

Predictors of malignancy in endometrial polyps: a multi-institutional cohort study

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Summary

Purpose of investigation: The risk of endometrial cancer in women with endometrial polyps (EPs) has been reported to vary between 0.3% and 4.8%. There is a lack of data about the management of asymptomatic women with incidental diagnosis of EPs. In the present study the authors correlated demographic and clinical characteristics with histopathological features of the EPs hysteroscopically removed. **Materials and Methods:** An observational multi-institutional cohort study was conducted from February 2010 to December 2012 to identify all the premenopausal and postmenopausal women consecutively undergoing hysteroscopic polypectomy. The data of women were reviewed and clinical features were related to histopathologic results. **Results:** The patients recruited were 813. The mean age was 52.5 years (range 22-87). The results showed a correlation between older age, high body mass index (BMI) and obesity, postmenopausal state, abnormal uterine bleeding (AUB), hypertension, and risk of malignant EPs. On multivariable analysis, the correlation remained only for age (OR 1.08, 95% CI 1.03 - 1.14) and AUB (OR 3.53, 95% CI 1.87 - 6.65). **Conclusion:** Older patients in postmenopausal status with AUB, a high BMI, and hypertension are at higher risk for premalignant and malignant polyps. In these patients a surgical approach should be used, consisting in hysteroscopic removing of the polyp.

Key words: Endometrial polyps; Body mass index; Hypertension; Endometrial cancer; Hysteroscopic polypectomy.

Introduction

The introduction of routine ultrasound and office hysteroscopy in the evaluation of dysfunctional or organic lesions of uterine cavity have increased the number of diagnosis of uterine polyps [1]. Endometrial polyps (EPs) are a localized overgrowth of endometrial tissue and may contain varying amounts of stroma and blood vessels covered by pseudostratified epithelium [2]. The diagnosis of EPs occur in 10% to 40% in women with abnormal uterine bleeding (AUB) and up to 12% of asymptomatic women in routine gynecological examinations [3, 4].

These lesions may be pedunculated or sessile, single or multiple, usually representing a benign condition, although the risk of carcinoma has been reported to vary between 0.3% and 4.8% [5]. Additionally, premalignant changes showed in the polyps are the same observed in the atypical endometrial hyperplasia [6,7].

Recently, some studies attempted to evaluate the risk and predict factors of endometrial cancer in women with EPs reporting often lacking and conflictual data in terms of clinical and surgical management [8, 9].

Previous studies have demonstrated an increased rate of premalignant and malignant lesions in patients in postmenopausal status with EPs who have associated vaginal bleeding [10, 11]. Furthermore, some authors reported the onset of endometrial malignant polyps exclusively in symp-

tomatic or postmenopausal women [12]. Others described risk factors are obesity, arterial hypertension, and use of hormonal and tamoxifen therapies [13, 14]. Therefore, the correct management of asymptomatic women with EPs is actually unclear. In fact, gynecologists must balance the risk of malignant progression with the risk of complications of hysteroscopy and analgesia/anesthesia and the costs of the intervention [15-17]. Currently, the management of the EPs either asymptomatic or symptomatic is the hysteroscopic resection in women of any age.

The aim of this study was to determine the prevalence of atypical lesions on EPs removed by hysteroscopic procedures. Furthermore, the authors wanted to evaluate the association between clinical parameters and demographical characteristics as well as the histopathological features of these lesions.

Materials and Methods

The medical records of premenopausal and postmenopausal women consecutively undergoing operative hysteroscopy for endometrial polypectomy between February 2010 and December 2012 at the Department of Gynaecological Sciences and Human Reproduction, University of Padua (Padua, Italy) and at the Woman's Health Sciences Department, Università Politecnica delle Marche (Ancona, Italy) were retrospectively analyzed in an observational multi-institutional cohort study (Canadian Task Force II-2).

An informed consent was obtained from all patients, which explained the involved side effects, risks, and benefits of medications and the procedures. The study protocol was approved by the ethics committee of both Centers.

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All women underwent presurgical evaluation with physical examination, transvaginal ultrasound, and office hysteroscopy. Diagnostic outpatient hysteroscopy was performed using saline solution as a distention medium, and an endoscope with a five-mm diagnostic sheath. The vaginoscopic approach (without speculum or tenaculum) was used in all cases to avoid patient discomfort or pain not directly related to uterine examination. Neither analgesia nor local anesthesia were administered to any patient.

Demographic characteristics and data on diabetes, hypertension, and menopausal status were collected, and anthropometric parameters were analyzed. Patients were considered postmenopausal if they reported a period of at least 12 months of amenorrhea. AUB was defined as any vaginal bleeding in postmenopausal women not receiving hormonal replacement therapy (HRT) or in premenopausal woman with not regular bleeding or in treatment with HRT. Women in treatment with tamoxifen in adjuvant therapy for breast cancer were also included in the study group. Arterial hypertension (diastolic pressure >90 mmHg and/or systolic pressure >140 mmHg), body mass index (BMI) (women with BMI more than 30 were considered obese), diabetes mellitus (fasting glucose >126 mg/dl), presence or absence of symptoms, hormonal and tamoxifen therapy, parity, and history of previous diagnosis of breast cancer were recorded. Exclusion criteria were: cervical cancer, complex adnexal pathology, severe liver pathology, and pregnancy.

The diagnosis of EPs was histologically made after a hysteroscopic polypectomy, carried out rarely under spinal anesthesia [18] or usually under general anesthesia. Procedures were performed using a nine-mm resectoscope 12° forward-oblique lens with a monopolar loop 90°, and glycine as distension medium or a ten-mm resectoscope 0° forward lens with a 2.5 mm twizzle electrode. The electrode worked on bipolar energy, so saline was used as the distension media. Myomas or polyps were hysteroscopically distinguished and additional information about surrounding endometrium was obtained. The aim of the resection was the complete removal of the EP. Evaluation of the endocervical canal, endometrial surface, vascularity, tubal ostia or synechiae was performed.

In premenopausal women the procedure was performed in proliferative phase of the menstrual cycle. In perimenopausal women, with heavy bleeding, a transcervical endometrial resection was associated [19]. Hysteroscopic polypectomies were performed by senior gynaecologist surgeons. No intraoperative or postoperative complications were recorded.

Specimens removed by hysteroscopic resection (EPs and endometrial areas) were sent for histopathological examination to the Institute of Pathological Anatomy of the University of Padua and the Institute of Pathological Anatomy of the Ospedali Riuniti, Ancona, Italy. Cases of submucous leiomyoma or uterine adenomyoma were excluded by the analysis.

Diagnosis distinguished between polyps that were recognized as benign (atrophic, proliferative, or hyperplastic polyps and simple hyperplasia and complex hyperplasia without atypia), premalignant (complex hyperplasia with atypia), and those harboring carcinoma [20]. The histopathologic definitions of endometrial hyperplasia and adenocarcinoma were according to the following definitions [21]. Endometrial simple hyperplasia was defined by the endometrial architecture that was moderately distorted. The lining epithelium of the glands was pseudostratified showing mitotic activity with no atypia of cells. Atypical simple hyperplasia was defined by architecture similar to simple hyperplasia, but the glands were more irregular. The glands were lined by atypical cells. Endometrial carcinoma was defined by crowded malignant tubular glands varying in size and invading the stroma.

Table 1. — *Demographic and clinical characteristics of the study population (813 cases).*

Age (mean ± DS, range)	52.5 ± 13.1 (22-87)
Menopausal status	Premenopausal 421 (51.8%) Postmenopausal 392 (48.2%)
Parity	Nulliparity 222 (27.3%) Pluriparity 591 (72.7%)
AUB	267 (32.8%)
BMI (mean ± DS, range)	25.1 ± 5.2 (16.7-58.6)
Hypertension	206 (25.3%)
Diabetes Mellitus	25 (3.1%)
History of breast cancer	34 (4.2%)
HRT	84 (10.3%)
Tamoxifen	22 (2.7%)

Table 2. — *Histopathological diagnosis of the resected lesions.*

Histology	N. of patients	%
Benign polyps and polyps with hyperplasia without atypia	766	94.2
Polyps with hyperplasia with atypia	23	2.8
Cancerous polyps	24	3.0

The statistical analysis was performed with Medcalc 13.1. Student's *t*-test was applied, as appropriate, to compare continuous variables. Proportion were compared with Chi-squared test. Statistical significance was considered achieved when $p < 0.05$. Univariable and multivariable logistic regressions were performed to verify the presence of statistically significant correlation among age, BMI, menopause, AUB hypertension, (independent variables), and the presence of EPs or adenocarcinoma.

Results

The main demographic and clinical characteristics of the study population (813 cases) are shown in Table 1. The mean age was 52.5 years (range: 22-87) and 392 (48.2%) patients were in postmenopausal status. Mean BMI was 25.1 (5.2 SD) with a 16.7% of obese patients.

Table 2 shows the histopathological diagnosis of the resected lesions. Forty-seven (5.8%) premalignant and malignant lesions were found, consisting of 23 (2.8%) polyps with complex hyperplasia with atypia and 24 (3.0%) carcinomas.

Association between clinical parameters and histopathologic results are shown in Table 3. Of these factors, age ($p < 0.001$), BMI ($p < 0.001$), menopause ($p < 0.001$), AUB ($p < 0.001$), and hypertension ($p < 0.001$) showed any significant association. In particular, older women (> 60 years) had a statistically significant higher risk of premalignant and malignant lesions, while younger women (< 40 years and 40-50 years) had more frequently benign polyps. Higher BMI values were correlated with higher risk of malignant lesion, with a specific attention to BMI values in the range of obesity (>

Table 3. — Association between clinical parameters and histologic results.

Variable	Benign polyps and hyperplasia without atypia (766 cases)	Preneoplastic and neoplastic lesions (47)	<i>p</i>
Age (mean±DS)	51.8 ± 12.8	64.1 ± 12.4	< 0.001
< 40 years	132 (17.2)	2 (4.3)	0.03
40-50 years	238 (31.1)	4 (8.5)	0.001
50-60 years	176 (23)	10 (21.3)	0.9
> 60 years	220 (28.7)	31 (65.9)	< 0.001
BMI (mean ± DS)	24.9 ± 5.2	27.8 ± 5.1	< 0.001
BMI < 25	457 (59.7)	15 (31.9)	< 0.001
BMI 25-30	187 (24.4)	18 (38.3)	0.05
BMI > 30	122 (15.9)	14 (27.8)	0.05
Menopause	354 (46.2)	38 (80.9)	< 0.001
AUB	239 (31.2)	28 (59.6)	< 0.001
Nulliparity	210 (27.4)	12 (25.6)	0.9
Diabetes mellitus	22 (2.9)	3 (6.4)	0.4
Hypertension	183 (23.9)	23 (48.9)	< 0.001
Breast cancer	32 (4.2)	2 (4.3)	0.7
Tamoxifen	22 (2.9)	0 (-)	0.5
HRT	79 (10.3)	5 (10.6)	0.9

All values are n (%) unless otherwise specified;

Table 4. — Multivariable logistic regression, of age, menopause, AUB, hypertension, BMI, and the presence of preneoplastic and neoplastic lesions

Independent variable	Preneoplastic and neoplastic lesions		
	<i>p</i>	OR	95% CI
Age	<0.001	1.08	1.03 - 1.14
BMI	0.3	1.03	0.97 - 1.10
Menopause	0.8	1.18	0.41 - 3.37
AUB	<0.001	3.53	1.87 - 6.65
Hypertension	0.6	0.84	0.39 - 1.76

30) and overweight (25-30). Among the other clinical variables, menopause, hypertension and the presence of AUB were statistically found to be more frequent in patients with preneoplastic and neoplastic changes of the EPs. Other clinical data, such as nulliparity, presence of diabetes mellitus, history of breast cancer, tamoxifen therapy or HRT were not significantly correlated with malignant progression of those lesions. The variables with a significant association with cancer progression were included in a multivariable logistic regression model. On multiple regression analysis (Table 4), all the independent variables lost their statistical significance, except for age and AUB with a OR of 1.08 (95% CI 1.03-1.14) and 1.87 (95% CI 1.87-6.65), respectively.

Discussion

With the increased use of diagnostic tools for the study of the uterine cavity, such as ultrasounds, hysterosonography and office hysteroscopy, the diagnosis of EPs are increas-

ing. In fact, literature reports a prevalence rate of EPs in asymptomatic women up to 20% [5], but it increases up to 40% in women with AUB [3].

EPs are often a benign lesions, but a risk of malignant progression was described that varies from 0.3% to 4.8% [5, 6, 22-25]. It might be useful to identify clinical, hysteroscopic, and demographical characteristics correlated with a high risk of malignant progression. In this study, the authors attempted to correlate some demographic and clinical factors with the rate of progression.

The present results show a high prevalence of premalignant and malignant lesions (5.8%), probably because the population had an gradually increasing average age compared to older studies. In univariate analysis, older age and in particular age over 60 years, hypertension, postmenopausal status, and AUB were identified as statistically significant factors associated with premalignancy and malignancy in EPs (Table 3). These results appear similar to the others published in literature. In fact, Costa-Paiva *et al.* and Antunes *et al.* identified age as a risk factor for malignant polyps [3, 9]. The same relationship was identified by the group of Baiocchi *et al.* [21]. Accordingly to the studies of Baiocchi *et al.*, Giordano *et al.*, Costa-Paiva *et al.*, and Savelli *et al.*, hypertension and postmenopausal status were also predictive of malignancy in women with EPs [3, 21, 22, 26]. In the present univariate analysis, AUB was identified as a risk factor for endometrial cancer in women with EPs. This association has been reported in most studies in the literature [3,23]. However, the present study showed a linear relationship between BMI and risk of endometrial malignancy. A recent study reports the same correlation between BMI >25 and endometrial cancer [27]. Many epidemiological studies show that overweight (BMI 25-29.9) and obese (BMI >30) patients have a higher tumor general risk, and also for endometrial neoplasia [28]. In a meta-analysis from WCRF/AICR (2007) from 28 case-control studies, the authors estimated a relative risk of 1.56 for endometrial cancer (95% CI: 1.45 – 1.66) for increments of five kg weight. Same results has been reported in two other meta-analysis by Renehan *et al.* and Crosbie *et al.* [29, 30]. It can be assumed that multiple factors lead to carcinogenesis. This factors probably involve insulin growth factor (IGF) -1 [23] and hyperestrogenism. Chronic hyperinsulinemia could provoke the estrogen-dependent tumors also by inhibiting the synthesis of sex hormone binding globulin and increase the bioavailability of estrogens [31]. In women with AUB, both in pre- and postmenopausal status, the surgical approach is often advocated [6, 23, 24]. However, data is limited on the management of asymptomatic women with an incidental diagnosis of EP [32]. Therefore, gynecologists must balance between the risk of endometrial cancer and the risk of complications of hysteroscopy and analgesia/anesthesia and the costs of the intervention [15, 16]. In fact, this procedure that often entails a hospital stay with an amount

healthcare costs, can involve a high risk of surgical and anesthesiologic complications much more in elderly women, and has to be performed by skilled gynecologist. Removing polyps is necessary because they are abnormal lesions. They have to be ruled out to exclude a malign lesion, by histological evaluation, nevertheless they have a low-risk of malignancy [22] and they could resolve spontaneously [12,33].

While some authors have recommended that all women with polyps undergo surgical evaluation, it may be better to evaluate each individual case. In fact, patients are subjected to the risks of surgery and intervention in a large number of cases and are associated with substantial healthcare costs. In general, asymptomatic premenopausal women are at low risk but should be observed carefully as occasionally cancer is detected [5]. While the present study benefits from the inclusion of a relatively large number of patients, the authors recognize some limitations. Because of the retrospective design of this study, severity and time lapsed from the onset of diabetes, hypertension, AUB, and obesity were not checked for risk assessment of EPs. Another limit of this study is that BMI, glucose levels, and blood pressure were examined as dichotomous variables and not as continuous variables. Moreover, the data were collected exclusively from medical charts that may be responsible for incomplete or inconsistent information.

Conclusion

Older symptomatic women with a diagnosis of EP need to have this lesion removed considering the higher risk of premalignant and malignant changes. Other coexisting factors, such as obesity, menopause, and hypertension must be taken into account because they may represent additional risk factors to cancerization.

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