Editorial

Fertility Preservation in Young Patients with Endometrial Cancer

Georgios Androutsopoulos[1,*], Ioannis C. Kotsopoulos[2] and Georgios Decavalas[1]

[1]*Department of Obstetrics and Gynecology, University of Patras, Medical School, Rion, Greece*

[2]*Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead, United Kingdom*

Endometrial cancer (EC) represents the most common malignancy of the female genital tract in developed countries [1-10]. Based on recent data, the average life time risk for EC worldwide is approximately 1.71%.[11] Although the disease mainly affects postmenopausal women, approximately 4% of patients are younger than 40 years [1-10, 12-15]. In the majority of the patients, abnormal uterine bleeding remains the most common symptom [1-7, 9, 10, 12, 13].

According to the recommendations of many international scientific societies (ACOG, FIGO, SGO, ESGO and ESMO), systematic surgical staging represents the initial treatment approach in all patients with EC [2-4, 6-10, 12, 16, 17]. This is mainly because systematic surgical staging offers many diagnostic, prognostic and therapeutic benefits in these patients [2-4, 6, 8, 12, 16, 17]. The extent of surgery should be carefully individualized according to the type of EC and the patient's general medical status [8].

In this light, patients younger than 40 years who wish to preserve their fertility, should be carefully counselled that fertility sparing treatment is a non-standard approach and the available data on outcomes is limited [8, 12, 15, 18, 21]. Moreover, they should be able to accept close follow-up during and after the fertility sparing treatment [8, 12, 19]. Furthermore, they should be informed about the need of systematic surgical staging in case of treatment failure or after childbearing [8, 12, 15, 18, 19, 21].

In particular, only patients with FIGO stage IA, grade 1 and type I (endometrioid) EC are eligible for fertility sparing treatment [8, 12, 14, 15, 22]. These patients should have strong desire for fertility preservation, no contraindications for medical treatment and informed consent about fertility sparing treatment [8, 12, 15]. Additionally, they should be referred to specialised centres [8, 12, 18].

An appropriate endometrial specimen should be obtained with dilatation and curettage, hysteroscopy or office endometrial biopsy [8, 12, 15, 23-26]. However, dilatation and curettage is superior to office endometrial biopsy, because it provides a better specimen [8, 12, 23, 24, 26]. The specimen should be examined by an expert pathologist, in order to diagnose accurately the grade and the type of EC [8, 12, 15, 26]. Additionally, the assessment of hormone receptor status (estrogen, progesterone) and the expression of molecular prognostic markers (p53, Ki-67, HE-4), might provide useful information regarding the biologic behavior of tumor [8, 12, 14, 15, 27]. Patients with highly aggressive tumors are not eligible for fertility sparing treatment [8, 12, 15].

Furthermore, the presence of myometrial invasion and/or extrauterine disease (synchronous ovarian tumor, ovarian metastases, suspicious retroperitoneal nodes) should be evaluated with magnetic resonance imaging (MRI), ultrasound and/or computing tomography (CT) [8, 12, 15, 26, 28-30]. Magnetic resonance imaging is superior to ultrasound and computing tomography, in evaluating the depth of myometrial invasion in these patients [8, 12, 15, 26, 28-30]. Laparoscopy, although it is optional, might provide useful data regarding disease stage [12, 15].

Fertility sparing treatment in young patients with FIGO stage IA, grade 1 and type I (endometrioid) EC, is based on oral progestins [8, 12, 15, 31-33]. The most commonly used progestin regimens are medroxyprogesterone acetate and megestrol acetate [8, 12, 15, 26, 31-33]. The combined use of

*Address correspondence to this author at the Assistant Professor, Department of Obstetrics and Gynecology, University of Patras, Medical School, Rion 26504, Greece; Tel: +306974088092; Fax: +302613604010;
E-mail: androutsopoulos@upatras.gr; androutsopoulosgeorgios@hotmail.com

E-ISSN: 2413-7308/16

levonorgestrel releasing intrauterine device with GnRH-analogues, shows promising results and represents an alternative choice [8, 26, 32, 34]. The average daily dosage of medroxyprogesterone acetate is 400-600 mg, while that of megestrol acetate is 160-320 mg [8, 12, 15, 35]. Moreover, the average duration of treatment with oral progestins is approximately 6 months [8, 12, 15, 26]. In the past, many patients were treated for more than 6 months [15, 36, 37]. Nevertheless, there are no evidence to support the prolonged use of oral progestins, in order to achieve late response [15, 26, 36, 37].

During the treatment, all patients should be evaluated with endometrial sampling (dilatation and curettage or hysteroscopy) every 3 months [8, 12, 15, 26, 32, 38]. After completion of the 6-month treatment, they should be further evaluated with magnetic resonance imaging in order to assess the response to the fertility sparing treatment [8, 12, 15, 26, 29, 38].

If there is no response after the 6-month treatment with oral progestins, then patients should have systematic surgical staging according to the recommendations of the international scientific societies (ACOG, FIGO, SGO, ESGO and ESMO) [2-4, 6-10, 12, 15-17, 26].

On the other hand, if there is a complete response after the 6-month period, then patients should be referred to a fertility clinic in order to achieve pregnancy as soon as possible [8, 12, 15, 39-42]. Worth to notice that pregnancy significantly associated with a lower risk for recurrence [8, 12, 15, 32, 39]. If they do not wish pregnancy at this time, they should continue the treatment with oral progestins and they should have a re-evaluation every 6 months [8, 12, 15, 26, 32, 39].

Based on recent studies, the overall response rate in EC patients having fertility sparing treatment is approximately 75% [8, 12, 15, 20, 26, 39, 43]. However, the overall recurrence rate ranges between 30% and 40% [8, 12, 15, 20, 39, 43]. This is the main reason why, all young EC patients should have systematic surgical staging after childbearing [8, 12, 15, 26].

In conclusion, fertility sparing treatment using progestins is a promising treatment approach for well selected young patients diagnosed with FIGO stage IA, grade 1 and type I (endometrioid) EC. Nevertheless, this management still represents a non-standard approach for them [2-4, 6-10, 12, 16, 17]. In this light, all patients should be carefully informed about the effectiveness of that innovative treatment approach and the need of systematic surgical staging in case of treatment failure or after childbearing [8, 12, 15, 20, 39, 43].

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

[1] Siegel R, Miller K, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66(1): 7-30. https://doi.org/10.3322/caac.21332

[2] Androutsopoulos G. Current treatment options in patients with endometrial cancer. J Community Med Health Educ 2012; 2(12): e113. https://doi.org/10.4172/2161-0711.1000e113

[3] Androutsopoulos G, Decavalas G. Management of endometrial cancer. Int J Translation Community Dis 2013; 1(1): 1-3.

[4] Androutsopoulos G, Decavalas G. Endometrial cancer: current treatment strategies. World J Oncol Res 2014; 1(1): 1-4.

[5] Sorosky J. Endometrial cancer. Obstet Gynecol 2012; 120(2 Pt 1): 383-97. https://doi.org/10.1097/AOG.0b013e3182605bf1

[6] Androutsopoulos G, Michail G, Adonakis G, Decavalas G. Current treatment approach of endometrial cancer. Int J Clin Ther Diagn 2015; S1(3): 8-11.

[7] Androutsopoulos G, Adonakis G, Decavalas G. Present and future in endometrial cancer treatment. Obstet Gynecol Int J 2015; 2(2): 00031. https://doi.org/10.15406/ogij.2015.02.00031

[8] Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J, *et al*. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2016; 27(1): 16-41. https://doi.org/10.1093/annonc/mdv484

[9] Androutsopoulos G, Michail G, Decavalas G. New insights in endometrial cancer treatment. Clinics in Oncology - Endometrial Cancer 2016; 1: 1040.

[10] Androutsopoulos G, Decavalas G. Standard and novel therapies in endometrial cancer. J Gynecol Women's Health 2016; 1(3): 555564. https://doi.org/10.19080/jgwh.2016.01.555564

[11] WHO. Estimated cancer incidence, mortality and prevalence worldwide in 2012. GLOBOCAN 2012.

[12] ACOG. ACOG practice bulletin # 149: Endometrial cancer. Obstet Gynecol 2015; 125: 1006-26. https://doi.org/10.1097/01.AOG.0000462977.61229.de

[13] Koufopoulos N, Carrer D, Koureas N, Sofopoulos M, Paraoulakis I, Androutsopoulos G, *et al*. Pathological data on 19 cases of endometrioid carcinoma of the endometrium in women of reproductive age. Int J Gynecol Cancer 2013; 23(8 Suppl 1): 322.

[14] Duska L, Garrett A, Rueda B, Haas J, Chang Y, Fuller A. Endometrial cancer in women 40 years old or younger. Gynecol Oncol 2001; 83(2): 388-93. https://doi.org/10.1006/gyno.2001.6434

[15] Erkanli S, Ayhan A. Fertility-sparing therapy in young women with endometrial cancer: 2010 update. Int J Gynecol Cancer 2010; 20(7): 1170-87. https://doi.org/10.1111/IGC.0b013e3181e94f5a

[16] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009; 105(2): 103-4. https://doi.org/10.1016/j.ijgo.2009.02.012

[17] Burke W, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye A, *et al*. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014; 134(2): 385-92. https://doi.org/10.1016/j.ygyno.2014.05.018

[18] Feichtinger M, Rodriguez-Wallberg K. Fertility preservation in women with cervical, endometrial or ovarian cancers. Gynecol Oncol Res Pract 2016; 3: 8. https://doi.org/10.1186/s40661-016-0029-2

[19] Parlakgumus H, Kilicdag E, Simsek E, Haydardedeoglu B, Cok T, Aytac P, *et al*. Fertility outcomes of patients with early stage endometrial carcinoma. J Obstet Gynaecol Res 2014; 40(1): 102-8. https://doi.org/10.1111/jog.12132

[20] Gallos I, Yap J, Rajkhowa M, Luesley D, Coomarasamy A, Gupta J. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2012; 207(4): 266.e1-12. https://doi.org/10.1016/j.ajog.2012.08.011

[21] Kesterson J, Fanning J. Fertility-sparing treatment of endometrial cancer: options, outcomes and pitfalls. J Gynecol Oncol 2012; 23(2): 120-4. https://doi.org/10.3802/jgo.2012.23.2.120

[22] Navarria I, Usel M, Rapiti E, Neyroud-Caspar I, Pelte M, Bouchardy C, *et al*. Young patients with endometrial cancer: how many could be eligible for fertility-sparing treatment? Gynecol Oncol 2009; 114(3): 448-51. https://doi.org/10.1016/j.ygyno.2009.05.038

[23] Larson D, Johnson K, Broste S, Krawisz B, Kresl J. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. Obstet Gynecol 1995; 86(1): 38-42. https://doi.org/10.1016/0029-7844(95)00105-Z

[24] Leitao M, Jr., Kehoe S, Barakat R, Alektiar K, Gattoc L, Rabbitt C, *et al*. Comparison of D&C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. Gynecol Oncol 2009; 113(1): 105-8. https://doi.org/10.1016/j.ygyno.2008.12.017

[25] Falcone F, Laurelli G, Losito S, Di Napoli M, Granata V, Greggi S. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. J Gynecol Oncol 2016: e2.

[26] Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, *et al*. European Society of Gynecological Oncology Task Force for Fertility Preservation: Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients. Int J Gynecol Cancer 2015; 25(7): 1258-65. https://doi.org/10.1097/IGC.0000000000000493

[27] Shah M, Wright J. Management of endometrial cancer in young women. Clin Obstet Gynecol 2011; 54(2): 219-25. https://doi.org/10.1097/GRF.0b013e318218607c

[28] Kim S, Kim H, Song Y, Kang S, Lee H. Detection of deep myometrial invasion in endometrial carcinoma: comparison of transvaginal ultrasound, CT, and MRI. J Comput Assist Tomogr 1995; 19(5): 766-72. https://doi.org/10.1097/00004728-199509000-00013

[29] Rockall A, Qureshi M, Papadopoulou I, Saso S, Butterfield N, Thomassin-Naggara I, *et al*. Role of Imaging in Fertility-sparing Treatment of Gynecologic Malignancies. Radiographics 2016; 36(7): 2214-33. https://doi.org/10.1148/rg.2016150254

[30] Kinkel K, Kaji Y, Yu K, Segal M, Lu Y, Powell C, *et al*. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology 1999; 212(3): 711-8. https://doi.org/10.1148/radiology.212.3.r99au29711

[31] Burke W, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye A, *et al*. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol 2014; 134(2): 393-402. https://doi.org/10.1016/j.ygyno.2014.06.003

[32] Park J, Nam J. Progestins in the fertility-sparing treatment and retreatment of patients with primary and recurrent endometrial cancer. Oncologist 2015; 20(3): 270-8. https://doi.org/10.1634/theoncologist.2013-0445

[33] Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, *et al*. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 2007; 25(19): 2798-803. https://doi.org/10.1200/JCO.2006.08.8344

[34] Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol 2011; 22(3): 643-9. https://doi.org/10.1093/annonc/mdq463

[35] Koskas M, Uzan J, Luton D, Rouzier R, Darai E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril 2014; 101(3): 785-94. https://doi.org/10.1016/j.fertnstert.2013.11.028

[36] Randall T, Kurman R. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstet Gynecol 1997; 90(3): 434-40. https://doi.org/10.1016/S0029-7844(97)00297-4

[37] Kaku T, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, *et al*. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett 2001; 167(1): 39-48. https://doi.org/10.1016/S0304-3835(01)00462-1

[38] Koskas M, Azria E, Walker F, Luton D, Madelenat P, Yazbeck C. Progestin treatment of atypical hyperplasia and well-differentiated adenocarcinoma of the endometrium to preserve fertility. Anticancer Res 2012; 32(3): 1037-43.

[39] Park J, Kim D, Kim J, Kim Y, Kim K, Kim Y, *et al*. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer 2013; 49(4): 868-74. https://doi.org/10.1016/j.ejca.2012.09.017

[40] Zapardiel I, Cruz M, Diestro M, Requena A, Garcia-Velasco J. Assisted reproductive techniques after fertility-sparing treatments in gynaecological cancers. Hum Reprod Update 2016; 22(3). https://doi.org/10.1093/humupd/dmv066

[41] Park J, Seong S, Kim T, Kim J, Kim S, Bae D, *et al*. Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. Obstet Gynecol 2013; 121(1): 136-42. https://doi.org/10.1097/AOG.0b013e31827a0643

[42] Chao A, Chao A, Wang C, Lai C, Wang H. Obstetric outcomes of pregnancy after conservative treatment of endometrial cancer: case series and literature review. Taiwan J Obstet Gynecol 2011; 50(1): 62-6. https://doi.org/10.1016/j.tjog.2009.10.006

[43] Chen M, Jin Y, Li Y, Bi Y, Shan Y, Pan L. Oncologic and reproductive outcomes after fertility-sparing management

with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. Int J Gynaecol Obstet 2016; 132(1): 34-8. https://doi.org/10.1016/j.ijgo.2015.06.046

Received on 22-11-2016 Accepted on 30-11-2016 Published on 06-12-2016

http://dx.doi.org/10.15379/2413-7308.2016.03.05