FERTILITY PRESERVATION IN PATIENTS WITH ENDOMETRIAL CANCER

***Hasan Onur Topçu, Zeynep Aslı Oskovi, Mehmet Mutlu Meydanlı**

Zekai Tahir Burak Women's Health Care Education and Research Hospital, Ankara, Turkey
**Correspondence to dronurtopcu@gmail.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 01.12.14 **Accepted:** 19.02.15
Citation: EMJ Repro Health. 2015;1[1]:81-86.

ABSTRACT

Endometrial carcinoma (EC) is the most common gynaecological cancer, with 2-14% of cases occurring in women <40 years of age. When considering the increase in the delay of pregnancy in developing countries, the incidence of EC in nulliparous women is likely to increase. Younger women with EC have a chance to preserve their fertility due to the probability of being diagnosed with early-stage and low-grade endometrioid carcinomas. However, it should be noted that the most important step of fertility preservation in patients with EC is patient selection. The appropriate clinical criteria should include: a) well-differentiated histology; b) absence of myometrial invasion; c) absence of extrauterine or pelvic and pre-aortic lymphatic spread; and d) absence of synchronous ovarian tumour. There is no consensus regarding endometrial suppression therapy or the follow-up period for fertility preservation in women with EC. Therefore, this review aims to evaluate the current literature.

Keywords: Endometrial cancer, fertility preservation, fertility sparing, progestin, conservative treatment.

INTRODUCTION

Endometrial carcinoma (EC) is the most common gynaecological malignancy amongst women, with a lifetime risk of 2.6% in developed countries.[1] It is predominantly seen in the postmenopausal period; however, 15-25% of cases are premenopausal[2] and 2-14% of cases affect women <40 years of age.[3] The endometrial tumours of those of a younger age are low-grade ECs that are usually diagnosed at earlier stages and therefore have an excellent prognosis, with a 98% 10-year disease-free survival rate.[3] The incidence of nulliparity in premenopausal women with EC is 55%.[4] The standard treatment of EC is comprehensive surgical staging, which includes total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy.[5] For younger patients who have not completed pregnancy, this kind of definitive surgical management is not an acceptable option.

For gynaecological and non-gynaecological cancers of premenopausal women, a new concept termed 'oncofertility', which describes a multidisciplinary approach involving oncology and reproductive endocrinology, has come to prominence, especially during the last decade.[6] Young patients should be counselled by oncologists in the decision-making process with updated information for both surgical treatment and chemotherapeutic drugs with gonadal toxicity. The age of the patient, stage of EC, life expectancy, previous history of infertility, risk of progression and recurrence, duration of treatment, and when to consider hysterectomy should be discussed with patients before suggesting a fertility-preserving management option.

EC of young patients is usually related to unopposed excessive oestrogen exposure with risk factors such as infertility, obesity, polycystic ovary syndrome (PCOS), and chronic anovulation; which is described as 'Type 1' endometrial cancer. As this type of EC is reported to be highly hormone-dependent due to it being well differentiated, conservative fertility-sparing medical treatment strategies are also discussed for special patient populations.[7,8] Considering the aetiology of EC, evaluation of the risk of underlying infertility before planning pregnancy is recommended, and assisted reproductive technology (ART) is suggested in selected groups to shorten the treatment period.[8] In clinical studies,

medroxyprogesterone acetate (MPA), megestrol acetate (MA), hydroxyprogesterone acetate, 17α-hydroxyprogesterone caproate, norethindrone, gonadotropin-releasing hormone (GnRH) agonists, aromatase inhibitors, levonorgestrel-releasing intrauterine devices (LNG-IUDs), hysteroscopic excision procedures, and photodynamic treatment have been tried in selected patient groups.[6,7,9,10]

PATIENT SELECTION

Patient selection criteria for fertility-sparing therapy in complex atypical hyperplasia (CAH) and EC are identified in several clinical studies. Young patients still of child-bearing age, who accept the risks of unresponsiveness, progression, and recurrence, and who are convinced to attend follow-ups regularly are ideal candidates for conservative management. The patient should also be convinced that this is not the standard treatment, and comprehensive surgery will be planned after achievement of pregnancy or in case of failure in conservative management. The appropriate clinical criteria are: a) well-differentiated histology (Grade 1 Stage 1A), b) absence of myometrial invasion, c) absence of extrauterine or pelvic and pre-aortic lymphatic spread, and d) absence of synchronous ovarian tumour.[11] The age of the patient is unrelated to the possibility of remission, recurrence, progression, or pregnancy, and therefore there is no recommended age limit for fertility-sparing treatment.[7] However, storage of oocytes and likelihood of pregnancy decreases in patients >40 years of age.[12,13] Kudesia et al.[12] reported a live birth rate of >30% in a small-population *in vitro* fertilisation group who underwent fertility-sparing management, with a median age of 38.5±4 years. Besides the patient's age, ovarian reserve tests, such as follicle-stimulating hormone and anti-müllerian hormone levels, and antral follicle count should be considered in order to predict the likelihood of pregnancy or response to ART.[13]

Patient selection is an important step for fertility preservation in EC because hormonal therapy of EC with Lynch syndrome is ineffective and, therefore, fertility-sparing management is not an appropriate option for these patients.[14-16] Clinicians should consider Lynch syndrome in younger patients with a low body mass index (BMI) or undifferentiated and dedifferentiated carcinomas.[17] Transvaginal ultrasound (US) and computed tomography (CT) for evaluation of extrauterine spread and magnetic resonance imaging (MRI) for evaluation of myometrial invasion are recommended.[18] MRI is described as the most useful imaging technique to determine myometrial invasion, with a sensitivity of 57% and specificity of 96% when diagnosing whether a tumour is restricted to the endometrium.[19]

Co-existing synchronous ovarian tumours are not rare in EC cases. In a recent report by Song et al.,[20] the incidence of synchronous ovarian cancer (OVC) in women with EC and <40 years of age was reported as 4.5%. However, Walsh et al.[21] reported an incidence of 25% among women <45 years and these cases were mostly endometrioid adenocarcinomas. The presence of synchronous ovarian tumours with EC is more common in patients with a high BMI, and they generally have low-grade endometrioid tumours and favourable prognosis.[22-24] Laparoscopic evaluation with adnexal exploration and peritoneal cytology is recommended before starting conservative treatment.[25] Although preoperative imaging and diagnostic laparoscopy may help to detect adnexal involvement, 15% of synchronous tumours display normal preoperative imaging and 15% of patients display benign-appearing ovaries at the time of surgery. Therefore, patients should be informed about the risk of disease progression at the end of medical treatment due to the risk of occult OVC.

HORMONE TREATMENT

Type 1 ECs that commonly affect younger age groups are defined as well-differentiated carcinomas and therefore hormone receptor expression is expected to be positive in most cases. The most commonly used progestin agents are MPA and MA.[2,7] In a recent meta-analysis, Gunderson et al.[26] reported that in EC patients: 49% received MPA, 25% received MA, and 19% received an LNG-IUD. There is no consensus on the ideal agent, dosage, or duration of treatment in the literature. MPA is used with doses of 200-600 mg daily; while some studies report that a 200 mg daily dose of MPA is an appropriate regimen,[27] others advocate that a better response is observed with the high-dose regimen.[11,28,29] MA treatments have been given at a daily dose of 160 mg or 320 mg in clinical studies and they were both considered effective, with response rates >80%.[18,30,31] GnRH agonists are used mostly as an adjuvant drug to progestin therapy or can be used alone.[18,32,33] LNG-IUDs have also been found to be effective in clinical studies but this may not be a good option for fertility-seeking

patients. MA was found to be associated with a higher probability of remission and lower progression rates in a recent meta-analysis by Koskas et al.,[7] and was recommended as a first-line agent for medical treatment. However, Park et al.[34] suggested that, despite similar response rates to MA, the long-term outcomes of MPA treatment were more successful and with lower recurrence rates.

The minimum duration of treatment for regression is 3 months, with a median of 4-6 months.[2] At least 12 months of progesterone treatment is recommended for these patients.[35] Remission probability within 12 and 24 months of treatment is reported as 78% and 81.4%, respectively. Therefore, if no remission is attained by this time, radical surgery should be considered because the likelihood of remission after 12 months of treatment is not significant.[7] Response to progestin treatment strongly depends on the hormonal receptor status, and better response is seen in low-grade tumours.[36] Compared with CAH, the response rate is lower while the disease persistence rate is higher in EC.[26] Increased BMI is associated with lower response rates.[34] Gunderson et al.[26] reported a 77.7% response rate to hormonal therapy, with a durable response rate of 53.2% after 39 months of follow-up. Similarly, Park et al.[34] also reported a response rate of 77.7%, with a 68% rate of 5-year recurrence-free survival.

HYSTEROSCOPIC TECHNIQUES

Hysteroscopic resection of tumoural tissue followed by progesterone treatment has also become an option in conservative management. It is advocated that the addition of surgical resection to medical therapy shortens the time to remission and reduces recurrence rates, therefore giving the possibility of a faster return to fertility.[37] Gradual resection of the lesion also helps to provide pathological assessment of the depth of invasion. Mazzon et al.[10] report a pregnancy rate of 67% using a three-step technique: resection of the lesion, resection of the adjacent endometrial tissue, and resection of the myometrium, followed by MA administration with a dose of 160 mg/dl for 6 months. Laurelli et al.[38] treated patients with hysteroscopic resection of the lesion and the myometrium below, followed by oral MA for 6 months or LNG-IUD for 12 months. Arendas et al.[37] reported two cases of hysteroscopic resection of endometrial and endomyometrial tissue followed by use of oral MPA and a LNG-IUD, with no recurrence reported within 4 years of follow-up.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is an alternative option in gynaecological malignancies and involves selective destruction of tumour tissue by using a selective tumour photosensitiser, haematoporphyrin derivative, and laser light.[39] Choi et al.[9] evaluated 16 patients undergoing PDT for EC during a mean follow-up period of 78 months; the final response rate was reported as 68% and the pregnancy rate was reported at 57% among 7 patients who attempted to become pregnant.

FOLLOW-UP PROTOCOL

Follow-up of patients is essential in order to intervene in cases of persistence, progression, recurrence, and also in cases of co-existing synchronous OVC. First biopsy is recommended after 12 weeks of treatment because 12 weeks is considered the minimum time for response.[11] Follow-up protocols should be repeated every 3-6 months and the patient should be evaluated with pelvic examination, endometrial biopsy, hysteroscopy, testing for cancer antigen 125 (CA-125), and imaging techniques such as transvaginal US, MRI, or CT.[2,8] Endometrial sampling with dilatation and curettage (D&C) after removal of an LNG-IUD was reported to be more accurate than endometrial aspiration biopsy with an LNG-IUD in place, with a diagnostic concordance of 32.1% between examinations, while endometrial aspiration biopsy detected only three of the nine cases of endometrial adenocarcinoma detected by D&C.[40] D&C also reduces the tumour burden when compared with endometrial biopsy.[41] A flow chart describing the management of women with EC or CAH and eligible for fertility-sparing treatment is shown in Figure 1.

There is research into new biomarkers for predicting the response or recurrence rates for EC. Human epididymis protein 4, with a cut-off value of 70 pmol/l, was found to be superior to CA-125 with a cut-off of 35 U/ml as a predictor of recurrent disease.[42] Annexin-A2 expression was found to be effective in the prediction of recurrent disease in EC.[43] The younger patients, those with previous pregnancy, infertility, or treatment with MA were found more likely to achieve remission.[7] The risk of progression was investigated as

well, and it was found that the risk increased 3.95-fold when other medical therapies (MPA, hydroxyprogesterone caproate, norethisterone acetate, GnRH agonists, LNG-IUD, combination of GnRH agonists and LNG-IUD, bromocriptine, natural progesterone, ovulation induction, and oral contraceptives) were used in comparison with the use of MA.[7] However, clinicians should note that the study reported not only the progression outcomes of EC but also the progression outcomes of atypical endometrial hyperplasia. A recent systematic review of literature that compared outcomes of progestin therapy with CAH and Grade 1 endometrial adenocarcinoma revealed that the complete response rate was significantly higher in the CAH group (48%) than in the endometrial cancer group (66%); recurrence rate and persistent/progressive disease rate were higher in patients with carcinoma, 35% versus 23%, and 25% versus 14%, respectively. However, there was no difference between the reproductive outcomes.[26]

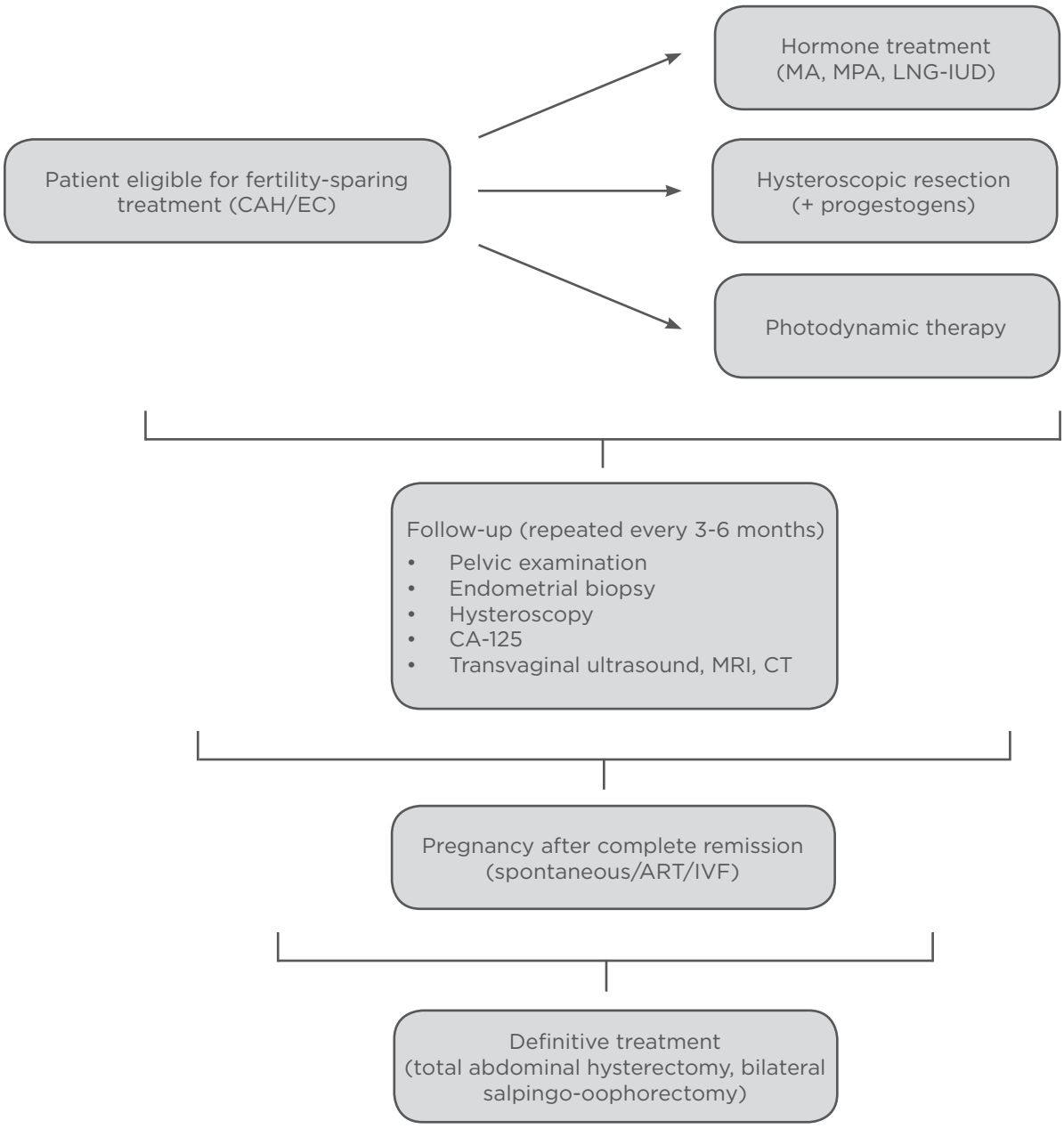

Figure 1: Flow chart describing the management of women with endometrial cancer (EC) or complex atypical endometrial hyperplasia (CAH) and eligible for fertility-sparing treatment.
MA: megestrol acetate; MPA: medroxyprogesterone acetate; LNG-IUD: levonorgestrel-releasing intrauterine device; CA-125: cancer antigen 125; MRI: magnetic resonance imaging; CT: computed tomography; ART: assisted reproductive technology; IVF: *in vitro* fertilisation.

PREGNANCY RATES

According to a meta-analysis by Koskas et al.,[7] 31.6% of the patients became pregnant. Among these patients, 54.1% achieved pregnancy by ART, 26.1% had spontaneous pregnancy, and 19.8% were not stated. Gallos et al.[44] found that the live birth rate was higher after ART (39.4%) than after spontaneous pregnancy (14.9%). ART is suggested especially in patients with PCOS, a higher BMI, and previous history of infertility, and it does not have a negative impact on the prognosis.[35] In a prospective study including CAH and low-grade early-stage EC, although complete remission of all cases had not been achieved, attempting pregnancy was allowed because it was thought that pregnancy could create an environment similar to a high-dose progesterone therapy. Live births occurred in this study and, after birth, persistent disease or EC relapse requiring definitive treatment was detected. With a median follow-up of 98 months, all patients were alive and free from disease.[45]

There are diverse and experimental fertility preservation options, such as gestational surrogacy,[12] embryo cryopreservation, oocyte cryopreservation, and ovarian tissue banking.[6] For women without partners, ovarian stimulation and oocyte cryopreservation may constitute an alternative because they do not require the use of a surgical procedure such as ovarian tissue cryopreservation.[46] However, ovarian tissue cryopreservation should be considered for oncological cases in which ovarian stimulation will cause a delay in treatment.[6] In a series of 11 patients diagnosed with different types of cancer, four patients achieved live births after treatment by oocyte vitrification.[47] The literature states that, for patients with EC who received fertility-preserving treatment, there is no increased risk of recurrence with the drugs used for ovulation induction.[35,48] Tamoxifen cannot be used because of its stimulatory effect on the endometrium.[13] Radiotherapy and chemotherapy are not a part of fertility-preserving treatment in endometrial cancer, therefore endometrial damage caused by these approaches is not a subject of fertility-preserving treatment in endometrial cancer. However, recurrent curettages and progestin use may cause intrauterine synechiae and disturbances in the endometrial lining, which may disrupt fertility.[49]

CONCLUSION

ECs in patients ≤40 years of age are not common. However, delayed pregnancy is likely to increase in the future, especially in developing countries. Fertility sparing in patients with EC should be an option in young prospective mothers. However, it should be considered that there has not been a consensus in the management of these patients. Appropriate patient selection, management, and follow-up protocols should be standardised after future prospective trials.

REFERENCES

1. Jemal A et al. Cancer statistics, 2008. CA Cancer J Clin. 2008;58(2):71-96.

2. Kalogera E et al. Preserving fertility in young patients with endometrial cancer: current perspectives. Int J Womens Health. 2014;6:691-701.

3. Garg K, Soslow RA. Endometrial carcinoma in women aged 40 years and younger. Arch Pathol Lab Med. 2014;138(3):335-42.

4. Soliman PT et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol. 2005;105(3): 575-80.

5. Burke WM et al; Society of Gynecologic Oncology Clinical Practice Committee. Endometrial cancer: a review and current management strategies: part I. SGO Clinical Practice Endometrial Cancer Working Group. Gynecol Oncol. 2014;134(2):385-92.

6. Dursun P et al. Oncofertility for gynecologic and non-gynecologic cancers: fertility sparing in young women of reproductive age. Crit Rev Oncol Hematol. 2014;92(3):258-67.

7. Koskas M et al. 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.

8. Tong XM et al. Fertility-preserving treatment and pregnancy outcomes in the early stage of endometrial carcinoma. Chin Med J (Engl). 2013;126(15):2965-71.

9. Choi MC et al. Fertility preservation via photodynamic therapy in young patients with early-stage uterine endometrial cancer: a long-term follow-up study. Int J Gynecol Cancer. 2013;23(4):698-704.

10. Mazzon I et al. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. Fertil Steril. 2010;93(4):1286-9.

11. Chiva L et al. Sparing fertility in young patients with endometrial cancer. Gynecol Oncol. 2008;111(2 Suppl):S101-4.

12. Kudesia R et al. Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma. Am J Obstet Gynecol. 2014;210(3):255.e1-4.

13. Dudani S, Gupta A. Fertility preservation in young patients' with cancer. J Midlife Health. 2014;5(4):165-7.

14. Shih KK et al. Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger. Gynecol Oncol. 2011;123(1):88-94.

15. Garg K et al. Endometrial carcinomas in women aged 40 years and younger:

tumors associated with loss of DNA mismatch repair proteins comprise a distinct clinicopathologic subset. Am J Surg Pathol. 2009;33(12):1869-77.

16. Schmeler KM et al. Endometrial cancer in young, normal-weight women. Gynecol Oncol. 2005;99(2):388-92.

17. Tafe LJ et al. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently underrecognized neoplasms. Mod Pathol. 2010;23(6):781-9.

18. Jafari Shobeiri M et al. Fertility sparing treatment in young patients with early endometrial adenocarcinoma: case series. Pak J Med Sci. 2013;29(2):651-5.

19. Sironi S et al. Myometrial invasion by endometrial carcinoma: assessment by MR imaging. AJR Am J Roentgenol. 1992;158(3):565-9.

20. Song T et al. Synchronous primary cancers of the endometrium and ovary in young women: a Korean Gynecologic Oncology Group Study. Gynecol Oncol. 2013;131(3):624-8.

21. Walsh C et al. Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol. 2005;106(4):693-9.

22. Soliman PT et al. Synchronous primary cancers of the endometrium and ovary: a single institution review of 84 cases. Gynecol Oncol. 2004;94(2):456-62.

23. AlHilli MM et al. Incidence and factors associated with synchronous ovarian and endometrial cancer: a population-based case-control study. Gynecol Oncol. 2012;125(1):109-13.

24. Shamshirsaz AA et al. Young patients with endometrial carcinoma selected for conservative treatment: a need for vigilance for synchronous ovarian carcinomas, case report and literature review. Gynecol Oncol. 2007;104(3):757-60.

25. Morice P et al. A need for laparoscopic evaluation of patients with endometrial carcinoma selected for conservative treatment. Gynecol Oncol. 2005;96(1):245-8.

26. Gunderson CC et al. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol. 2012;125(2):477-82.

27. Thigpen JT et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999;17(6):1736-44.

28. Ushijima K 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.

29. Hahn HS et al. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. Int J Gynecol Cancer. 2009;19(6):1068-73.

30. Shan BE et al. A prospective study of fertility-sparing treatment with megestrol acetate following hysteroscopic curettage for well-differentiated endometrioid carcinoma and atypical hyperplasia in young women. Arch Gynecol Obstet. 2013;288(5):1115-23.

31. Wang CJ et al. Fertility-preserving treatment in young women with endometrial adenocarcinoma: a long-term cohort study. Int J Gynecol Cancer. 2014;24(4):718-28.

32. Minig L et al. 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.

33. Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. Fertil Steril. 2003;80(6):1315-24.

34. Park JY 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.

35. Ricciardi E et al. Fertility-sparing treatment of endometrial cancer precursors among young women: a reproductive point of view. Eur Rev Med Pharmacol Sci. 2012;16(14):1934-7.

36. Shabani N et al. Prognostic significance of oestrogen receptor alpha (ERalpha) and beta (ERbeta), progesterone receptor A (PR-A) and B (PR-B) in endometrial carcinomas. Eur J Cancer. 2007;43(16):2434-44.

37. Arendas K et al. Hysteroscopic resection in the management of early-stage endometrial cancer: report of 2 cases and review of the literature. J Minim Invasive Gynecol. 2015;22(1):34-9.

38. Laurelli G et al. Conservative treatment of early endometrial cancer: preliminary results of a pilot study. Gynecol Oncol. 2011;120(1):43-6.

39. Godoy H et al. Photodynamic therapy effectively palliates gynecologic malignancies. Eur J Gynaecol Oncol. 2013;34(4):300-2.

40. Kim MK et al. Comparison of dilatation & curettage and endometrial aspiration biopsy accuracy in patients treated with high-dose oral progestin plus levonorgestrel intrauterine system for early-stage endometrial cancer. Gynecol Oncol. 2013;130(3):470-3.

41. Daniel AG, Peters WA 3rd. Accuracy of office and operating room curettage in the grading of endometrial carcinoma. Obstet Gynecol. 1988;71(4):612-4.

42. Brennan DJ et al. Serum HE4 detects recurrent endometrial cancer in patients undergoing routine clinical surveillance. BMC Cancer. 2015;15(1):33.

43. Alonso-Alconada L et al. Annexin-A2 as predictor biomarker of recurrent disease in endometrial cancer. Int J Cancer. 2015;136(8):1863-73.

44. Gallos ID et al. Prediction of regression and relapse of endometrial hyperplasia with conservative therapy. Obstet Gynecol. 2013;121(6):1165-71.

45. Signorelli M et al. Fertility-sparing treatment in young women with endometrial cancer or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. BJOG. 2009;116(1):114-8.

46. Oktay K et al. Efficiency of oocyte cryopreservation: a meta-analysis. Fertil Steril. 2006;86(1):70-80.

47. Martinez M et al. Obstetric outcome after oocyte vitrification and warming for fertility preservation in women with cancer. Reprod Biomed Online. 2014;29(6):722-8.

48. Ichinose M et al. The influence of infertility treatment on the prognosis of endometrial cancer and atypical complex endometrial hyperplasia. Int J Gynecol Cancer. 2013;23(2):288-93.

49. Wang CB et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer. 2002;94(8):2192-8.