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Oncologic and pregnancy outcomes of fertility-sparing treatment with medroxyprogesterone acetate in women with premalignant and malignant endometrial lesions: A case series

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ABSTRACT

Introduction: Current trends of delaying childbearing and the increasing incidence of endometrial cancer in nulliparous woman necessitate research and development of fertility sparing treatments. Hormonal therapy with progestins offers an alternative to surgical treatment for a select group of patients of reproductive-age, who wish to preserve their reproductive potential.

Materials and methods: The study evaluates the effectiveness of medroxyprogesterone acetate therapy in patients with early-stage endometrial cancer, atypical endometrial hyperplasia or atypical polypoid adenomyoma, seeking to preserve fertility. This prospective case series encompasses nine patients (6 with endometrial cancer, 2 with atypical endometrial hyperplasia and 1 with atypical polypoid adenomyoma) treated in the period between 2015 and 2022 with high-dose medroxyprogesterone acetate therapy. Treatment and monitoring were conducted at the University Clinic for Gynecology and Obstetrics in Skopje, R. Macedonia, with clinical assessments carried out every three to six months via hysteroscopy with endometrial biopsy or exploratory curettage.

Results: Primary response was achieved in 4 patients (44.4 %). Secondary response was achieved in the remaining 5 cases (55.6 %). Therefore, all 9 patients (100 %) showed complete response to progestin treatment in the time interval 3–9 months. Recurrence occurred in 3 cases (33.3 %) after follow-up of 15, 33 and 84 months, respectively. During the study period, 2 patients (22.2 %) underwent definitive surgery with hysterectomy because of disease recurrence (both with endometrial cancer, stage IA). Fertility was achieved in 1 patient (11.1 %), who had a full-term delivery with caesarean section.

Conclusion: Conservative treatment approach to patients with endometrial cancer aiming to preserve fertility can be safe and have acceptable outcomes in terms of oncologic response as well as pregnancy results, with high-dose medroxyprogesterone acetate therapy being an effective option. The selection of endometrial cancer patients, for whom fertility-sparing progestin therapy is appropriate, is of great importance to achieve the best outcomes. Continuous and careful monitoring of patients undergoing conservative treatment is essential, due to the risk of disease recurrence and progression.

1. Introduction

Endometrial cancer is the sixth most common cancer in women worldwide, with over 400,000 new cases per year [1]. Even though endometrial cancer is considered a postmenopausal cancer, with approximately 80 % of cases occurring in women older than 50 years, it still affects 20 % of women in premenopausal age, with 3–5% of all cases of endometrial cancer occurring in women under 40 years of age [2,3].

Several risk factors are associated with the development of endometrial cancer, including high BMI or obesity, hyperinsulinemia, diabetes, hypertension, nulliparity, anovulatory cycles [4,5], younger age at menarche, late age at menopause, and long-term use of unopposed

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estrogens during hormone replacement therapy [6].

The cornerstone of treatment of endometrial cancer involves total hysterectomy with bilateral salpingo-oophorectomy (BSO) and surgical staging that includes lymph node assessment for most women [7]. Surgery is highly effective in low-risk cases, such as FIGO stage IA, endometroid, and grade 1–2, with an overall survival rate of over 95 % [8]. However, this approach compromises fertility in younger patients. Taking into consideration current trends of delaying childbearing, but also the increasing incidence of endometrial cancer in nulliparous woman, research and development of fertility sparing treatments is of crucial importance.

Hormonal therapy with progestins offers an alternative for a select group of patients of reproductive age, who wish to preserve their reproductive potential. This treatment involves high doses of the progestin to manage and potentially reverse cancer progression, allowing some patients to conceive before considering definitive surgical options.

Progestin acts by downregulating estrogen receptors, thereby suppressing endometrial growth and activating estrogen metabolism. It also exerts a direct cytotoxic, anti-tumor effect on the endometrium [9]. Oral progestins and the levonorgestrel-releasing intrauterine system (IUS) have therefore been used as non-surgical hormonal treatment for endometrial cancer [10], and have consistently shown good overall response rates.

The selection of endometrial cancer patients for whom fertility-sparing progestin therapy is appropriate is of great importance in order to achieve the best outcomes. Reliable selection of the patients who will benefit from fertility sparing treatment can be guided by current and emerging prognostic biomarkers which predict treatment response. Patient outcomes are influenced by clinical, histopathologic, and molecular factors. Clinical factors include age, body mass index, comorbidities, race etc. Established histopathologic prognostic biomarkers in endometrial cancer include the histological type, FIGO stage, histologic grade, lympho-vascular space invasion and myometrial invasion [11].

Some of the optimal indications for fertility sparing progestin therapy include a histologically confirmed endometrioid type endometrial adenocarcinoma that is well-differentiated, the disease is confined to the endometrium, there is no evidence of myometrial invasion on imaging study and there is no clinical evidence of extrauterine spread of the disease. Well-differentiated tumor cells are more likely to express progesterone receptors and therefore respond to progestin therapy [12]. Also, well-differentiated tumors have a very low risk of myometrial invasion and extrauterine spread [13]. In endometrioid carcinoma, the histologic grade is prognostically significant. Based on architectural features, low-grade endometrioid carcinomas are subdivided into grade 1 and grade 2 tumors which exhibit up to 5 % and 6%–50 % solid non-glandular growth, respectively, while high-grade endometrioid carcinomas (grade 3) are characterized by 50 % or more solid component [14]. The fertility-sparing strategies have considered only the group of patients with endometrioid endometrial cancer stage IA, grade 1. Although there is limited evidence for early-stage grade 2 endometrioid adenocarcinoma and well-differentiated grade 1 endometrioid adenocarcinoma with minimal myometrial invasion (1–2 mm), fertility sparing treatment may be considered in these cases [15].

Advances in the understanding of molecular characteristics of endometrial cancer, achieved with The Cancer Genome Atlas (TCGA) data, have led to the distinction of molecular subgroups which have prognostic and therapeutic implications. According to FIGO, the performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial cancer and should be performed routinely in all high-grade tumors [14,16]. Although the use of the molecular classification of endometrial cancer has an important implication in predicting prognosis and treatment decision making, data regarding its impact on outcomes of fertility sparing treatment are limited [17–19]. Patients with p53 wild-type tumors have the greatest benefit from progesterone treatment, while conservative therapy for p53abn tumors would probably be inappropriate due to their likelihood of progression. Mismatch repair-deficient tumors are usually of higher stage and less responsive to progesterone therapy, while for POLE-mutated carcinomas the benefit of conservative treatment is still unclear [15]. Evidence from prospective studies of larger sample sizes is essential to establish the role of molecular classification in fertility-sparing treatment for early-stage endometrial cancer, but the low prevalence of the disease in patients wishing to preserve fertility is a limiting factor [20].

Other indications in considering fertility sparing treatment include a strong desire to preserve fertility, no contraindications for the medical treatment and an informed consent with an understanding that this is not standard treatment and carries a high risk of recurrence [21].

According to ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial cancer, a combined approach consisting of hysteroscopic tumor resection, followed by oral progestins and/or levonorgestrel-intra-uterine device, is the most effective fertility-sparing treatment both for complete response rate and live birth rate compared with other treatment options [15]. Continuous medroxyprogesterone acetate (MPA) (400–600 mg/day) or megestrol acetate (MA) (160–320 mg/day) are two of the suggested oral progestin regimes [22].

Intensive follow-up to assess the response to therapy and detect any recurrence of the disease is necessary. Endometrial sampling should be performed every 3–6 months by dilation and curettage or by hysteroscopic biopsy [15,23–27]. Two consecutive complete response endometrial biopsies with a minimal interval of 3 months are necessary to consider the success of the fertility-sparing treatment and to recommend pregnancy [28]. After a complete response is achieved, a 3- to 6- month follow-up biopsy is required until pregnancy or until definitive surgery is performed [29].

Conservative treatment with progestins is considered safe as no significant toxicity among patients has been reported in most studies. Some reported adverse effects include thrombophlebitis, pulmonary emboli, weight gain, hypertension, and headaches [21].

The aim of this study is to evaluate the effectiveness of medroxyprogesterone acetate therapy in patients with early-stage endometrial cancer, atypical endometrial hyperplasia or atypical polypoid adenomyoma, seeking to preserve fertility.

2. Materials and Methods

A prospective case series was investigated. This case series encompasses nine patients treated in the period between 2015 and 2022. Five patients had endometrioid adenocarcinoma of the endometrium stage IA, grade 1; one patient had endometrioid adenocarcinoma of the endometrium stage IA, grade 2; two patients had atypical endometrial hyperplasia and one patient had atypical polypoid adenomyoma. All the patients were initially being evaluated due to infertility. Five of the patients had an endometrial polyp and the remaining four patients had abnormal uterine bleeding, therefore they underwent hysteroscopy with polypectomy and endometrial biopsy or exploratory curettage. After the histopathological diagnosis of a premalignant or malignant endometrial lesion, patients elected to undergo high-dose medroxyprogesterone acetate therapy for 6–12 months to preserve fertility. Criteria to conservative treatment included histologically confirmed early-stage, well-differentiated, endometrioid type endometrial adenocarcinoma with no evidence of myometrial invasion or extrauterine spread, grade 1–2 or atypical endometrial hyperplasia or atypical polypoid adenomyoma, a strong desire to preserve fertility, and no contraindications for the medical treatment.

Patients were counselled that hormonal therapy is not the standard treatment for endometrial cancer and carries a high risk of recurrence, and therefore continuous and careful monitoring with hysteroscopy with endometrial biopsy or exploratory curettage will be required. After obtaining informed consent, patients were treated with MPA with doses

of 500–1000 mg/day orally. Treatment and monitoring were conducted at the University Clinic for Gynecology and Obstetrics in Skopje, R. Macedonia.

Primary response was defined as absence of malignant cells on histopathology of endometrial specimens after three months of treatment. In cases without response after the initial three months, the treatment was continued for additional 3–6 months. Patients were reassessed at three and six months and therefore, secondary response was defined as absence of malignant cells on histopathology of endometrial specimens after the additional treatment.

After achieving complete response, patients were referred to the Department of Infertility and Assisted Reproduction to begin fertility treatment. Meanwhile, patients were closely followed and underwent condition assessments every three to six months via hysteroscopy with endometrial biopsy or exploratory curettage. Progression free survival was measured since treatment initiation to recurrence. Additionally, the number of pregnancies and live births were assessed.

3. Results

As shown in Table 1, among the 9 patients treated with MPA, 6 patients had endometrioid adenocarcinoma of the endometrium stage IA, 2 patients had atypical endometrial hyperplasia and 1 patient had atypical polypoid adenomyoma. The patients' mean age was 33 years, with an age range of 27–42 years. All the patients were nulligravid.

The median observation period was 25 months (11–120 months). Primary response was achieved in 4 patients (44.4 %). Secondary response was achieved in the remaining 5 cases (55.6 %). Therefore, all 9 patients (100 %) showed complete response to progestin treatment in the time interval 3–9 months.

Recurrence occurred in 3 cases (33.3 %) after follow-up of 15, 33 and 84 months, respectively.

During the study period, two of the patients with disease recurrence underwent definitive surgery with hysterectomy (both with endometrioid adenocarcinoma of the endometrium stage IA, grade 1). The third patient was lost to follow-up.

During the observation period, fertility was achieved in 1 patient (11,1 %), who had a full-term delivery with caesarean section. The remaining 5 cases (55.5 %) showed no disease recurrence, nor conception during the study period.

4. Discussion

In the search of fertility sparing options for women diagnosed with endometrial cancer, progestins have become a favoured treatment, providing an opportunity for these women to fulfil their reproductive goals. A lot of studies have shown the effect of progestins in the treatment of endometrial cancer in highly selected patients. The effectiveness of fertility-sparing treatment of early-stage endometrial cancer and atypical endometrial hyperplasia ranges from 57 % to 100 % [30–38].

In this case series of patients treated with high-dose medroxyprogesterone acetate for early-stage endometrial cancer, atypical endometrial hyperplasia and atypical polypoid adenomyoma, all 9 studied patients achieved a complete response (100 %) and 1 conceived spontaneously and had a full-term delivery (11.1 %). Recurrence occurred in 3 cases (33.3 %). Progestins as treatment for endometrial cancer in reproductive-age patients are a promising fertility sparing treatment option. Although results are encouraging, due to the risk of recurrences and progression of the disease, this treatment should only be considered by experienced gynaecological oncologists using well-defined protocols with detailed patient information and close follow-up.

A case-series study by Mousavi et al. involving 22 subjects with stage IA, grade 1 endometrial cancer who underwent conservative treatment with megestrol acetate, medroxyprogesterone acetate (MPA) or MPA and metformin reported complete remission rate of 45.5 %, relative remission rate of 9.1 %, persistence in 18.2 % of subjects and disease progression in 27.3 % subjects [39].

In a systematic review and meta-analysis involving 445 patients with early-stage endometrial cancer treated with oral progestin, Qin et al. reported disease regression rate of 82.4 %, a relapse rate of 25.0 %, a pregnancy rate of 28.8 %, and a live birth rate of 19.6 % [40].

In a retrospective study, Park et al. analysed the long-term oncologic outcomes of a fertility-sparing management using oral progestin (medroxyprogesterone acetate or megestrol acetate) in 148 young women with stage IA, grade 1, endometrioid endometrial cancer. They reported a complete response rate of 77.7 %, and a recurrence rate of

Table 1
Results and outcomes (MPA-medroxyprogesterone acetate; TAH- Total Abdominal Hysterectomy; AIH- Artificial Insemination; CS- Caesarean Section).

Patient	Age (years)	Treatment	Primary response	Secondary response	Time of response (mos)	Time of recurrence (mos)	Follow-up period (mos)	Outcome	Primary histopathologic diagnosis
1	40	MPA	Yes	–	3	15	25	TAH- Endometrioid adenocarcinoma of the endometrium Stage IA	Endometrioid adenocarcinoma of the endometrium, grade 1
2	33	MPA	Yes	–	3	84	120	AIH No II non effecta; TAH- Endometrioid adenocarcinoma of the endometrium, Stage IA	Endometrioid adenocarcinoma of the endometrium, grade 1
3	27	MPA	Yes	–	3	33	60	AIH No IV non effecta; Lost to follow-up	Endometrioid adenocarcinoma of the endometrium, grade 1
4	37	MPA	No	Yes	8	–	48	Successful pregnancy - Delivered by CS (39 weeks 6 days)	Endometrioid adenocarcinoma of the endometrium, grade 1
5	30	MPA	No	Yes	9	–	11	No conception during the study period	Atypical polypoid adenomyoma of the endometrium
6	42	MPA	No	Yes	6	–	25	AIH non effecta	Atypical endometrial hyperplasia
7	26	MPA	No	Yes	6	–	12	No conception during the study period	Atypical endometrial hyperplasia
8	35	MPA	No	Yes	7	–	19	No conception during the study period	Endometrioid adenocarcinoma of the endometrium, grade 2
9	30	MPA	Yes	–	3	–	14	No conception during the study period	Endometrioid adenocarcinoma of the endometrium, grade 1

30.4 %. Factors including BMI <25 kg/m2, treatment with MPA (compared to MA), maintenance treatment and pregnancy were associated with lower risk of recurrence [41]. Obesity has been shown to be an important risk factor in developing endometrial cancer [42,43]. Although progestin therapy has a high efficacy in the treatment of early-stage endometrial cancer in young women, it is associated with a significant increase in body weight [44]. A study by Park et al., evaluated the influence of body weight change during fertility-sparing treatment of women with early-stage endometrial cancer on the oncologic and pregnancy outcomes. They conclude that it has little influence on complete response, recurrence, pregnancy, and live birth rates, but pre and posttreatment BMIs of ≥25 kg/m2 were significant predictors for poor treatment response and high recurrence, highlighting the importance of maintaining patients' normal BMIs during progestin therapy [45].

Piatek et al. conducted a systematic review including 25 studies with a total of 812 patients with early-stage endometrial cancer or atypical endometrial hyperplasia and reported a response (complete/partial) rate to treatment of 83 %, a relapse rate of 25.3 %, with 17 % of patients being refractory to fertility-sparing treatment. They assessed the adverse effects of progestin therapy in 9 studies and found that the most commonly reported were weight gain, transient liver dysfunction, coagulation abnormality, breast pain and weight loss [31]. We report no adverse effects in our study.

Regarding pregnancy outcomes, a study by Chae et al. involving 118 patients presumed to have stage IA, grade 1–2 endometrioid endometrial cancer who were treated with medroxyprogesterone acetate/levonorgestrel-release intra-uterine device reported that 71 had complete remission, and 49 of them tried to conceive, with a total live birth rate of 66.6 %. This study also shows the impact of pregnancy on recurrence of endometrial cancer. Namely, they reported that recurrence in the pregnant group was lower than that in the non-pregnant group, 18.2 % vs 51.9 %, respectively, and the time to recurrence was significantly longer in the pregnant group than in the non-pregnant group, 26 months (range 20–38) and 12 months (range 4–48) respectively [46]. The positive effect of pregnancy on the prognosis of endometrioid endometrial cancer has also been reported in a study by Park et al., who have reported a recurrence rate of 20.5 % and 36.6 % in the pregnant and non-pregnant groups, respectively [41]. This can be explained by the fact that pregnancy provides prolonged exposure to endogenous progesterone, resulting in lower recurrence rate of endometrioid endometrial cancer.

5. Conclusion

Conservative treatment approach to patients with endometrial cancer aiming to preserve fertility can be safe and have acceptable outcomes in terms of oncologic response as well as pregnancy results. High-dose medroxyprogesterone acetate therapy is an effective option for fertility preservation in women with well-differentiated endometrioid adenocarcinoma stage IA. The selection of endometrial cancer patients for whom fertility-sparing progestin therapy is appropriate is of great importance to achieve the best outcomes. Continuous and careful monitoring of patients undergoing conservative treatment is essential, due to the risk of disease recurrence and progression.

CRediT authorship contribution statement

Gligor Tofoski: Conceptualization, Methodology, Writing – review & editing. **Goran Dimitrov:** Conceptualization, Methodology. **Elena Dzikova:** Methodology, Project administration. **Ana Daneva Markova:** Project administration, Writing – review & editing. **Irena Aleksioska Papestiev:** Project administration, Writing – review & editing. **Rosa Naumovska:** Investigation, Data curation. **Iskra Dukova:** Formal analysis, Data curation. **Natasha Ilieva:** Writing – original draft, Writing – review & editing, Data curation. **Biljana Ognenovska-Jankovska:** Investigation, Data curation. **Aleksandra Biljan:** Writing – original draft, Writing – review & editing. **Jean Calleja-Agius:** Writing – review & editing.

Declaration of interests

The author Jean Calleja-Agius is a Guest Editor for the European Journal of Surgical.

Oncology and was not involved in the editorial review or the decision to publish this article.

The authors declare that they have no other known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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