Update on fertility-sparing treatment in primary and recurrent endometrial cancer

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SUMMARY: Update on fertility-sparing treatment in primary and recurrent endometrial cancer.

Endometrial cancer is one of the most frequent female cancers in women. Around 3-14% of endometrial cancers are diagnosed in young women wishing to preserve their fertility. Incidence of endometrial cancer in this age group is increasing, for which fertility-sparing treatment is the most common type of fertility-sparing therapy. The aim of this review is to assess and analyse most recent findings concerning fertility-sparing progestin therapy for young women with primary and recurrent endometrial cancer. Diagnosis, treatment, follow-up, and oncologic and reproductive outcomes are investigated. Fertility-sparing progestin therapy is highly effective in selected young women with primary and recurrent endometrial cancer. Patients' careful selection as to be mandatory to achieve the best outcomes without compromising survival. Because of the not negligible recurrence rate after conservative treatment, close surveillance is required and prophylactic hysterectomy has to be performed in patients completing family planning. Pregnancy outcomes are very encouraging, thanks to assisted reproductive technologies. Medroxyprogesterone acetate and megestrol acetate are the ideal progestins employed for fertility-sparing therapy, but further studies should be made to establish the optimal dose and treatment timing in this setting.

KEY WORDS: Endometrial cancer - Fertility-sparing treatment.

Status of art

Endometrial cancer (EC) represents one of the most invasive and frequent neoplasm of the female genital tract (5% of all female tumours), with an estimated 46,470 diagnosed cases and 8,120 deaths in 2011 in the United States with 25.4 cases on 100.000 women per year in Italy (1). Endometrial adenocarcinoma commonly occurs in postmenopausal women and its incidence increases dramatically between the ages of 45 and 65 (2). Risk factors for endometrial carcinoma include long-term estrogen over-stimulation, obesity, diabetes, metabolic syndrome, polycystic ovary syndrome, estrogen-producing tumors, a history of nulliparity or infertility, early menarche, late menopause (3).

Abnormal uterine bleeding (AUB) is the most common symptom related to EC (over 90% of patients).

Thanks to this usual presentation, 75% of ECs are diagnosed at an early stage. Atypical endometrial hyperplasia (AEH) is felt to be a precursor of lesions with around 29-43% of risk-progression to EC (4, 5). In addition, AEH is associated with a coexisting EC in approximately 20% of patients (6).

Although EC is mainly identified in postmenopausal women, around 14% of cases might be present in pre-menopausal women, including 4% diagnosed in women equal or under 40 years of age, as a consequence of a hyperestrogenic state, who wish to preserve their fertility.

Likewise, conservative management of endometrial carcinoma has become a necessity. Fertility preservation treatment might be considered as a therapeutic option in carefully selected women with well-differentiated EC without myometrial invasion or adnexal disease. A satisfactory assessment of myometrial invasion can be achieved with imaging (ultrasound, MRI, CT) or histology (hysteroscopy-guided deep biopsy).

The principal issue regarding conservative management of EC is disease progression after initial response to me-
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Drical treatment. Women deciding for fertility-sparing therapy should be mindful that hormonal therapy is not the standard of care for EC patients. Potential adverse outcomes should be considered and carefully explained to these patients. Surgical treatment, including complete hysterectomy, removal of remaining adnexal structures, and an appropriate surgical staging, represents the milestone of curative therapy for patients with EC. Adjuvant therapy is necessary in patients with high-grade and stage endometrial cancer. Conservative treatment approaches should be used in selected cases for women with a desire for fertility preservation.

Recent conservative treatment modalities include hormonal therapies involving progestins (7-9), progestin-releasing intrauterine devices (10-14), oral combined contraceptives (15), progesterone (16), selective estrogen receptor modulators or SERMs (17-19), gonadotropin-releasing hormone agonists (20) and aromatase inhibitors (21). Of Therapies progesterone-based are the most used and well tolerated. The aim of the present review is giving an overview of current outcomes and findings for fertility-sparing management with progestin in patients with EC who have desire of being pregnant.

Oral progestin treatment

Oral megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are the most frequently progestins involved in fertility-sparing therapy, with approximately 80% of the treated patients receiving continuous daily oral doses (22-24). Endometrial effects reported are comparable (25, 26). Nevertheless, there is no specific study comparing the efficacy of these two oral agents as fertility sparing therapy. Although Park et al. (27) observed that the complete response rate was similar in those two treatment and that the recurrence rate was lower for MA-treated cases in their subgroup analysis, further analyses are needed.

The optimal dose of oral MPA and MA for fertility-sparing therapy is still debating. In several studies, the progestin doses varied from 60 to 1,800mg per day for MPA and 10 to 400 mg per day for MA.

The most commonly doses ranged between 200-800 mg per day for MPA and 40-400 mg per day for MA respectively (22-24). A high daily dose of oral progestin is usually used in clinical practice, but it is not clear whether low- or high-dose progestin is more effective. In a previous Gynecologic Oncology Group (GOG) randomized trial of advanced and recurrent EC, response rate and progression-free survival outcomes following MPA therapy were better in low-dose group (200 mg/day) than in high-dose group (1,000mg/day) (28). On the other hand, this comparison has never been made in a randomized controlled setting as fertility sparing treatment.

Mean treatment duration to a complete response is different in some studies of progestin-treated EC patients. Ramirez et al. (22) recorded that the average time interval to a complete response was around 12 weeks (range 4-60 weeks). Therefore, a treatment period of at least 3 months is required to determine treatment failure.

The total progestin treatment duration varies from 3 to 36 months in preceding studies (23, 24), with an average time of 6 months.

Due to fact that the impact of progestins on EC cells appears around 10 weeks after the start of treatment, and an initial exposure period of at least 12 weeks should pass before response assessment (29, 30) a reasonable time to assess a first pathologic response should be 3 months after starting the progestins. Then, pathologic responses should be evaluated by histologic biopsy of endometrium every 3 months until a complete response is attained. Surveillance after successful progestin therapy should include periodic clinical examination anamnesis and transvaginal ultrasonography at 3-month intervals. Patients should be carefully advised to inform immediately the doctor on every new symptoms onset.

Intrauterine devices

One of the first studies concerning progesterone use by containing intrauterine device (IUD) for the treatment of EC, was directed by Montz et al. at Johns Hopkins Hospital in 2002. Enrolled women presented American Society of Anesthesiologists class III or IV, grade 1 endometrioid cancer and no imaging evidence of myometrial invasion. Patients underwent HSC, curettage, and IUD placement, followed by endometrial biopsy every 3 months for 1 year. Sixteen patients were included in the study, one was excluded at the time of IUD placement (grade 2 disease identified) and one was lost to follow-up. Twelve subjects have been followed up to 36 months; results of biopsies were negative in 7 out of 11 at 6 months and 6 of 8 at 12 months. Additional recurrence of EC has not been recorded in any of the six women who had complete regression and continued IUD treatment for 36 months. No IUD related complications, except for one expulsion, occurred. Sixteen complications (one fatal) occurred in 9 of the 15 control patients. This study demonstrates that IUD progesterone is able to control presumed stage IA, grade 1 disease in women at high risk for perioperative morbidity (31). More recently Kim et al. evaluated the feasibility of using MPA and levonorgestrel intrauterine system (LNG-IUS) to control early stage EC in young women desiring to preserve their reproductive potential. Complete remission was observed in 4 out of 5 patients, and one patient showed partial remission. Histologic biopsy was negative in two patients at 3 months, in one patient at 6 months, and in one patient at 12 months. No treatment-related complications were observed. No recurrence was
documented during the follow-up period (range 6-16 months). This study demonstrates that the concomitant use of MPA with LNG-IUS is feasible for conservative treatment of early-stage endometrial cancer in young women who want to preserve their reproductive potential (32). A recent pilot study assessed the feasibility and efficacy of combined operative HSC and hormone therapy as fertility preserving treatment in selected young women with early EC. Fourteen patients with FIGO stage IA EC wishing to preserve fertility were enrolled. Treatment comprised of hysteroscopic ablation of the disease and the myometrial tissue below, followed by oral MA 160 mg/day for 6 months (in 6 patients) or 52 mg levonorgestrel-medicated intrauterine device (LNG-IUD) for 12 months (in other 8 patients). Median follow-up was 40 months (range 13-79). One patient relapsed after 5 months from operative HSC and underwent definitive surgery, one patient showed an endometrial hyperplasia without atypia at the 3- and 6-month HSC control, with negative controls thereafter. Three patients have tried to conceive and one of them conceived and delivered a healthy baby. These preliminary results demonstrate that combined operative HSC and progestin therapy might be considered a safe and effective option for conservative management of early EC in selected patients wishing to preserve fertility (33).

Pregnancy outcomes after conservative treatment

Pregnancy outcomes after conservative therapy completely understood due to a shortage of the literature. Studies present in the literature are mainly case series or case reports and particularly focused on oncologic effects instead of rate of birth and neonatal outcomes. In a meta-analysis conducted by Gallos et al. on 34 studies with a total of 408 women with EC, the live birth rate was 28% (95% CI, 21.6%-36.3%) and the recurrence rate was 40.6% (34).

Furthermore, Park et al. (35) reported an analysis on 141 patients with stage IA grade 1 endometrial endometrial adenocarcinoma who achieved complete remission. Fifty-one (73%) of 70 women who tried to conceive obtained positive results and 46 (66%) gave birth to 58 live neonates. The spontaneous abortion rate, ectopic pregnancy rate, and preterm delivery rates in that series were 24%, 2.8, and 11.5%, respectively. The 5-year disease-free survival was similar between patients who received fertility drugs (n=44) or who did not (n=97; p=0.335), and this rate was significantly higher in patients who achieved at least one pregnancy (n=51) than those who did not (n=90; p=0.028).

Considering that several anovulatory disorders are associated to EC, these patients are often infertile or sub-fertile and require assisted reproductive technologies to be able to conceive, reaching promising pregnancy rate and live birth rate at the end (34, 35). On the other hand, the use of fertility drugs, including clomiphene citrate and gonadotropins, is associated with increased estrogen production during the follicular phase of the ovulation induction cycle (34). Even if some Authors identify this condition as risky in terms of recurrence rate (35, 36), a relationship between hyperstimulation and EC is not supported by others (37-39).

Medical treatment in recurrent EC: is it reasonable?

Most endometrial cancer patients preserving uterus with recurrent disease need to proceed with definitive surgical management including hysterectomy. If these patients have not had a successful pregnancy at the time of recurrence, they may still want to preserve their fertility. Due to the fact that most relapses in EC cases involve well-differentiated tumours confined to the endometrium, a second round of fertility-sparing progestin therapy can be considered. However, the treatment outcomes are not well known in such cases, and few studies have addressed this as a part of their wider analyses (9, 40-47). An optimal response rate to progestin re-treatment is from 52 to 100% for relapses. Recently, Park et al. (48) reported their findings for the largest endometrial cancer series yet analysed regarding this subject. Of 33 patients with recurrent EC in that study submitted to a second round of fertility-sparing progestin therapy, a complete response rate of 89% and re-recurrence rate of 42% were recorded, with no disease progression (48). These outcomes were quite comparable to primary fertility-sparing progestin therapy ones. Again, progestin retreatment in patients with recurrent disease can therefore be considered a safe and effective intervention for patients who still want to preserve their fertility.

Conclusions

Total hysterectomy plus bilateral salpingo-oophorectomy is still the mainstay for EC patients. Since EC in fertile women has a brilliant prognosis after surgery (49, 50), there is a therapeutic dilemma regarding conservative management in young women who strongly desire to preserve their fertility. Findings of progestin treatment are still controversial, expressly compared with over the 90% cure rate of surgical approach (51-54). Hence conservative treatment should be offered to selected women with EC, data about its safety in terms of disease free survival are still lacking.

Multicenter randomized trials are strongly required to better define the selection criteria, dose and regimen of choice, the duration of treatment and follow-up protocols. The pilot study by Montz el al. (31) suggests that reasonably
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long-term continuous intrauterine administration of progestosterone can control most of early stages grade 1 endometrioid carcinoma, at least during the first year nonetheless the possibility of undetected permanent disease does not remain negligible. The progestosterone-containing IUD has also been used to treat potential endometrial hyperplasia in women receiving postmenopausal systemic estrogen replacement therapy. Moreover, intrauterine progestosterone devices might be indicated in women whose medical conditions place them at unusual risk for surgery-related morbidity (such as elderly unfit for surgery, severe obese, etc.) (55).

In conclusion, fertility-sparing treatment with progesterone can be an adequate and reasonable therapeutic option in patients with well-differentiated early-stage endometrioid endometrial adenocarcinoma who want to maintain their uteri, become pregnant or have absolute contraindications to primary surgical treatment.

In patients wishing to preserve their fertility even after they have completed childbearing, cyclic oral contraceptive or progestin-releasing intrauterine devices to avert disease relapse should be recommended.

Staging hysterectomy should be performed after the completion of the childbearing period.

Numerous studies have advised that patients with differentiated tumours and positive progesterone receptors could be the best candidates for conservative therapy. Further investigations on molecular assessment may be advantageous for a better selection of patients fitting for a fertility-sparing management.

References

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