SHOULD WE BE MORE AWARE OF ENDOMETRIAL CANCER IN ADOLESCENTS?

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Abstract

Although endometrial cancer is generally diagnosed in women after menopause, it may incidentally develop in young women or even in adolescents. Diagnostic tools should be applied in young teenage girls complaining of abnormal genital bleeding, particularly those with hereditary cancer syndromes (such as Cowden or Lynch syndromes). Adolescents affected by polycystic ovary syndrome and obesity may also be at increased risk for the development of atypical endometrial hyperplasia and endometrial cancer, and should be carefully managed when the distressing symptoms occur. In the present article, we briefly summarize the principal clinical correlates associated with endometrial cancer in adolescents.

Key words: adolescent, conservative treatment, Cowden syndrome, endometrial cancer, fertility preservation, Lynch syndrome

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer with a rising rate of incidence. It is estimated that by 2030 this type of cancer will have become the sixth most common cancer overall, and the third most common in women [1]. This pathology affects mostly postmenopausal women and only approximately 5-14% of the cases occur in patients younger than 40 years of age [2]. EC is rarely diagnosed in adolescents, although during the last two decades an increase in the number of teenagers affected by this disease has been observed [3]. This may be partially related to the increase in childhood and adolescent obesity and its endocrine and metabolic consequences [2]. The youngest EC patients reported worldwide were 14 and 15 years old [4-6].

Based on pathological findings and clinical outcomes, EC has been subdivided into two types [7-11]. Type I represents the majority of cases, is associated with unopposed estrogen stimulation, and is often preceded by atypical endometrial hyperplasia. Histologically, well (grade 1) and moderately (grade 2) differentiated endometrioid endometrial adenocarcinomas are frequently found. Risk factors responsible for the development of type I cancer, such as obesity, early menarche and late menopause, are strictly related to the imbalance in exposure to estrogen and progesterone [11, 12]. In contrast, type II is estrogen-independent, believed to be developing on the basis of endometrial atrophy, and derived from endometrial intraepithelial neoplasia [9, 11]. There is a lack of clearly defined risk factors for this type of cancer. Type II tumors are generally poorly differentiated (grade 3) and patients affected by such lesions have poorer outcomes compared with type I [10, 11]. Finally, EC subtypes demonstrate different genetic abnormalities, as well as immunohistochemical markers expression [8, 13-16]. Table I presents the principal features of type I and type II EC after a recent handbook of oncology [17].

In postmenopausal women, a typical symptom of EC is abnormal uterine bleeding. In menstruating women, EC may manifest as menorrhagia, abnormal vaginal/uterine bleeding or even serosanguinous discharge [18]. In most cases, EC is recognized at an early stage, however, in more advanced disease, the symptoms are related to the size of the tumor and the invasion/disseminatio n of the cancer. Symptomatic patients should be carefully examined with ultrasound imaging and endometrial biopsy or dilatation and curettage should be performed. Pap smear should be done to differentiate from cervical pathology. When the disease is limited to the uterus only, clinically speaking stage I, the prognosis is favorable, with a 5-year survival rate from 76% to 100% of the patients. Magnetic resonance (MRI) and computed tomography
(CT) are helpful to preoperatively assess the stage of the
disease in order to plan the surgical protocol [10, 18].
Treatment of EC in adolescents and young women
(below 25 years of age) is challenging [19]. In older
patients, treatment protocols mostly consist of a broad
surgical resection: total hysterectomy with bilateral
salpingo-oophorectomy. In case of EC of grade 2 or 3,
depth invasion of the myometrium, non-endometroid
histological type, or the presence of an extrauterine
tumor, pelvic and para-aortic lymphadenectomy should
additionally be performed. Adjuvant radiation therapy is
reserved for advanced stages. In young patients, the aim
is not only to perform radical treatment, but if possible
also to apply conservative therapeutic options to preserve
their fertility [20].

In the case of fertility preserving approaches, oral
progestins may be applied for patients with EC grade
1 and stage I. Monitoring of response is crucial for the
safety of this approach. Endometrial sampling should be
performed every 3 months. In a review by Chiva et al. [21],
a short-term complete response rate in 76% of early-stage
EC patients was reported. A long-term complete response
was observed in 66% of them, whereas 34% relapsed. Most
patients display a response during the first 3 months of
treatment. It is important that almost 40% of the successfully
treated patients conceived afterwards and had uneventful
pregnancies [20, 22]. Another study, Fahri et al. [23],
reported on successful conservative treatment of grade
1, stage Ia ECs in two 15-year-old girls. Progestrone was
administered and the patients were asymptomatic, one at
3 months and another at 10 years of follow-up [23]. An
alternative to such a therapy may be the application of a
progestin-releasing intrauterine device (IUD), particularly
in adolescents and young women [22]. Some authors
reported that IUD is superior to oral progestin therapy with
higher rates of regression of complex atypical endometrial
hyperplasia and early-stage EC [22]. In many women, this
approach is better tolerated than oral progestins, however,
a proportion of patients may experience amenorrhea,
abnormal uterine bleeding or nausea related to the local
and systemic actions of the progestin released. Moreover,
the levonorgestrel-releasing intrauterine device IUD was
unable to preserve fertility in a 25-year-old-woman with
1 grade EC [24]. In the Montz study [25], all the patients
(N = 6) who had complete regression of grade 1 and
stage Ia EC and continued treatment with progesterone-
releasing IUD, were free from the disease at 3 years from
the beginning of treatment. Minig et al. [26] reported on
a 95% complete response rate in patients with atypical
endometrial hyperplasia (N = 20) and a 57% complete
response rate in those with grade 1 EC (N = 14) treated
with the insertion of a levonorgestrel-releasing IUD for 1
year supplemented by a 6-month course of a gonadotropin-
releasing hormone analog. Progression of disease occurred
in 5% of the patients in the group with atypical endometrial
hyperplasia, and in 28% with EC. Disease recurrence was
observed in 20% of the atypical endometrial hyperplasia
group, and 14% of the grade 1 endometrial cancer group,
with an average relapse time of 36 months [26]. Reports
about the use of IUD in the cases of grade 2 endometrial
cancer also exist, but the data are limited. Brown et al. [22]
described the application of an IUD in an 18-year-old patient
diagnosed with grade 2 endometrial adenocarcinoma who
remained free from disease at the 13-month follow-up
from initial IUD placement.

EC is a rare condition in children and adolescents
and, therefore, the literature in general consists of case
studies [4, 6, 27-29].

For example, Liu et al. [29] described a 15-year-old
morbidly obese girl (Body Mass Index: BMI: 50.2),
who complained of asthenia and menorrhagia lasting
6 months. At examination, the uterus was enlarged to
approximately 14 gestational weeks, and the hemoglobin
level was 66 g/L. Ultrasound examination revealed an
intrauterine mass, which was confirmed during diagnostic
hysteroscopy. Histopathologic evaluation revealed a
moderate to well-differentiated endometrioid type EC.
In MRI, myometrial invasion was reported. The patient
underwent total abdominal hysterectomy with right
salpingo-oophorectomy, partial dissection of the left
ovary and pelvic and para-aortic lymphadenectomy. Final
pathologic results confirmed grade 1 EC with myometrial

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**Table I. Characteristics of type I and type II endometrial cancer. Adapted from Chu et al. [17].**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed estrogen stimulation implicated as cause</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lesion growth</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Precancerous condition</td>
<td>Atypical endometrial hyperplasia</td>
<td>EIN (Endometrial Intraepithelial Neoplasia)</td>
</tr>
<tr>
<td>Histologic type(s)</td>
<td>Endometrioid</td>
<td>Serous or clear cell</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Depth of invasion</td>
<td>Superficial (usually)</td>
<td>Deep (often)</td>
</tr>
<tr>
<td>Prominent genetic changes</td>
<td>PTEN or KRAS mutations, microsatellite instability</td>
<td>TP53 mutation</td>
</tr>
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invasion of less than 50% of the muscle's thickness, and polycystic ovaries. Positive expression of progesterone receptors (PRs) and weak positive expression of estrogen receptors (ERs) were found by immunohistochemistry. During a 5-year follow-up, the patient was asymptomatic. In this case, in spite of obesity, serum hormonal levels suggested anovulation and both ovaries were polycystic, contributing to her risk factors for endometrial pathology. It needs to be underlined that in case of persistent uterine bleeding resulting in anemia, the existence of EC should always be taken into consideration during the diagnostic process, even in young teenage girls [29, 30].

In the last few decades, a significant increase in childhood and adolescent obesity has been observed. Some data support the opinion that obesity is the strongest risk factor for the development of EC [1]. Overweight and obese teenagers are more likely than their slimmer peers to have gynecological complications during adolescence and later life [2]. Obesity is related to higher levels of circulating estrogens (in postmenopausal women) and lower concentrations of sex-hormone binding globulin (SHBG) to which they bind [11].

Chronic anovulation, often present in obese adolescents, increases the risk of endometrial hyperplasia and EC due to the effect of unopposed estrogen stimulation. The earlier menarche and sexual development observed in obese adolescents are also related to the increased risk of EC. Many reports confirmed a strong association between obesity and the occurrence of EC [31-33]. The authors of two studies found out that high BMI at the age of 18 to 20 was significantly associated with a risk of EC [31, 32]. Weight gain over 35% of the upper normal limit in early adulthood showed a trend to develop EC 10 years earlier than in women without weight excess. Interestingly, in another study, already a 5% increase in weight from baseline at the age of 25 was found to increase the risk of EC after menopause [33].

The association between EC and type 2 diabetes mellitus has also been reported worldwide [34]. Hyperinsulinemia, typical for type 2 diabetes, significantly increases the levels of bioactive estrogens by decreasing the hepatic production of SHBG [1, 34]. Mitamura et al. [6] reported on EC in a 14-year-old teenager with polycystic ovary syndrome who presented with menorrhagia. Initially, she was treated with a combination of estrogen and progesterin, without success. Ultrasound examination demonstrated an enlarged uterus, thickened endometrium, and polycystic ovaries. Endometrial biopsy revealed grade 2 endometrioid adenocarcinoma, and MRI and CT confirmed the lack of invasion of the myometrium. Expression of ERs and PRs were positive in 60% and 90% of the specimens studied, respectively. The patient received 400 mg of medroxyprogesterone acetate p.d. for a month and in repeat biopsy no histological change was noted. The authors suggested that invasive cancer can be suspected when the tumor turns out insensitive to progestin treatment for one month, whereas the lack of response after a 3-month treatment indicates failure. Final pathological examination performed after surgery (hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection) confirmed the preoperative diagnosis. Immunohistochemical evaluation revealed the presence of p53, the epidermal growth factor receptor, and the human epidermal growth factor receptor 2 expression in 90%, 90% and 60% of the tumor cells examined, respectively. No mutations at exons 7 or 8 of phosphatase and tensin homolog gene (PTEN) or K-ras codon 12 mutations were detected. Moreover, no dominant-negative TP53 mutation was found by a yeast functional assay. At a one-year follow-up, the patient demonstrated no recurrence [6].

In another report, El Naggar et al. [5] described a 15-year-old girl with Cowden syndrome diagnosed with EC. In Cowden syndrome, PTEN mutations are present, antagonizing the phosphatidylinositol 3-kinase (PI3K/AKT) and mitogen-activated protein kinase (MAPK) pathways [4, 28]. These mutations are associated with an increased lifetime risk for breast, renal, thyroid, colorectal and endometrial carcinomas. For EC, this risk increases up to 19%. It is worth underlining that PTEN mutations are present in approximately 40% of endometrial adenocarcinomas, therefore it is important to recognize the features of Cowden syndrome, as well as clinical manifestations of associated cancers which may develop in adolescence [5]. The patient described complained of 5- to 7-day-long heavy uterine bleedings occurring twice or thrice monthly. In speculum examination, a polyp in the external cervical os was found and removed by ablation. Pathological examination revealed grade 1 EC arising from an endometrial/cervical polyp. The diagnosis was confirmed by subsequent hysteroscopy and radical surgical treatment was performed. At follow-up after 3 years, the patient was asymptomatic. Earlier, an adolescent girl affected by grade 2 EC who harbored germline PTEN mutations was described by Schmeler et al. [28]. More recently, Baker et al. [4] presented a case of EC in a 14-year-old girl with Cowden syndrome who was also diagnosed with fibrocystic breast disease and colon polyps at the age of 20. Finally, Kocova et al. [35] described the case of a 21-year-old with Turner syndrome who developed EC with no history of previous hormone replacement therapy. There are reports of ECs manifesting after prolonged hormonal therapy with unopposed estrogens but the development of such a malignancy in a young subject with Turner syndrome is uncommon. In this study, the patient experienced heavy and prolonged uterine bleedings. Ultrasound examination revealed an enlarged uterus with a polyp in the cervical canal. After dilatation and curettage procedure, EC in polypo was initially diagnosed. The patient was treated with depot medroxyprogesterone acetate for 6 months, but then her parents requested surgical treatment. Interestingly, the postoperative pathological results of the hysterectomy specimen did not reveal any carcinomatous tissue [35].

Other germ-line mutations, such as those associated with Lynch syndrome, also increase the risk for EC. The estimated cumulative lifetime risk for EC in Lynch syndrome varies, ranging from 21% up to 71% [36]. Mutations in any of 5 DNA-mismatch-repair genes cause this genetic disorder, also known as hereditary non-polyposis colorectal cancer or HNPCC. Mutation carriers are at increased risk for many malignancies, including EC and colon, stomach, ovary, skin, urinary
tract, biliary tract, and brain cancers [37]. Of clinical importance, in patients with germ-line mutations associated with Lynch Syndrome, prophylactic hysterectomy and bilateral salpingo-oophorectomy has been shown to fully prevent the possible development of uterine and ovarian malignancies when compared with controls who did not undergo prophylactic surgery [38]. However, this line of prevention is dedicated only to patients who have completed their childbearing.

In conclusion, although EC is generally diagnosed in women after menopause, it may incidentally develop in young women or even in adolescents. Diagnostic tools should be applied in young teenage girls complaining of abnormal genital bleeding, particularly in subjects with hereditary cancer syndromes (such as Cowden or Lynch syndromes). Adolescents affected by polycystic ovary syndrome and obesity are also at increased risk for the development of atypical endometrial hyperplasia and EC, and should be carefully managed when the distressing anxious symptoms occur.

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REFERENCES


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