European Journal of Obstetrics & Gynecology and Reproductive Biology 195 (2015) 61–66

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series and review of the literature

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ARTICLE INFO

Article history:
Received 17 August 2015
Received in revised form 20 September 2015
Accepted 28 September 2015

Keywords:
Fertility preservation
Management of low-grade endometrial stromal sarcoma
Hysteroscopic surgery
Hormonal therapy

ABSTRACT

Objective: Low-grade endometrial stromal sarcoma (LG-ESS) is a rare malignancy, often occurring before menopause. There is no consensus regarding its optimal management. Total hysterectomy and bilateral salpingo-oophorectomy precludes future fertility and may thus be undesirable by women wishing to maintain their reproductive potential. However, experience of fertility-sparing management in LG-ESS is very limited. In this paper, the disease outcome is presented in six young women with LG-ESS conservatively treated by combined hysteroscopic resection and hormonal therapy.

Study design: From October 2009 to February 2013, at the Gynecologic Oncology Department of the National Cancer Institute of Naples, six women, with early-stage LG-ESS aged 18–40 years who desired childbearing and/or retaining their fertility, were enrolled into a pilot study of fertility-sparing management. Diagnosis of LG-ESS was made on specimens from hysteroscopic resection performed on a presumed benign lesion. All patients were planned to be treated with adjuvant megestrol acetate for two years. Hormonal therapy was started within 6 weeks from the hysteroscopic resection, with orally megestrol acetate at 40 mg daily, increasing gradually according to patient's tolerance to the recommended total dose of 160 mg daily.

Results: All patients were submitted to hysteroscopic resection in a one-step procedure. Five patients started megestrol acetate within 6 weeks from the hysteroscopic resection (one patient did not start hormonal therapy because of early pregnancy after the hysteroscopic resection). Hormonal therapy was well tolerated; one patient stopped megestrol acetate after 12 months because of self-supporting strong desire to conceive; the other four patients regularly completed the hormonal therapy. To date, all patients show no evidence of disease.

Conclusions: Although fertility-sparing management is not the current standard of care for young women with early-stage LG-ESS, our preliminary data are promising. Larger series with a longer follow-up are needed to further assess safety and efficacy of combined hysteroscopic resection and hormonal therapy.

Introduction

Low-grade endometrial stromal sarcoma (LG-ESS) is a very rare malignant tumor accounting for less than 1% of all uterine malignancies [1]. Compared to other uterine sarcomas, LG-ESS affects younger women, and in many cases tends to occur before menopause [2]. LG-ESS usually exhibits an indolent behavior, with a 5-year disease-specific survival (DSS) of approximately 90% for stages I–II and 50% for advanced stages. An up to 50% recurrence rate, however, has been reported even in early stages [3]. Owing to the rarity of the disease, current treatment recommendations are based on small retrospective studies and case reports.

The mainstay of treatment in operable stages is total abdominal hysterectomy and bilateral salpingoophorectomy (TAH-BSO). The majority of LG-ESS express estrogen (ER) and progesterone receptors (PR) and this expression seem to have significant

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http://dx.doi.org/10.1016/j.ejogrb.2015.09.041
0301-2115/

prognostic value. Although there are no prospective studies regarding the role of adjuvant hormonal treatment in LG-ESS, most of empirical data available advocate its importance, even in case of no residual disease after surgery [4].

The initial treatment of TAH-BSO precludes future fertility and may thus be undesirable by women wishing to maintain their reproductive potential. Given the relatively good oncologic outcomes associated to LG-ESS and the frequent young age at presentation, the importance of improving quality of life and preserving fertility while maintaining excellent DSS has been recognized. Due to the rarity of this tumor, however, experience of fertility-sparing management is very limited [2,5–15]. In this paper, the disease outcome is presented in six young women with LG-ESS conservatively treated by combined hysteroscopic resection and hormonal therapy. In addition, a review of the limited literature is also provided.

Materials and methods

From October 2009 to February 2013, at the Gynecologic Oncology Department of the National Cancer Institute of Naples, six women 18–40 years aged, diagnosed with early stage LG-ESS and wishing to preserve their fertility, were enrolled into a pilot study of fertility-sparing management. Ethical approval was obtained from the Institutional Ethics Committee. The patients showed histologically proven LG-ESS on specimens from conservative hysteroscopic resections performed on presumed benign lesions. There were no hysteroscopic and radiologic (abdomen–pelvis Magnetic Resonance, MR) evidence of residual or distant (chest Computed Tomography, CT) disease following the excision of the tumor. All the patients showed strong desire to preserve fertility and were counseled about the experimental conservative protocol. They were enrolled in the case of ER and PR positivity at immunohistochemistry, no contraindication for adjuvant progestin treatment, and following written informed consent, including availability for completing the follow-up program and definitive surgery after completing childbearing.

Hysteroscopic resections were performed under deep sedation, with cervix dilation to 10 mm (by Hegar's dilators), introduction of a 10 mm bipolar resectoscope (with 0° or 12° lens), and uterine distension and irrigation with normal saline. A continuous flow was used for optimal distension, irrigation, and visibility. The inflow was pressurized with a peristaltic pump, with a maximum pressure setting of 70 mmHg and a maximum flow setting of 700 mL/min. The outflow was passive. A 5 mm cutting loop electrode and 100 W of pure cutting output power were used to resect the intracavitary polipoid lesions and a small layer of the myometrium below. Cold loops were used for the excision of both the intramural submucous masses according to 'cold loop' myomectomy developed by Mazzon. Using this technique, the hysteroscopic procedure was characterized by a sequence of three different operating times: (I) excision of the intracavitary component of the fibroid with the usual technique of slicing; (II) once the cleavage plane was identified, enucleation of the intramural component of the fibroid with cold loop; (III) excision of the intramural component totally dislocated inside the uterine cavity.

Adjuvant hormonal therapy consisted of oral megestrol acetate (MA) started within 6 weeks from the hysteroscopic resection at 40 mg daily and increased gradually according to patient's tolerance to the recommended total dose of 160 mg daily for 2 years.

Three months after starting MA, patients entered the follow-up phase undergoing: three-monthly general and gynecological examinations, transvaginal ultrasound and diagnostic hysteroscopy; abdomen–pelvis MR at 6 months; total-body CT at 12 months, and six-monthly thereafter.

After 24 months, patients still in complete remission wishing pregnancy were encouraged to conceive (with or without assisted reproduction technology, ART). In case of conception, pregnant patients were followed through a routine obstetrical schedule, with a follow-up visit three months after term of pregnancy. Definitive surgery (TAH-BSO) was recommended after childbearing completion.

Results

Six patients with LG-ESS were enrolled in this pilot study, all presenting with abnormal uterine bleeding. Tumor presented as intracavitary polyp in four cases, and the other two appeared as a well-defined myometrial nodule mimicking submucous myomas of 4 cm and 3 cm in size, respectively. Four patients were nulligravidae, with a history of infertility in one (case 1); women of cases 2 and 6 have had babies, and wishing further pregnancies. All patients were submitted to hysteroscopic resection of the lesions in a one-step procedure, on a day-surgery basis. No perioperative complications occurred. Table 1 reports about demographics, clinical characteristics of the disease, and surgical treatment; histological and immunohistochemical features of the surgical specimens are also reported. In all cases LG-ESS invaded myometrium with only focal finger-like projections which never reached 3 mm in length, and a lymphatic/vascular invasion occurred in only three cases. According to the hormone receptor status, all patients of our series were candidate to receive an adjuvant hormonal treatment and five patients started MA within 6 weeks from the hysteroscopic resection. The remaining patient

Table 1
Demographics, clinicopathologic and immunohistochemical characteristics of LG-ESS conservatively treated.

Case #	Age (years)	BMI (kg/m^2)	Previous pregnancy (n)/live births (n)	Clinical presentation	Surgical approach	Histological features			Immunohistochemical features			FIGO stage
						Myometrial finger-like projections (n/lenght)	Lymphovascular invasion	Mitotic activity	ER/PR	Desmin	CD 10	
1	38	31	–/n/a	Polypoid	HR	>3/<3 mm	No	No	+/+	+	+	
2	33	25	2/2	Submucousal	HR	<3/<3 mm	Yes	<3 per 10 HPF	+/+	+	+	IA
3	40	26	–/n/a	Polypoid	HR	<3/<3 mm	Yes	No	+/+	+	+	IA
4	18	32	–/n/a	Polypoid	HR	>3/<3 mm	No	<3 per 10 HPF	+/+	+	+	IA
5	34	23	–/n/a	Submucousal	HR	<3/<3 mm	Yes	<5 per 10 HPF	+/+	+	+	IA
6	30	26	1/1	Polypoid	HR	>3/<3 mm	No	No	+/+	+	+	IA

BMI: body mass index; ER: estrogen receptors; HR: hysteroscopic resection; LG-ESS: low-grade endometrial stromal sarcoma; n/a: not applicable; PR: progesterone receptors.