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Is the endometrial evaluation routinely required in patients with adult granulosa cell tumors of the ovary?

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HIGHLIGHTS

- Granulosa cell tumors (GCTs) are the most common estrogen-secreting ovarian tumors.
- Steroid hormones play a major role in the development of atypical hyperplasia and endometrioid-type endometrial cancer.
- Endometrial carcinoma and atypical hyperplasia were rarely observed in GCT patients under the age of 40 years.

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ABSTRACT

Objective. Granulosa cell tumors (GCTs) are the most common estrogen-secreting ovarian tumors; perhaps due to the persistent hyperestrogenism, a wide spectrum of associated endometrial pathologies ranging from endometrial hyperplasia to carcinoma has been documented in patients with GCTs. The aim of this study is to evaluate the incidence of endometrial pathologies in a large series of GCT patients treated in MITO centers.

Methods. A retrospective multi-institutional review of patients with granulosa cell tumors of the ovary treated or referred to MITO centers was conducted. Descriptive statistics were used to characterize the patient population and to assess the association of GCT and endometrial abnormalities at the time of diagnosis; multivariate regression analysis was also performed to identify independent predictors of endometrial abnormalities.

Results. A total of 150 patients with primary adult GCT was identified. During the preoperative assessment, endometrial pathology was found in 35.9% of symptomatic patients and in 90.9% of asymptomatic women with endometrial thickening at transvaginal ultrasound. At the time of surgery, hyperplasia was documented in 29.2% of patients, whereas endometrial cancer occurred in 7.5% of patients. Almost all of the patients (97.6%) with endometrial hyperplasia were older than 40 years. All patients with endometrial cancer were older than 40 years and postmenopausal.

Conclusions. Endometrial carcinoma/atypical hyperplasia were commonly observed in GCT patients >40 years; based on these data, endometrial sampling should be performed in symptomatic women at least 40 years of age. In asymptomatic women <40 years, endometrial sampling is of low yield.

Introduction

Granulosa cell tumors (GCTs) of the ovary account for an estimated 2–5% of ovarian cancers [1]. This tumor is the most common among the ovarian sex-cord stromal tumors and its cells show many morphological, biochemical and hormonal features of granulosa cells, including

Abbreviations: GCT, granulosa cell tumor; MITO, Multicenter Italian Trials in Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; US, ultrasound; WHO, The World Health Organization; IGF, insulin-like growth factor; IGF-BPs, insulin-like growth factor binding proteins; IGF-R, insulin-like growth factor cell surface receptors.

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estrogen biosynthesis. Prolonged exposure of the endometrium to the high levels of estradiol produced by granulosa cells is responsible for the development of several types of endometrial pathology [2]. Endometrial hyperplasia and concomitant endometrial cancer have been reported in up to 50% and 10% of GCT patients respectively [3,4]. Endometrial adenocarcinoma occurring in the setting of GCT is usually well-differentiated, early stage and associated with a good prognosis [5].

Current guidelines for treatment of this malignancy recommend comprehensive surgical staging including bilateral salpingo-oophorectomy, hysterectomy, peritoneal cytology, omentectomy, endometrial biopsy, peritoneal biopsies and removal of any suspicious lesion [6,7]. In patients who wish to preserve their fertility, conservative treatment with unilateral salpingo-oophorectomy can be performed, if disease is confined to one ovary and endometrial biopsy is negative [8].

The aim of this study is to evaluate the incidence of endometrial pathologies in a large series of GCT patients managed by several Institutions participating to the Italian Cooperative MITO (Multicenter Italian Trials in Ovarian Cancer) Group.

Materials and methods

MITO-9 (Multicenter Italian Trials in Ovarian Cancer) is an Italian multicenter retrospective study aiming at describing clinical characteristics and treatment strategies of rare ovarian tumors.

A series of 150 patients diagnosed with primary adult GCTs of the ovary treated or referred after primary treatment to MITO centers from 1965 to 2013 was retrospectively analyzed. In order to be included in the analysis, patients needed to have at least one clinical visit at a MITO Institution where a review of the histologic specimens had to be performed.

Patients with juvenile GCTs of the ovary were excluded from the study.

Patients' data were recorded in a database which included information about age at diagnosis, clinical presentation, type of surgery, intra-operative findings and surgical outcome, stage, histology, adjuvant chemotherapy, relapse characteristics and relapse treatment, and follow-up.

Surgery was the first treatment for all patients. Surgical staging was considered complete when including bilateral salpingo-oophorectomy, hysterectomy, peritoneal washing, multiple peritoneal biopsies, omental biopsy or omentectomy, and biopsy of any suspicious area.

Fertility-sparing surgery, defined as the preservation of the uterus and one ovary, was performed in young patients who desired to preserve fertility, only in case of disease confined to one ovary. In case of conservative surgery, endometrial biopsy aimed at ruling out a concomitant uterine disease should be performed.

The staging system used for GCT is the same applied for epithelial ovarian cancer (FIGO staging system) [9].

Endometrial tissue biopsy was obtained before surgical treatment in case of abnormal bleeding or endometrial thickening at transvaginal ultrasound examination (endometrial stripe ≥4 mm in postmenopausal women). During surgery endometrial tissue was sampled by curettage of uterine cavity or by hysterectomy.

Endometrial hyperplasia was categorized into four groups according to The World Health Organization (WHO) classification [10]: simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia, and complex atypical hyperplasia. Simple hyperplasia not otherwise specified and glandular cystic hyperplasia were all classified as simple hyperplasia without atypia. Complex hyperplasia or atypical hyperplasia were both classified as complex atypical hyperplasia.

In the absence of endometrial hyperplasia or cancer, endometrial tissue was defined normal.

Statistical analysis

Descriptive statistics were used to characterize the patient population and to assess the association of GCT and endometrial abnormalities at the time of diagnosis.

Patients were divided into two groups according to age at diagnosis: those younger than 40 years and those 40 years or older; we compared these two groups in terms of incidence of endometrial pathologies.

Statistical analysis was performed with the χ^2 analysis to compare frequencies among the two groups.

Multivariate regression analysis was performed to identify independent predictors of endometrial abnormalities.

Differences were considered statistically significant at $p < 0.05$.

The SPSS statistical software program (SPSS Inc., Chicago, IL) was used.

Results

A total of 150 patients with primary adult GCTs of the ovary were evaluated for the present analysis. The median age of patients was 50.3 years (range: 26–82).

The most common presenting symptoms were the presence of a mass and/or abdominal distension (39.8%) followed by abdominal and/or pelvic pain (30.2%) and menstrual irregularities/abnormal bleeding (26%), while only 4% of patients presented ascites at the time of initial diagnosis.

Baseline characteristics at the time of diagnosis of GCT are shown in Table 1.

Fig. 1 shows both the distribution of cases according to time of endometrial evaluation, and type of endometrial abnormalities. Given the main endpoint of the study, 10 patients were excluded since hysterectomy have been already performed before GCT diagnosis, thus leaving 140 patients available for final analysis. Moreover, we excluded from the final analysis 19 patients who underwent fertility-sparing surgery without endometrial evaluation.

Preoperative endometrial evaluation was performed in 50 patients (41.3%) due to abnormal bleeding (N = 39) or US assessed endometrial thickening (N = 11). Among patients undergoing endometrial sampling due to abnormal bleeding, 6 (15.3%) had simple hyperplasia without atypia, 1 (2.6%) had simple atypical hyperplasia, 1 (2.6%) had complex hyperplasia without atypia, 3 (7.7%) had complex atypical hyperplasia and 3 (7.7%) had endometrial cancer. Overall, endometrial pathology was found in 35.9% of symptomatic patients during the preoperative assessment.

Table 1
Baseline patient characteristics at the time of GCT diagnosis.

Characteristics	No. of patients (%)
Age at diagnosis (years), median (range)	51.7 (26–82)
20–40	32 (21.3)
41–60	80 (53.4)
61–80	36 (24)
>80	2 (1.3)
Stage	
I	114 (76)
II–III–IV	36 (24)
Surgery	
Fertility sparing	46 (30.7)
Radical surgery	94 (62.7)
Endometrial histology[a]	
Normal	94 (67.2)
Hyperplasia	31 (22.1)
Cancer	8 (5.7)
No histology	7 (5)

[a] Ten patients were excluded from the analysis since a hysterectomy had been performed before GCT diagnosis.

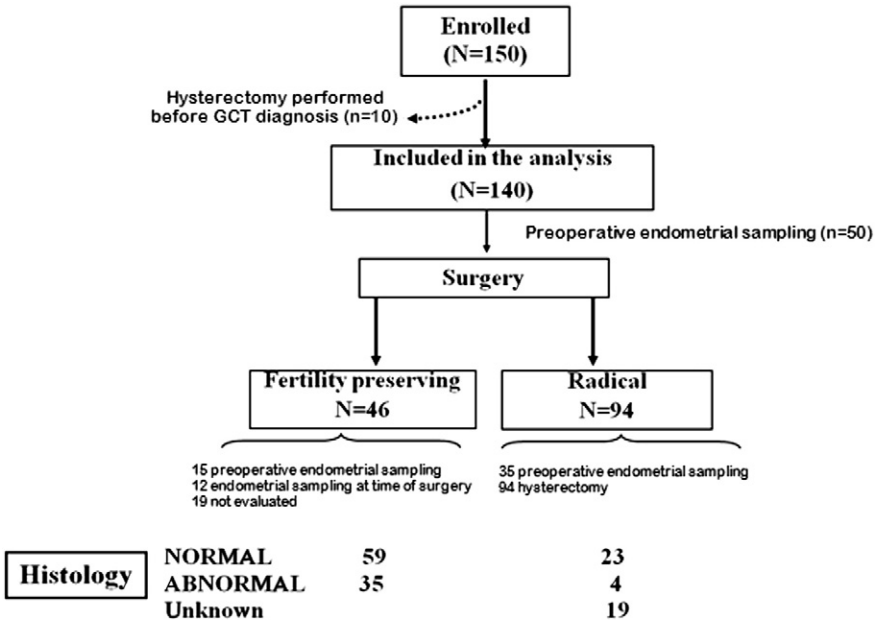

Fig. 1. Distribution of cases according to time of endometrial evaluation, and type of endometrial abnormalities.

Among patients undergoing endometrial sampling due to endometrial thickening at transvaginal US, endometrial hyperplasia was observed in 10 (90.9%).

As shown in Fig. 1, fertility-sparing surgery was performed in 46 patients (30.6%): endometrial histology was known in 27 cases, as documented at preoperative evaluation due to abnormal bleeding/endometrial thickening (N = 15), or at the time of surgery (N = 12). Pathologic endometrium was found in 4 cases (14.8%).

Conversely, radical surgery was performed in 94 patients (62.7%), and 35 of them showed endometrial abnormalities (37.2%); there was a 100% concordance between endometrial histology documented in uterine tissue specimens at the time of radical surgery and that obtained at preoperative evaluation in 35 cases (data not shown).

Overall, cases for which endometrial tissue was obtained at the time of surgery were 106 (87.6%); hyperplasia was found in 31 patients (29.2%), 19 of whom (61.3%) had simple hyperplasia without atypia, 3 patients (9.7%) had simple atypical hyperplasia, 3 patients (9.7%) had complex hyperplasia without atypia and 6 patients (19.3%) had complex atypical hyperplasia.

In order to perform univariate and multivariate analyses of parameters potentially associated with endometrial histology abnormalities, patients were divided into two groups according to age at diagnosis: those younger than 40 years and those 40 years or older; moreover, patients were grouped according to stage I versus >stage I disease; finally, tumor size and menstrual irregularities were also considered.

In univariate analysis age > 40 showed a statistically significant, direct association with endometrial hyperplasia/cancer ($p \leq 0.001$, Table 2). Endometrial abnormalities are common in patients >40 years of age: in particular, 97.6% of patients bearing endometrial hyperplasia were older than 40 years ($p = 0.020$, Table 2). Endometrial hyperplasia is rarely observed in GCT patients <40 years of age: only one patient younger than 40 years had atypical hyperplasia. Moreover, all patients showing endometrial carcinoma were older than 40 years.

Even the presence of menstrual irregularities/abnormal bleeding is significantly correlated with endometrial hyperplasia/cancer ($p \leq 0.001$, Table 2). We found a higher incidence of endometrial pathologies among patients presenting with abnormal bleeding compared to asymptomatic women at the time of diagnosis (35% versus 19.2%).

The independent, direct association of older age and menstrual irregularities/abnormal bleeding with endometrial abnormalities was maintained also in multivariate analysis (Table 2).

Finally, we were prompted at evaluating clinical outcome of cases (n = 46) who had preserved the uterus at the time of GCT diagnosis: after a median follow-up of 78 months, no endometrial abnormalities were recorded. Three patients (6.5%) had a recurrence but no patient with a recurrence developed endometrial pathologies.

Among patients treated with fertility-sparing surgery (n = 46), 5 women had simple hyperplasia without atypia diagnosed; endometrial abnormalities were resolved after the removal of the primary tumor and no one developed endometrial hyperplasia/cancer during follow-up.

Discussion

Endometrial hyperplasia is a condition of excessive proliferation of endometrial glands that may progress to or coexist with endometrial carcinoma. Endometrial hyperplasia virtually always results from chronic estrogen stimulation unopposed by the counterbalancing effects of progesterone.

This may occur in a number of settings, including obesity, chronic anovulation, estrogen-secreting tumors or exogenous estrogen exposure.

Endometrial hyperplasia and endometrial carcinoma typically present with abnormal uterine bleeding and are most common in women who are postmenopausal and in premenopausal women with increasing age. Evidence from the literature shows that the risk of endometrial pathologies is fairly low prior to age 45 and increases with advancing age [11–13]. Diagnosis is made upon the results of pathological evaluation of endometrial biopsy, curettage sample, or hysterectomy specimen.

Some ovarian tumors produce estrogen and may result in endometrial hyperplasia or carcinoma. It is well documented that GCTs are the most common estrogen-secreting ovarian tumors. Due to the persistent hyperestrogenism, a wide spectrum of endometrial pathologies ranging from endometrial hyperplasia and carcinoma has been reported [5,14,15].

Table 2
Predicting factors for endometrial hyperplasia/cancer.

Factor	Endometrial hyperplasia/cancer (% patients)	Univariate analysis		Multivariate analysis	
		P	RR	P	RR
Age > 40 years	25.9	<0.001	2.86	0.002	1.58
Age < 40 years	3.3				
FIGO stage at diagnosis I–II	25.7	NS		NS	
FIGO stage at diagnosis III–IV	6.7				
Tumor size (mass diameter > 10 cm)	30.2	NS		NS	
Tumor size (mass diameter < 10 cm)	31.7				
Menstrual irregularities/ abnormal bleeding	35	<0.001	2.07	0.006	1.39
Asymptomatic patients	19.2				

Concomitant endometrial abnormalities in GCT patients have been analyzed in a few studies. The incidence of endometrial hyperplasia ranges from 21% to 60%, whereas the incidence of endometrial carcinoma ranges from 1.3% to 12.8% [16,17].

To evaluate the need for endometrial sampling at the time of diagnosis, in the present study we analyzed the clinical data of 150 patients with GCTs of the ovary treated in MITO centers.

We found a higher incidence of endometrial pathologies among patients presenting with abnormal bleeding compared to asymptomatic women at the time of diagnosis (35% versus 19.2%).

At the time of surgery, endometrial hyperplasia was seen in 31 patients (18.7%), 9 of whom (5.4%) had atypical hyperplasia. The incidence of hyperplasia was greatest in women aged 50–56 and was rarely observed in patients under 40 years. The endometrial cancer incidence was 4.8%. It usually occurs in postmenopausal women (mean age 62.6 years) and no diagnosis of carcinoma was done in women under 40 years.

Therefore the two most important risk factors associated with endometrial abnormalities were symptoms and age > 40 years.

As previously reported by other authors [18,19], steroid hormones play a major role in the development of atypical hyperplasia and endometrioid-type endometrial cancer; both factors stimulate the proliferation of endometrial cells directly and through the modulation of the secretion of growth factors in normal and neoplastic endometrial tissue. In the endometrium, progesterone antagonizes estrogen action by down-regulating estrogen receptors and enhancing the conversion of estradiol to the less active estrone by increasing the activity of 17beta hydroxysteroid dehydrogenase. The interactions between steroid hormones and growth factor systems are very complex. For instance, the insulin-like growth factor (IGF) system is composed of peptide hormones (IGF-1 and IGF-2), cell surface receptors (IGF-R) and binding proteins (IGF-BP) [19]. Whereas IGF-1 and IGF-2 exert mitogenic effects after joining the IGF-Rs, IGF-BPs negatively regulate the bioavailability of IGF-1 and IGF-2 binding the ligands with a higher affinity than IGF-R. Progesterone is the most important stimulator of IGF-BP mRNA expression and protein secretion in endometrial stromal cells. Therefore in postmenopausal women the lack of local endometrial IGF-BP synthesis might translate into a higher binding of IGFs to IGF-Rs and consequently in an unopposed stimulation of endometrial cells by IGFs [18]. Therefore, the older the patient ages, the greater is the risk that unopposed estrogenic exposure leads to hyperplastic and neoplastic endometrial transformation.

In our study, no endometrial pathology occurred during follow-up in patients who had undergone fertility-sparing surgery or at GCT recurrences. This finding highlights how spontaneous regression may occur when the excess estrogen production is discontinued by the removal of the primary tumor.

In conclusion, endometrial carcinoma and atypical hyperplasia were rarely observed in GCT patients under the age of 40 years, as in the case of general population. On the contrary, endometrial abnormalities are common at the time of the diagnosis in patients with GCTs at least 40 years of age Therefore, it is recommended that endometrial sampling should always be performed at the time of diagnosis in patients over 40 years of age or who are symptomatic. In asymptomatic women less than 40 years of age, endometrial sampling is of low yield. This subgroup of patients will benefit from transvaginal US examination in order to rule out endometrium thickening.

The present study has some potential limitations; first, the retrospective design of the study, the long study period and the small sample size. Owing to its rarity, prospective studies on GCTs are uncommon and hard to initiate. Because of the rarity of the disease the long study period is inevitable. Moreover, compared to other studies about the rare adult GCT, we studied a relatively large group of patients.

Conflict of interest statement

All authors declare that they have no conflict of interest to disclose.

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