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Fertility-sparing treatment of endometrial cancer - is it possible? A case study

Milena Leziak: milena.leziak@wp.pl, ORCID: https://orcid.org/0000-0001-9911-5534
Klaudia Żak: zakklaudia3@gmail.com, ORCID: https://orcid.org/0000-0003-2421- 2553
Małgorzata Satora: msatoraa@gmail.com, ORCID: https://orcid.org/0000-0002-6010-9732
Justyna Szpyra: justyna.szpyra1@gmail.com, ORCID: https://orcid.org/0000-0003-0041-9584
Natalia Kluz: nataliakluz99@gmail.com, ORCID: https://orcid.org/0000-0002-5801-5913
Krzysztof Kułak: Krzysztof.kulak@gmail.com, ORCID: https://orcid.org/0000-0001-9059-484X

Milena Leziak[1], Klaudia Zak (Klaudia Żak)[1], Małgorzata Satora (Małgorzata Satora)[1], Justyna Szpyra[1], Natalia Kluz[1], Krzysztof Kulak (Krzysztof Kułak)[2]

1. Medical University of Lublin
   al. Racławickie 1, 20-059 Lublin, POLAND
2. 1st Department of Gynecologic Oncology and Gynecology,
   ul. Staszica 16, 20-081 Lublin, POLAND

Abstract

Background: Endometrial cancer is the most common gynecological malignant neoplasm, which occurs in the majority of cases postmenopausally. The current standard of treatment is surgical - total hysterectomy. However, it may also occur in younger patients, who are planning pregnancy and want to choose fertility-sparing treatment. For those patients oral high dose progestin therapy with or without hysteroscopic resection should be proposed. It is usually a good option for women with well-differentiated (G1) cancers. For patients with higher grade (G2, G3) or contraindications to progestins, fertility-sparing treatment of endometrial cancer seems impossible.
Case report: We present the case of a 34-year old woman diagnosed gynecologically due to abnormal bleeding from the genital tract. Based on USG, she was diagnosed with endometrial

polyp. As a treatment, hysteroscopic resection was performed. In the histopathological evaluation G2 endometrial cancer was diagnosed. The standard approach would be a total hysterectomy, but the patient was interested in fertility-sparing options. Due to contraindications to progestins a total hysteroscopic resection was performed counseling the patient about the risks of a novel approach. Histopathology revealed no residual disease and no other lesions during the first year of observations occurred.
Conclusion: Total hysteroscopic resection without further progestin therapy may offer the possibility to treat G2 endometrial cancer despite contraindications to the administration of progestins. Our case report should also encourage further evaluation of fertility-sparing management of endometrial cancer with higher than G1 grade.

Key words: endometrial cancer; fertility; oncology

Introduction

Endometrial cancer is the most common gynecological malignant neoplasm, responsible for 6% of worlds' new cancer cases and 3% of cancer deaths each year. The majority of women diagnosed with endometrial cancer are postmenopausal (median 62 years old) [1]. However, in some cases it may occur in younger patients, rarely in women under the age of 40 (4% of all diagnosed). 75% of patients with endometrial cancer are diagnosed in early stages (FIGO I or II), with a 5-year survival rate of 74-91%. In the comparison, in women with stage III or IV this rate is 57-66% and 20-26%, respectively [2].

Endometrial cancer is classified into two types: 1 and 2 based on epidemiology, clinical course and histological changes. Type 1 is endometrioid carcinoma (ECC) - often preceded by endometrial hyperplasia and rather confined to the uterus. It occurs in women mainly in the pre- and perimenopausal period. Type 2 is high-grade non-endometrioid carcinoma (NEEC). It mainly occurs in elderly women after menopause and has an aggressive clinical course [3].

The gold standard of treatment for endometrial cancer is based on surgery. Tumor's stage and its grade have a significant role in the choice of the therapy. Standard approach for stage I and II, grades 1 and 2 of endometrial cancer is surgery, postoperative vaginal brachytherapy and radiation therapy alone. Treatment for stage I and II, grade 3 of endometrial cancer is surgery and postoperative chemotherapy with or without radiation therapy. Treatment options for stage III and IV of endometrial cancer are surgery followed by chemotherapy or radiation therapy, chemotherapy and radiation therapy, hormone therapy or biological therapy [4]. The cornerstone of endometrial cancer treatment is total hysterectomy and removal of both fallopian tubes and ovaries. Surgery can provide valuable information for staging and molecular characterization assessments. This is useful for selecting the adjuvant treatment that patients will benefit most from [5]. However, hysterectomy is associated with the risk of intestinal or bladder damage, infection, haemorrhage, nerve injury, venous thromboembolism and vaginal cuff dehiscence [6]. After surgery the quality of sexual intercourse is most often deteriorated. What is most important for younger patients - this method also does not preserve the patient's fertility.

The question about fertility-sparing options, especially for women in the child bearing age is asked. The most common for that group of patients is the treatment of oral high dose progestin therapy, in which medroxyprogesterone acetate (MPA) or megestrol acetate (MA) are the most frequently prescribed drugs. Their effectiveness has been confirmed by several studies [7][8][9]. An alternative endometrial cancer fertility-sparing treatment is using the combination of hysteroscopic resection followed by progestin therapies [9][10]. A close monitoring and total hysterectomy after child bearing completion or disease progression are inherent. Both are good options for women of childbearing age with intramucous, well-differentiated (G1), endometrioid type cancer [7]. For moderately differentiated (G2/G3) tumors, data concerning the efficacy and safety of fertility-sparing treatment is very limited.

Case report

A 34-year old woman with abnormal vaginal bleeding from the genital tract was admitted to the gynecology department for diagnosis and treatment. Transvaginal USG was performed and endometrial polyp (11mmx40mm) was diagnosed. As a treatment, hysteroscopic resection of the polyp was performed. The procedure was free of complications and the patient remained in a good condition. The collected material was subjected to histopathological evaluation in which G2 (moderately differentiated) endometrial cancer type 1 was diagnosed. Postoperatively, in the FIGO classification system, the stage of disease was defined as IA, which means that "the cancer was found only in the endometrium or less than one-half of the myometrium". It was defined as a low risk endometrial carcinoma [11]. The standard approach would be a total hysterectomy with bilateral salpingo-oophorectomy, but the patient refused it and was interested in fertility sparing options. Due to contraindications to progestins (history of deep vein thrombosis) only a total hysteroscopic endometrial resection was performed. Histopathological evaluation revealed no residual disease. Very important was informing the patient that it was not a standard treatment and counseling about the risk of this novel approach. The patient was discharged home and close monitoring including transvaginal ultrasound and physical examination every 6 months was recommended. During the follow-up hysteroscopic and endometrial biopsy were planned only in case of abnormal uterine bleeding or atypical ultrasound findings. The postoperative period was uneventful. After the patient's child bearing plans are finished or in case of disease recurrence, a total hysterectomy is planned.

Discussion

There are several types of treatment for the fertility-sparing management of endometrial cancer. Progestins and hysteroscopic resection are the most common modalities of treatment. It has not been established which agent, dose or duration of treatment provides the most benefits [3, Leone]. Fertility-sparing treatments should be considered in patients with atypical hyperplasia or endometrioid intra-epithelial neoplasia or grade 1 endometrioid carcinoma without myometrial invasion and without genetic risk factors [ESMO]. Only a few studies have

reported results of fertility-sparing treatment in patients with more advanced disease [12][13][14][15][16][17].

Park et al. described the results of fertility-preserving treatments in 48 patients under 40 years old with stage IA and grade 1-3 endometrial cancer. Patients were given oral progestins and the median treatment duration was 10 months. Patients were divided into three groups: first with stage IA grade 2-3 and no myometrial invasion, patients with stage IA grade 1 with superficial uterine muscle infiltration and patients with stage IA grade 2-3 with superficial uterine muscle infiltration. The complete response rates (CR) were 76.5%, 73.9%, and 87.5%, respectively. Recurrence rates for those groups were 23.1%, 47.1%, and 71.4%, respectively. As a conclusion, progestin therapy was not proposed as a reasonable solution for patients with stage IA grade 2-3 with superficial uterine muscle infiltration [12].

Chae et al. retrospectively analyzed patients diagnosed with stage IA, grade 1-2 endometrial cancer who had received fertility-conserving treatment with levonorgestrel-releasing intrauterine devices and medroxyprogesterone. Researchers found that higher grade of endometrial cancer was associated with a higher rate of pregnancy failure after treatment [15].

There are some more promising studies confirming progestin treatment as an option for higher than grade 1 endometrial cancer, but the number of examined patients is still limited [14][16]. Some studies suggest also that adding metformin to progestin therapy seems to provide some improvements, especially in patients with metabolic syndrome [17][9].

The most common fertility-sparing treatment of endometrial carcinoma is oral high dose progestin therapy, sometimes also with performing hysteroscopic resection before pharmacological treatment. Hysteroscopic resection followed by progestogens is associated with a higher complete response rate, live birth rate, and lower recurrence rate than oral progestogens alone [9]. In our case only a total hysteroscopic endometrial resection was performed, because there was a contraindication to taking progestins due to the patient's history of deep vein thrombosis. There are more contraindications to progestins: suspection or history of breast cancer or other estrogen- or progesterone-dependent neoplasia, active deep vein thrombosis, pulmonary embolism or a history of these conditions, active or recent (within the past year) arterial thromboembolic disease, known liver dysfunction or disease, missed abortion and known or suspected pregnancy. For patients with those contraindications, fertility-sparing treatment of endometrial cancer seems impossible.

Obviously, the patient needs to be monitored for recurrence for the long term. Evaluation of response to treatment is crucial, and there is currently no widely accepted standard protocol. Despite all the limitations, it may be an alternative option of fertility-sparing treatment for patients with G2 endometrial cancer with contraindication to progestins, which will offer them the opportunity to maintain fertility. However, this method should be tested on a larger group of patients. More research is needed in order to test its effectiveness and safety.

Conclusions

There is no high-quality evidence to establish the efficacy and safety of fertility-conserving treatment for patients with G2 endometrial cancer. There are also no studies assessing the effects of hysteroscopic endometrial resection without the addition of progestins. The patient, which is treated this way, should be aware of the risk of this method. However, such a solution may offer the possibility to treat G2 endometrial cancer despite contraindications to the administration of progestins. Above-mentioned studies and our case report should encourage further evaluation of fertility-sparing management.

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