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Review

Conservative treatment in early stage endometrial cancer: a review

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Summary. Endometrial Cancer (EC) is the commonest gynecological cancer and its incidence is increasing. The diagnosis of endometrial carcinoma in young women of childbearing age is rare. Indeed, only 4% of patients with endometrial carcinoma are <40 years of age. It's typically diagnosed in postmenopausal women. The standard approach for the management of endometrial cancer in young women of childbearing age is hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy but is not ideal for women interested in future fertility. We reviewed the published literature to clarify in fertile women who have not yet fulfilled their desire for motherhood, what are the strategies, the risks of a conservative treatment of early stage of Endometrial Cancer and what are the obstetric outcomes in this patients. Recently, several studies have reported encouraging results on fertility-sparing management of EC with high dose of progestins in selected women associated or not with hysteroscopic resection. (www.actabiomedica.it)

Key words: endometrial cancer, fertility sparing surgery, conservative treatment, hysteroscopic resection uterine preservation

Introduction

Endometrial cancer (EC) is one of the most common gynecological cancers. More than 90% of cases of endometrial cancer occur in perimenopause women and 25% are premenopausal (1, 2). However, 4% of women with endometrial cancer are younger than 40 years old and over 70% of them are nulliparous at diagnosis, due to the fact that in the current era women delay their childbearing. The majority of endometrial cancers are diagnosed early stage (80% in stage I), with 5-year survival rates over 95%. Most endometrial cancer cases are sporadic, with only 10% considered familiar.

Endometrial carcinoma has been classified into two main clinic-pathological and molecular types: Type I and Type II.

Type I is the endometrioid type (EEC) (3) because it's similar to the endometrium and is characterized by genetic predisposition (eg. Lynch syndrome-LS), such as obesity, polycystic ovarian syndrome (PCOS), anovulatory cycles, irregular menstruation that causes hyper estrogenic state, that is a main predisposing factor for developing Type I EC. Type I EC has a favorable outcome due to minimal myometrium invasion (4).

Type II cancers are associated with higher patient age, high stage and grade, non-endometrioid histology, and poor prognosis, instead. It includes several subtypes such as serous, clear cell and undifferentiated carcinomas (5).

Most patients with endometrial cancer have an excess of estrogen and typically show a characteristic clinical profile: high body mass index (BMI) that is considered as overweight (BMI 25-30) or obese (BMI 30), often with other components of metabolic syndrome (hypertension, diabetes) (6). This is the most commonly identified risk factor because obesity is as-

sociated with peripheral estrogen conversion via aromatization in adipose tissue (7, 8). Nulliparity and infertility are classical risk factors for endometrial cancer. Other risk factors include unopposed estrogen therapy, estrogen-producing tumors such as ovarian granulose, theca cell tumors and early menarche/late menopause. Studies also show that exposure to tamoxifen increases the risk of endometrial cancer-related estrogen as well as an unbalanced hormone replacement therapy (9). Only endometrial carcinoma type I may be subject to a fertility sparing treatment.

Materials and methods

We performed a Pubmed, Medline search of articles published in English between 1959 and 2018 with the key words 'Endometrial cancer', 'fertility sparing surgery', 'conservative treatment', 'hysteroscopic resection' and 'uterine preservation'. Moreover, we identified several articles from bibliographies of these publications including case reports, case series, original articles, review articles, and meta-analyses, with the purpose of analyzing the different methods of treatment reproductive outcomes and follow-up after fertility sparing treatment in women with an early stage of EC.

Selection of patients: stage, grade and histopathology

When considering a conservative management approach, we should consider clinical and pathological characteristics of the tumor for can select the appropriate medical intervention. A conservative management approach could be considered in patients: <40 years old (relative indication), have to intent to preserve fertility and plan to conceive as soon as possible after remission, with no contraindication for medical treatment and with a histological diagnosis of grade I endometrial carcinoma; histotype: endometrioid with positive hormone receptor (tipe I), tumor diameter <2.0 cm, stage IA without myometrial and adnexal involvement, negative lymph-vascular space invasion (LVSI) and diffuse immunohistochemical expression of progesterone receptors on endometrial biopsy. These patients are considered as " low risk" population. According to Gynecologic Oncology Group (GOG) and Federation International of Gynecologic and Obstretric (FIGO),the most important prognostic factors (10) for lymph node metastasis in patients with EC were the grade of tumor and the depth of myometrial invasion with the risk of involvement less than 1% and excellent 5-year progression-free survival of 95% if the tumor is grade 1 with an overall survival of 90%. In the absence of risk factors, a conservative approach to surgical staging is feasible, safe and not associated with an increase in cancer-related mortality (11).

Diagnosis

Diagnosis should be performed by Hysteroscopy and endometrial biopsy (12, 13). The Society of Gynecologic Oncology (SGO) recommends that the preferred tissue formats include curettage and biopsy and that devices that result in crushed, cauterized, or very small samples are unacceptable (14). Imaging performed by MRI or Transvaginal Ultrasound by experts, helpful to detect possible myometrial invasion and exclude synchronous ovarian tumor or suspicious lymph-adenopathy. Seems that MRI is slightly more sensitive than ultrasound for the evaluation of myometrial invasion and that the implementation of both techniques increase sensitivity (15-16).

Selection of drug, dose, length of treatment

The standard treatment for EC is a hysterectomy with bilateral salpingo-oophorectomy, with or without lymph node dissection with pelvic washing, sometimes combine with adjuvant chemoterapy or radiotherapy is necessary. Although this is a highly effective approach, carrying a 5-year survival rate of 93%, it also results in a permanent loss of reproductive potential which is often unacceptable to younger women who wish to preserve their fertility. Therefore, selected patients with EC, are candidates for a conservative approach (2). Hence, fertility-sparing treatment with progestin is a good compromise for these women. Recently, hysteroscopic resection in addition to hormonal therapy followed by pregnancies in young women have been reported (17, 18).

Medical treatment

Conservative management of EC is based principally on medical treatment with oral progestins. Medical treatment Hormonal therapy, alone or in a combination with hysteroscopic ablation. Progestins (19, 20) are medroxyprogesterone acetate or megestrol acetate. Although today there is no consensus on the optimal dosage or duration of treatment, it appears that 62-75% of these women respond well to progestational treatment and the absence of progesterone receptors (PR), can make inhomogeneous the success of progestin treatment (2, 21). First Kistner in 1959 (22) to use for EC a progesterone formulation using various dosing strategies. Another method of treatment is Levonorgestrel-releasing IUD (23-25), removing the IUD when patients are ready to attempt pregnancy. With or without GnRH analogues, or a combination of IUD and oral progesterone (26). With a high response rates in patients with grade I EC, despite some patients with prior progesterone treatment.

Surgical treatment by hysteroscopy

Mazzon et al (17) reported a series of patient treated with hysteroscopyc resection of tumor with resection of the adjacent endometrial margins and the myometrium underlying the tumor with biopsies of uterine cavity and under general anesthesia followed by oral therapy with progestin, Megestrol acetate (160 mg daily) or Medroxyprogesterone acetate (400 mg/day), beginning the fifth day after the surgery and continuing for six months (27). Other authors describe the use of IUD for 12 months. Shan et al. instead performed hysteroscopy curettage during which resected the major part of tumor tissue, later followed by complete endometrial resection with hysteroscopy. Marton et al. performed an initial polypectomy resulted in the diagnosis of carcinoma. One month later performed a complete endometrial ablation (29). Park et al (28, 29) described the possible adverse effects of hysteroscopy resection prior to hormone therapy with an increase in adhesive syndrome after resection. This can influence the obstetric outcome.

Follow-up

In order to assess response, hysteroscopy and imaging at 6 months must be performed and not before. If no response is achieved after 6 months, standard surgical treatment should be performed. In case of complete response, conception must be encouraged and referral to a fertility clinic is recommend. Maintenance treatment should be considered in responders who wish to delay pregnancy. Patients not undergoing hysterectomy should be re-evaluated clinically every 6 months. After completion of childbearing, a hysterectomy and salpingo-oophorectomy should be recommended (30, 31). The preservation of ovary can be considered depending on age and genetic risk factors. Hence, the follow-up of these patients under conservative treatment in the first year included serial transvaginal Ultrasonography (TV-US) every three months. A computed tomography scan (CAT) six months after surgery is recommended. Several authors performed check-ups with only TV-US or in association with CAT scans, every six month starting from the second years. A strictly follow-up during the period treatment is recommended (21, 32). Hysterectomy should be recommended as the definitive treatment for patients with persistent disease. The need for bilateral salpingo-oophorectomy depends on the risk factor and therefore this possibility must be discussed with the patient. Patients who after 6 months of treatment have a partial response could be offered continuation of treatment for another 3 to 6 months.

A recent study concerning the use of antidiabetic drug metformin and its effect on EC cells has shown that metformin suppresses EC cell growth (associated with the reduction of the proliferation marker Ki-67) (33, 34) and have an anti-proliferative effect in women with EC and insulin resistance or PCOS (35). In the future a treatment could be possible in association with progestin and active weight management early stage of EC (36).

In premenopausal women who are obese, the use of aromatase inhibitors in adjunct to oral progesterone, initially Megestrol acetate 160 mg/day for 6 months subsequently as second treatment after second biopsy with persistent aypical hyperplasia or Grade I endometrioid endometrial cancer is added to Meges-

trole acetate 160 mg/day Anastrozole 1mg/day for 6 months or intrauterine device for 8 months if at the second biopsy the result was Grade III endometrioid endometrial cancer (37, 38), seems like a reasonable therapeutic option, as they have a significant proportion of their estrogen production coming from peripheral conversion in adipose tissue. Agorastos et al. in 2005 (39), demonstrate that aromatase inhibitors reduce endometrial thickness in patients who cannot be subjected to hysterectomy.

Strategies of fertility preservation

One of the strategies to preserve fertility is ovocyte cryopreservation. Patients with previous history of infertility or other risk factors for infertility should be encouraged to the use of assisted reproductive techniques. Reassuring data confirm the safety of Assisted Reproduction Techniques (ART) (40). Ovulation induction does not appear to be associated with increased risk of relapse, and subsequent pregnancies do not worsen oncological outcomes (41-43).

Outcomes

Primary outcomes are the evaluation of complete response to therapy, defined as the absence of disease on subsequent endometrial biopsy; we define partial response if the disease was downgraded to complex atypical hyperplasia. No response, defined as who have no evidence of response and progression is defined the presence of a higher grade of cancer on biopsy. Secondary outcomes are obstetrical outcomes (44, 45).

Pregnancy rate described in literature for exclusively hormonal treatment is between 35-60%, but after a combined treatment, hysteroscopic and hormonal pregnancy rate increases to about 70%. The recurrence rate of EC after conservative treatment is between 30-40% in from 4 to 66 months (44, 46, 47) and can be offered a re-treatment with progestin.

The mortality associated with conservative treatment of early stage of EC is very low despite the fact that the rate of recurrence is high (48).

Conclusion

Uterine preservation is a safe and feasible option in select young women who have not yet fulfilled their desire for motherhood with stage IA low-grade progesterone receptor positive endometrioid tumors with no metastatic involvement or risk factors. An adequate evaluation and a correct diagnosis by expert physician confirming the absence of myometrial invasion. The treatment of choice is progestin associated or not to hysteroscopy with a monitoring for long periods. Hysteroscopic surgery prior to hormone therapy may improve the rate of recurrence when the resection margins are free, although serve further studies. Individualization of care is important as each patient has different characteristics as well as different needs and expectations.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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