatic endometrial polyps were not significantly at risk of premalignant and malignant changes of polyps compared with those without bleeding. AUB was found to be the significant predictor of polyp malignancy even in those populations with the lowest risk of malignancy (among premenopausal women) compared with asymptomatic women [21, 25], but still women without vaginal bleeding harbor a risk of malignancy a possible explanation of this fact could be related to earlier diagnosis of polyps by transvaginal ultrasound that detects small polyps, as endometrial thickness, before they start bleeding.

In our cohort, it would be helpful to detect clinical characteristics as reliable risk factors related to premalignant and malignant transformation of endometrial polyps. The present results showed that old age, obesity, associated PCOS, polyp volume >10 ml, and multiple polyps were identified as significant factors associated with premalignancy or malignancy in endometrial polyps in univariate analysis.

Similar observations were reported by others [22, 26] who demonstrated that old women have a prevalence of malignant polyps about 5 times greater than the young women. The progression from simple to complex and atypical hyperplasia takes many years and possibly depends on the accumulation of specific genetic aberrations, which explains the reason why patient age increases the possibility of premalignant and malignant polyps [12].

Obesity was assessed as an independent risk factor of premalignant and malignant polyps. Obese women have higher levels of circulating estrogen which stimulate the endometrium to create endometrial polyps and probably malignant endometrial polyps [27].

In multiple logistic regression analysis, only PCOS, polyp volume >10 ml, and polyp number were found to be the factors associated with malignancy in endometrial polyps.

Women with PCOS had a prevalence of premalignant or malignant polyps greater than that of women without PCOS ($p < 0.001$; OR 4.61; 95 % CI 1.9–27). PCOS was found to be a significant risk factor predicting malignancy in endometrial polyps. Endometrial hyperplasia is seen in 35 % of women with PCOS who are not receiving either

contraceptive steroids or periodic progestin withdrawal [28]. Moreover, those at the highest risk of endometrial hyperplasia are women who have less than 4 menses per year and ultrasound endometrial thickness more than 7 mm [29]. It is generally assumed that chronic anovulation with unopposed estrogen stimulation of the endometrium is a main factor. Obesity, hyperinsulinemia, hyperandrogenism, and recurrence of AUB after hysteroscopic polypectomy, which are also the features of PCOS, are the risk factors for endometrial malignancy [28, 30].

The polyp volume >10 ml was significantly associated with an abnormal histology by multivariate analysis in symptomatic and asymptomatic patients ($p < 0.001$; 5.83; CI 4.31–9.17). Notably, the OR for polyp volume >10 ml was 5.83. This additional risk confirms the significance of the polyp volume in the detection of malignant changes rather than associating bleeding in premenopausal women. Few studies have evaluated the relationship between polyp size and malignancy risk. Some authors have suggested that larger polyps are associated with a higher risk of malignancy [21, 25]. However, others stated that polyp size is not a distinctive feature of malignancy [27, 31]. A recently published meta-analysis concluded that the authors reported the size of polyps in centimeters, millimeters, grams, and milliliters, making the analysis of this association more difficult [32].

Women with multiple polyps had a significant prevalence of premalignant or malignant polyps compared with women with solitary polyps ($p = 0.01$; OR 2.05; CI 1.09–3.76). Malignant transformation of endometrial polyp was found to be more frequent in women who had 3 or more polyps [9, 31]. This finding was also confirmed by Kilicdag et al. [33] who reported that women with 3 or more polyps had a prevalence of premalignant or malignant polyps, which was 31.3 times greater than that of women with 1 polyp (95 % CI 3.9–254).

In conclusion, PCOS, polyp volume >10 ml, and multiple polyps may increase the risk of premalignant and malignant transformation of endometrial polyps in premenopausal women whether symptomatic or not. However, with no risk factors, routine removal of these polyps should be avoided in order to reduce surgical risks and costs.

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Compliance with ethical requirements and Conflict of interest The study protocol was approved by the Medical and Health Sciences Research Committee Involving Human Subjects of Ouhd Hospital, Al Madinah Almunawarrah, Saudi Arabia. The authors have no conflicts of interest to declare.

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