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Progestin therapy for patients with endometrial cancer

Tsangouri P. Sotiria, Lazarou Elias, Pappa Kalliopi

1st Department of Obstetrics and Gynecology, University of Athens School of Medicine, Alexandra Hospital, Athens, Greece

Correspondence
Sotiria P. Tsangouri, 80 Vasilissis Sofias ave., PC 11528, Athens, Greece, Tel. +306972020474, E-mail:stsagouri@gmail.com

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Introduction

Endometrial cancer is the fifth most common cancer in women worldwide, counting almost 320.000 cases in 2012, and is the sixth leading cause of female death related to cancer. In the United States of America there were 60.050 new endometrial cancer cases in 2016 while in Europe 88.068 and in the United Kingdom about 7.400 cases annually. Atypical endometrial hyperplasia or endometrial intraepithelian neoplasia, presents up to 40% lifetime risk of progressing to endometrial cancer[1]. The majority of the cases are diagnosed in post–menopausal women, while 14% of in pre- menopausal women with a percentage of 4% to be diagnosed in women less than 40 years old. The hysterectomy, bilateral oophorectomy and assessment of retroperitoneal lymph nodes is the standard procedure for endometrial cancer management but for younger women who desire to have family, fertility sparing options are more suitable. In this review we will discuss the role of progestins as a conservative management of endometrial cancer in young patients who wish to preserve fertility, or as a treatment option for advanced or recurrent disease.

Materials and methods

We performed a Medline search for articles published in English during 2015-2017 with the kea words: <<endometrial cancer>>, <<fertility sparing>>, <<conservative management>>, <<recurrent disease>>, <<progestin>>. We identified further articles from the bibliographies of these publications, including case reports, review articles, and meta-analysis. The most up to date findings regarding the topic of our review were extracted from these reports.

Results

Progesterone is a steroid hormone that opposes endometrium estrogen-driven growth. Excessive estrogen endometrial stimulation, unopposed by progesterone, leads to endometrial hyperplasia or cancer development. Progestins modulate endometrial glands secre-

tory differentiation, inhibit estrogen receptor function and endometrial cell mitosis, and also act as pro-apoptotic and anti-angiogenic agents. Furthermore, in vitro studies indicate that progestins stimulate stromal insulin-like growth factor binding protein-1 (IGFBP-1), which inhibits insulin-like growth factor-1 (IGF-1) both expression and activity. This is noteworthy, as IGF-1 is a proliferative (anabolic) and anti-apoptotic factor, which presents increased expression in endometrial hyperplasia. Apparently, progestins inhibit at least two proliferative pathways[2].

Oral Progestins

Oral medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are the most commonly used progestins when fertility preservation is necessary. Progesterone agents seem to elicit their antitumor effect through Wingless (Wnt) and/or phosphatidylinositol 3- kinase (PI3K)/Akt pathways[3]. The potency of these two agents has been reported to be similar. However, there has been no specific study comparing the efficacy of these two agents in fertility sparing therapy and although Park et al. suggested that the complete response rate was similar between MPA and MA and that the recurrence rate was lower for MPA-treated cases in their subgroup analysis, further evaluation is required.

The optimal dose of oral MPA and MA is not currently well defined. The most frequently used dose ranges of MPA and MA are 200-800 and 40-400 mg/dl/day respectively, with most of the patients receiving doses of >400 and <200 mg/dl/day, respectively. It is notable that a high daily dose of progestins is commonly used in clinical practice, but it is not clear whether the low or the high dose is more effective. In an earlier Gynecologic Oncology Group randomized trial dealing with advanced and recurrent endometrial cancer, the response rate and progression –free survival outcome following MPA therapy was higher in the low-dose group (200 mg/day), than in the high dose group, but this comparison has not been further investigated since this study[4].

The median treatment duration to a complete response differs between studies with endometrial cancer patients. Ramirez et al[5]. reported a median time interval to a complete response of 12 weeks (range, 4–60 weeks). A treatment period of at least 3 months is required to determine treatment failure. If the patient shows disease progression at this time point, definitely surgical management is required. However, if the disease persists without progression at this time point, further treatment with progestin is an option and in some cases complete response in achieved after 9–12 months. In this cases, different progestin dose and type can be considered. However, the efficacy of this strategy remains to be evaluated as the treatment duration varies between 3 and 36 months in different studies. Knowing that the impact of progestins on endometrial cancer cells becomes apparent as early as 10 weeks of treatment, an initial exposure period of at least 12 weeks should be offered before response evaluation and the first pathologic evaluation with dilatation and curettage (DC) should be considered 3 months after treatment initiation. Subsequently, pathologic evaluations should be scheduled every 3 months while treatment is continued until a complete response is achieved. The DC and also frequent hysteroscopic biopsy are the gold standard methods for treatment response evaluation, especially in patients treated with high doses of oral progestins although may have an adverse impact on future pregnancy outcomes due to the destruction of the basal layer of the endometrium, the development of fibrosis and potentially the thermal injury on the myometrium.

Intrauterine Device Levonergestrol (IUD-LNG)

This device can deliver locally a higher dose of progestin to the endometrium than orally administered progestin, skipping systemic complications associated with high doses of oral progestin including throm-

boembolism, weight gain, mood and libido changes, headaches, breast tenderness, sleep disorders, and leg cramps[6]. One of the first studies dealing with IUD-LNG use for endometrial cancer treatment by Montz et al. at Johns Hopkins Hospital in 2002, enrolled women with grade 1 endometrioid cancer with no evidence of myometrial invasion on imaging scanning and were in a high risk for perioperative morbidity. Patients underwent either hysteroscopy or dilatation and curettage, and IUD placement and 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 for 36 months; the biopsies were negative in 7 out of 11 at 6 months and 6 out of 8 at 12 months of following. Recurrence had 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 while complications (one fatal) occurred in 9 of the 15 control patients. This study proved that IUD-LNG is an adequate method for stage IA, grade 1 endometrial cancer management in women at high risk for perioperative morbidity. Kim et al. evaluated the feasibility of using MPA and IUD-LNG to control the early stages of endometrial cancer in young women who desired to preserve their fertility[7]. Complete remission of the disease was observed in 4 out of 5 patients, while one patient showed partial remission. The endometrial 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 and no recurrence was documented during the follow-up period (6–16 months). This study showed that the concomitant use of MPA and IUD-LNG is a realistic option for conservative treatment of early-stage endometrial cancer in young women who want to preserve their fertility. A recent study[8] which assessed the efficacy of combined operative hysteroscopy and hormone therapy as fertility preserving treatment in selected young women with early endometrial cancer consisted by fourteen patients with FIGO stage IA who underwent hysteroscopic ablation of the endometrium and the myometrial tissue below, followed by oral administration of 160 mg/day MA for 6 months (6 patients) or 52 mg IUD-LNG for 12 months (8 patients). The median of follow-up was 40 months (13–79 months). One patient relapsed after 5 months and underwent surgery and one patient showed an endometrial hyperplasia without atypia at the 3rd and 6th month. Three patients have tried to get pregnant and one of them conceived and delivered a healthy baby. These preliminary results demonstrated that combined operative hysteroscopy and progestin therapy might be considered a safe and effective option for conservative management of early endometrial cancer stages in selected patients who wish to preserve their fertility.

A number of clinicopathologic biomarkers predicting poor response in progestin based treatment in women with well differentiated endometrial adenocarcinoma are currently used[9]. The insulin resistance, the abnormal function of mismatch repair system and the overexpression of Nrf2 and AKR1C1 are some of the biomarkers which reveal progesterone resistance.

A number of studies have focused on determining ways to eliminate this resistance. A phase II study on MPA plus metformin 750-2250 mg/day[10], showed that metformin inhibited episodes of disease relapse after MPA therapy. Still though, the combination of metformin and MPA in endometrial cancer treatment should be studied further. Furthermore, the combination of oral progestins with tamoxifen and IUD-LNG with GnRH analogues showed effectiveness in patients with endometrial hyperplasia and cancer. The strict follow-up during and after treatment was crucial.

In general, the complete response rate with fertility-sparing therapy is reported to range between 25% and 89% with a mean complete response rate 66.7%

to 79.7% . The most recent meta-analysis, which 408 patients from 32 studies, reported a pooled complete response rate of 76.2% (95% confidence interval, 68%–85.3%)[11]. However, various types of fertility-sparing therapy were included in this meta-analysis and some studies were not limited to stage IA, grade 1 endometrioid endometrial cancer. Recently, Park et al. reported the largest series on fertility-sparing therapy including only oral progestin therapy and using strict inclusion criteria[12]. The complete response rate to progestin therapy was 77.7% in this study. Hence, it is clear that progestin therapy is highly effective in stage IA, grade 1 endometrioid endometrial adenocarcinoma. The most recent meta-analysis dealing with these patients reported a pooled recurrence rate of 40.6% (95% confidence interval, 33.1%–49.8%) and this fact clarify that this approach only delay the surgical management to allow child bearing and not to cure the disease. Close surveillance is therefore mandatory after achieving a complete response to progestin treatment.

The safety of progestin fertility-sparing therapy is supported by the fact that subsequent disease progression is not frequent even in patients who present resistance and by the fact that almost all recurrences are well-differentiated tumors confined to the endometrium still curable with surgical management[13]. In a retrospective population based cohort study in British Columbia from 2003 to 2015, with 50 women under 45 years old with complex atypical hyperplasia (n=29) and endometrial carcinoma (n=21), there were 32 women who underwent hysterectomy, 27 due to persistent/reccurent disease, and 5 due to patient demand despite complete response to progestins. The majority of hysterectomy specimens (85%) had minimal or no residual disease. In Zoe R.Greenwald et al. study with 6339 women, 161 received progestins and 6178 primary surgery. After 15 years of follow up, the mortality rate did not differ between the groups. According to the results of this study, young patients with low grade endometrial cancer, appear to have excellent survival rates, regardless the primary therapy type (progestins vs primary surgery), and the current selection for patients to preserve their fertility and be treated with progestins does not appear to worsen clinical outcomes.

ADVANCED-RECCURENT ENDOMETRIAL CANCER

Regarding progestin therapy for advanced or recurrent endometrial cancer treatment, a study of 331 cases, treated with MPA 50 mg three times a day, resulted in complete remission of the disease in 32 cases (9.6%) and partial remission in 26 cases (7.9%), presenting a median exacerbation-free survival period of 4 months and a median overall survival period of 10 months[14]. The comparison 200 vs 1,000 mg/day MPA, showed better outcomes in the low-dose group (17% complete remission and 8% partial remission) than in the high-dose group (9% complete remission and 6% partial remission). Median exacerbation-free survival period also differed significantly between the low-dose group (3.2 months) and the high-dose group (2.5 months).

Regarding dose levels, the Gynecologic Oncology Group (GOG) reported that for patients with advanced or recurrent cancer, the comparison between the low-dose MPA group (200 mg/day, n=145) and the high-dose group (1,000 mg/ day, n=154) revealed that the response rate was higher in the low-dose group (25%, including 25 cases with complete remission and 11 with partial remission) vs high-dose group (16%, 14 cases with complete remission and 10 with partial remission), with the response to be particularly favorable in endometrial cancer grade 1 and in progesterone-positive cases. Despite the good prospects of progesterone therapy, the variation in response rates indicates the need for predicting markers of a successful therapy. The expression of estrogen receptors, of progesterone receptors and PTEN, constitute a quite promising prognostic tool of progesterone response validation. Allred score is another prognostic tool also,

which validate the expression of estrogen receptor, progesterone receptor, androgen receptor and Ki67[15]. It seems that when Allred score is ≥3, progesterone therapy is more likely to have a positive result[16].

The therapy of endometrial cancer with progesterone can be enhanced with other agents such as tamoxifen, gonadotropin-releasing hormone agonist (GnRH agonist) and aromatase inhibitors .When these agents combined together seem to have better response.

Conclusions

Progestin therapy has been used for decades as an alternative to surgery for endometrial neoplasias. Fertility-sparing progestin therapy is highly effective in selected young women with primary and recurrent endometrial cancer[17]. The selection of appropriate patients through comprehensive pretreatment evaluations is of paramount importance to achieve the best outcomes without compromising survival outcomes. However, future studies should be performed to determine the most effective of all agents as well as the optimal dose and duration of treatment. Despite the lack of sufficient data sets to demonstrate the efficacy of progestin therapy in advanced endometrial cancer, the case series and pilot studies do demonstrate that progestin therapy can be used effectively when surgery is not a desirable option.

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