Polycystic ovary syndrome and increased polyp numbers as risk factors for malignant transformation of endometrial polyps in premenopausal women

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**ABSTRACT**

Objective: To determine the pre-malignant and malignant potential of endometrial polyps and to assess whether different clinical parameters are associated with malignancy in the polyps of premenopausal women.

Methods: The clinical records of operative office hysteroscopic and resectoscopic procedures for endometrial polyps in 417 premenopausal women who attended Baskent University were examined over a retrospective period of 30 months. Only premenopausal patients were included in the study. Results: In 97.8% of women, histology showed benign endometrial pathology. In 2.2% of women, pre-malignant or malignant conditions were found in the polyp. Polycystic ovary syndrome (PCOS) and the presence of 2 or more polyps were associated with significant pre-malignant or malignant changes. Conclusion: The presence of irregular vaginal bleeding was not a predictor of malignancy in the polyp. Premenopausal women with PCOS and those with 2 or more polyps had an increased prevalence of polyp malignancy. These groups of patients, whether symptomatic or not, should be evaluated by hysteroscopic resection of the polyps.

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1. Introduction

Endometrial polyps are localized overgrowths of endometrial tissue that contain stroma, glands, and vessels, and are covered by epithelium. Although the etiology is not clear, in general polypoid endometrial tissue is considered as local hyperplasia of the endometrium. The malignant potential of endometrial polyps is controversial, but the prevalence of endometrial malignancy in polyps has been reported as only 2–3% [1,2].

The menopause might be a risk factor for malignancy that originates in endometrial polyps [3]. Some studies have reported malignancy in endometrial polyps only in postmenopausal women [4], whereas others have found malignancy only in symptomatic women [5]. However, there are studies in which cases of malignancy have been reported in endometrial polyps in premenopausal women and in asymptomatic postmenopausal women [6]. Other risk factors, including late menopause, obesity, arterial hypertension, advanced age, use of hormone therapy, and use of tamoxifen therapy in women with breast cancer, have also been identified [7].

A high proportion of endometrial polyps are found in asymptomatic women diagnosed by chance during routine vaginal sonography. The presence of abnormal bleeding, during either the menopause or the perimenopause, was not found to be a risk factor for pre-malignancy or malignancy by Ben-Arie et al., and this finding was confirmed by Savelli et al. [8]. By contrast, Shushan et al. [5] and Fernandez-Parra et al. [3] reported malignancy in endometrial polyps only in symptomatic women—that is, those with irregular uterine bleeding [5]. Fernandez-Parra et al. [3] failed to find malignancy in the polyps of premenopausal or asymptomatic patients.

The aim of the present study was to determine the prevalence of pre-malignant and malignant lesions in endometrial polyps resected by surgical hysteroscopy in premenopausal women, and to evaluate the association of pre-malignancy and malignancy with abnormal bleeding, infertility, polycystic ovary syndrome (PCOS), and some clinical characteristics, with a view to identifying factors related to the malignancy of polyps.

2. Materials and methods

In the present retrospective study, the clinical records of operative office hysteroscopic and resectoscopic procedures for endometrial polyps in 417 women from Baskent University were examined over a retrospective period of 30 months. Only premenopausal women were included in the study, and patients who had been on tamoxifen were excluded. Before undergoing procedures, all women gave consent for their data to be used for future trials. Ethics approval was not required.

The diagnosis of PCOS was based on the Rotterdam criteria [9]. All women with oligomenorrhea (an irregular cycle duration of >45 days or <6 menstrual periods per year) and/or anovulation who also had at least 1 of the characteristics of hyperandrogenism (a hirsutism score of >7 according to Ferriman and Gallway [10], and/or an elevated serum testosterone level) were diagnosed with PCOS after all other causes of hyperandrogenism were excluded.

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Diagnostic hysteroscopy was performed in women with abnormal saline sonohysterography. Indications of sonohysterography were the presence of abnormal uterine bleeding or suspicion of endometrial polyps during routine vaginal sonography. Abnormal uterine bleeding was defined as irregular vaginal bleeding.

The mean diameter of the polyp was obtained by direct ultrasound measurements. Baseline patient characteristics such as age, body mass index, history of hypertension, and diabetes were recorded by accessing the clinical history of the participants. An abnormal outcome was defined by the presence of endometrial cancer or atypical hyperplasia. Atrophic fibroglanular polyps and typical hyperplastic endometrial lining were considered benign outcomes. When multiple polyps were present, the polyp with the worst pathologic report was considered for the present study.

All women included in the study underwent an endometrial evaluation at the gynecologic ultrasound unit. Scans were performed with a real-time ultrasound scanner (Advanced Laboratories 3000, Bothell, Washington, USA) equipped with a 5–9-MHz transvaginal probe and a Voluson 730 (Kretztechnik, Zipf, Austria) equipped with a 5–9-MHz transvaginal probe. The ultrasonographic diagnosis of an endometrial polyp was based on the presence of the bright edge of the polyps. The largest polyp diameter measured during the ultrasonography scan was recorded. Diagnostic hysteroscopy was performed by using a saline infusion as a distention medium, and a Storz endoscope (Tuttlingen, Germany) with a 5-mm diagnostic sheath.

When polyps were found in a patient, they were removed in the same session either by operative hysteroscopy or by resectoscopic polypectomy. The operative procedure was performed under general anesthesia. The specimens were placed in 10% formaldehyde for histologic examination. Histopathologic diagnosis distinguished between non-polypoid lesions that were mistakenly diagnosed as polyps (leiomyoma, atrophic, proliferative, or secretory endometrium) and endometrial polyps, which were classified as benign, hyperplastic (simple or complex hyperplasia), pre-malignant (simple or complex hyperplasia with atypia of cells), and malignant (harboring carcinoma).

Endometrial hyperplasia and adenocarcinoma were defined histopathologically as follows. Endometrial simple hyperplasia was defined by moderate distortion of the endometrial architecture, with crowding of glands, cystic dilation, and noncomplex budding; the lining epithelium of the glands was pseudostratified, showing mitotic activity with no atypia of cells. Endometrial complex hyperplasia was defined by crowding of branched complex glands, lined by stratified mitotically active cigar-shaped cells. Atypical simple hyperplasia was defined by an architecture similar to that of simple hyperplasia, but the glands were more irregular; the glands were lined by atypical cells with round hyperchromatic nuclei and granular chromatin. In atypical complex hyperplasia, the architecture was similar to that of endometrial complex hyperplasia, but the glands were crowded and lined with atypical cells with round pleomorphic nuclei. Endometrial carcinoma was defined by crowded malignant tubular glands varying in size and invading the stroma. The glands were lined by cells showing marked atypia and mitotic activity. The prevalence of pre-malignant lesions, including endometrial hyperplasia with atypia of cells, and the risk of adenocarcinoma confined to endometrial polyps were evaluated in different subgroups of women.

The results are presented as mean ± SD. Statistical analysis was performed by Student t test, χ² test and Fisher exact test, and the odds ratio (OR) and 95% confidence interval (CI) values were calculated where appropriate. A P value of less than 0.05 was considered significant. On the basis of the present study results, a retrospective power analysis was made.

The calculation of sample size was based on a comparison of event rates between 2 independent cohorts. For polyp number, it was calculated that a sample size of 301 women (66 cases and 235 controls) would be required to detect an increase in malignancy from 0.3% to 8.8%, using a 2-sided significance test of 0.05 and a power at least 90%. Because 417 women (91 cases and 326 controls) were enrolled, the study had adequate power to demonstrate that more than 1 polyp is associated with malignancy. For PCOS status, it was calculated that a sample size of 342 women (43 cases and 299 controls) would be required to detect an increase in malignancy from 1.1% to 9.6%, using a 2-sided significance test of 0.005 and a power at least 80%. Because 417 women (52 cases and 365 controls) were enrolled, the study had adequate power to demonstrate that PCOS status is associated with malignancy.

### 3. Results

In the present study, the clinical records of 417 premenopausal women with endometrial polyps were examined (Table 1). The mean age of the women in this study was 34.9 ± 6.3 years (mean ± SD). In 97.8% of women, benign endometrial pathology was detected; however, pre-malignant pathology and malignant pathology were detected in 2.2% of patients (Table 2).

The participants were divided into 2 groups according to whether the polyps had benign or malignant histology (Table 3). The mean age of the women was similar between those with benign pathology and those with pre-malignant–malignant pathology. The incidence of hypertension, diabetes mellitus, and abnormal bleeding was similar between the 2 groups. There was no relationship between polyp size and the appearance of carcinoma. However, the incidence of PCOS (P < 0.01) and polyp number (P < 0.01) were higher in women who had a pre-malignant or malignant lesion.

Women with PCOS had significantly more abnormal histology than women without PCOS (9.6% versus 1.1%; OR, 9.6; CI, 2.5–37). Women with 2 or more polyps had a prevalence of pre-malignant or malignant polyps that was 31.3 times greater than that of women with 1 polyp (95% CI, 3.9–254; Table 4).

In a correlation analysis using age, body mass index, history of hypertension and diabetes, PCOS status, polyp size and number, and presence of abnormal uterine bleeding, only polyp number and PCOS status were significantly associated with pre-malignant and malignant lesions (P < 0.01).

### Table 1

<table>
<thead>
<tr>
<th>PCOS and symptoms in the study group.</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCOS</strong></td>
<td>52 (12.5)</td>
</tr>
<tr>
<td>No PCOS</td>
<td>365 (87.5)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>321 (77)</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>96 (23)</td>
</tr>
</tbody>
</table>

**Abbreviation:** PCOS, polycystic ovary syndrome.

*Values are given as number (percentage).*

### Table 2

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>408 (97.8)</td>
</tr>
<tr>
<td>Endometrial polyps</td>
<td>364 (87.3)</td>
</tr>
<tr>
<td>Endometrial polyps with simple hyperplasia (no atypia)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Myoma</td>
<td>33 (7.9)</td>
</tr>
<tr>
<td>Polypoid adenomyoma</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Placental tissue</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Pre-malignant and malignant</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Endometrial polyps with complex hyperplasia and atypia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Polypoid adenomyoma and atypia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>7 (1.7)</td>
</tr>
</tbody>
</table>

*Values are given as number (percentage).*
Abbreviation: PCOS, polycystic ovary syndrome.

In the present study, polyp number and PCOS were found to be factors associated with malignancy in endometrial polyps during the premenopausal period. Among the large sample size of polyps resected by hysteroscopy, the prevalence of pre-malignancy or malignancy was 2.2% (0.5% hyperplasia with atypia and 1.7% endometrial adenocarcinoma). The prevalence of endometrial cancer in the PCOS group was high (7.7%).

Published data are conflicting with respect to the incidence of malignancy. One study reported an incidence of endometrial malignancy as low as 0.8%, but a prevalence of hyperplasia with atypia of 3.1%, and a high prevalence of hyperplasia without atypia (25.7%) [7]. Another study involving one of the largest sample sizes (653 polyps) reported a prevalence of malignancy of 1.5% [8]. These variations in reported prevalence have been attributed to the different methods used for the diagnosis and removal of polyps: some are based on the results of uterine curettage and others on hysteroscopy. At present, hysteroscopy is considered the gold standard for the diagnosis of endometrial polyps, resulting in high sensitivity and specificity [11,12]. Another explanation for the variations in results might be attributed to the characteristics of the different study populations, which have included symptomatic and asymptomatic patients, and women at high risk for malignancy such as those with postmenopausal bleeding and users of tamoxifen, among other factors. In the present study, only premenopausal patients were included, and none of the patients had taken tamoxifen.

Little is known about the incidence of malignancy arising from a polyp in women of different menopausal status or with different symptoms. In the present study, the incidence of malignancy in women diagnosed as having a polyp was 1.7%, a value within the range of those reported by others (0.8–4.8%) [2,5,6,13–15]. Of the risk factors (age, presence of abnormal bleeding, hypertension, diabetes mellitus, polyp number, polyp size, and PCOS status) analyzed, only polyp number and PCOS were identified as factors associated with malignancy in endometrial polyps during the premenopausal period.

Women with PCOS had a prevalence of pre-malignant or malignant polyps that was 31.3 times greater than that of women without PCOS (95% CI, 2.5–37). In contrast to previous studies, PCOS was found to be a significant factor predicting malignancy in the polyp. Endometrial hyperplasia occurs in 35% of women with PCOS who are not receiving either contraceptive steroids or periodic progesterin withdrawal [16]. Those at highest risk of endometrial hyperplasia are women who have fewer than 4 menses per year and an endometrial thickness, assessed by ultrasound, of more than 7 mm [17]. An association between PCOS and endometrial malignancy was first suggested in 1949. Since then, several studies have appeared to support this association, and it is common practice among gynecologists and physicians to prescribe hormonal treatment to reduce this perceived risk, although there is no consensus on the subgroup of patients with PCOS in whom this treatment is required. The mechanisms underlying any association are also unclear, but it is again widely assumed that chronic anovulation, which results in continuous estrogen stimulation of the endometrium unopposed by progesterone, is a major factor. Obesity, hyperinsulinemia, and hyperandrogenism, which are also features of PCOS, are risk factors for endometrial malignancy, but it does not necessarily follow that the incidence or mortality from endometrial malignancy is increased in women with this syndrome [16].

Some studies have suggested that older age, menopause status, polyp number, and polyp size are significant factors predicting malignancy in the polyp, although the positive predictive value for malignancy was found to be low [3,5]. In addition, some studies found malignancy arising from a polyp only in premenopausal women [4,13], whereas others found malignancy only in symptomatic women [5]. However, malignancy arising from a polyp has also been reported in premenopausal women and postmenopausal women without vaginal bleeding [6]. Malignancy was found to be more frequent in women who had 3 or more polyps [3,5]. Few studies have described the ability of hysteroscopy to diagnose malignancy in polyps. Marcone et al. [18] described atypical features of polyps visualized by hysteroscopy. The likelihood of observing carcinoma or atypical hyperplasia in an atypical polyp by hysteroscopy is low (21%), but in normal polyps the likelihood that the polyp will be benign is 99%. It should be noted, however, that histologic examination sometimes detects malignancy in polyps that appear normal by hysteroscopy, as others have pointed out [19]. In the present study, all of the participants were premenopausal and the incidence of abnormal pathology was not related to the presence of abnormal bleeding. Women with 2 or more polyps had a prevalence of pre-malignant or malignant polyps that was 31.3 times greater than that of women with 1 polyp (95% CI, 3.9–254).

The present results showed a high prevalence of malignancy in both symptomatic and asymptomatic premenopausal women with PCOS and those with 2 or more polyps. We propose that during the premenopausal period active management of hysteroscopic endometrial polypectomy should be offered to women with PCOS and those with more than 1 polyp, whether symptomatic or not. Moreover, although screening for endometrial cancer is not recommended, we are aware of many women who undergo “routine” pelvic sonography. Evidence-based management of incidental ultrasound findings such as endometrial polyps has gained importance for the modern gynecologist; therefore, understanding the significance of both symptomatic and asymptomatic endometrial polyps and their proposed management will be of great value.

Conflict of interest

The authors have no conflicts of interest.

References


