

The Clinical Management of Endometrial Cancer in Young Women

Chyong-Huey Lai · Chin-Jung Wang · Angel Chao

Published online: 30 November 2012
© Springer Science+Business Media New York 2012

Abstract Endometrial cancer (EC) remains the leading female genital tract malignancy in industrialized countries. Incidence rates are increasing in many Asia countries. A trend of increased fractions occurring in young women also has been observed. When fertility preservation is not a concern, standard surgical staging and tailored adjuvant therapy regardless of age should be practiced. High remission rates with subsequent pregnancies are seen in clinical stage IA without myometrial invasion and in grade 1 EC of young women using oral high-dose progestins as fertility-sparing treatment (FST), yet high recurrences and synchronous or metachronous ovarian malignancies should be cautioned. Intrauterine progestins seem efficacious but more investigations are needed. Aromatase inhibitors have limited data at present. Current selection criteria have been suboptimal for preserving uterine and/or ovary for young EC patients. Investigations on molecular profiles for selecting candidates for preserving ovary or FST and whether to do a consolidation hysterectomy are necessary.

Keywords Endometrial cancer · Gynecologic cancer · Young age · Fertility-sparing · Hormone therapy · Progesterone · Aromatase inhibitor · Female genital tract malignancy

Introduction

Endometrial cancer (EC) remains the leading female genital tract malignancy in industrialized countries [1]. A total of

47,130 estimated new cases and 8,010 deaths from EC are projected to occur in 2012 in the U.S. population [2]. Incidence rates of EC are increasing in many Asia countries including Taiwan [1, 3, 4], Korea, and Japan [1, 4, 5]. EC is a disease of postmenopausal women, 4–5 % occurred in women aged 40 years or younger according to population-based studies from the U.S. and western countries [2, 6–8]. In the recent Cancer Registry Report in Taiwan, 10.3 % of all EC were diagnosed in women younger than 40 years [3]. A trend of increased fractions of cases occurring in young women is observed in Taiwan [3, 4].

Clinical Features of EC in Young Women

Standard treatment for EC comprises hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy according to risk evaluation and tailored adjuvant therapy [7–9]. Traditionally, EC of younger women is mostly lower-stage, well-differentiated, endometrioid, and has a better prognosis than older EC patients but some studies have suggested that age was not independently prognostic adjusted for type and grade [7, 10–12]. In contrast, Duska et al. found that women younger than age 40 years who were not obese were at higher risk of both advanced disease and high-risk histology [13]. A recent Surveillance, Epidemiology and End Results (SEER)-based analysis indicated that stage IA (by American Joint Committee on Cancer codes) EC patients aged ≤ 40 years had 5-year survival rates of 98 % with or without ovarian preservation [14]. It is therefore advocated that ovarian preservation at the time of definitive surgery can be performed in selected cases [15]. Fertility-sparing options should be considered for young EC patients with knowledge-based approaches [16].

C.-H. Lai (✉) · C.-J. Wang · A. Chao
Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital and Chang Gung University, Linkou, 5 Fu-Shin Street, Kueishan, Taoyuan 333, Taiwan
e-mail: sh46erry@ms6.hinet.net

Preserve Ovary at Definitive Surgery for Young EC Patients

There are several issues that both physicians and patients have to consider before practice conservations for ovary alone or both uterus and ovary for young EC patients. Incidence rates of synchronous ovarian malignancies in young EC patients (younger than aged 40 or 45 years) are substantial, varied from 9.4–25 % [17, 18•, 19]. Synchronous or metachronous ovarian malignancies also were not infrequently found upon cancer recurrence in the uterus for young women undergoing fertility-sparing treatment (FST) or subsequently after definitive hysterectomy with ovary conserved [20–23, 24•].

Criteria of Selecting Candidates for Fertility Preservation

High remission rates with subsequent pregnancies are seen in clinical stage IA without myometrial invasion, grade 1 EC of young women using hormone therapy (HT; usually progestins) as FST [20–23, 24•, 25•, 26–35, 36•, 37]. Criteria of selecting candidates for FST varied. Most of the series requires (1) a strong desire to reserve fertility potential; (2) age younger than 40 years; (3) nulliparous (or more children required for family); (4) endometrioid carcinoma; (5) grade 1 differentiation (some series allowed grade 2); (6) presence of progesterone receptor (PgR; some do not perform PgR or estrogen receptor [ER] analysis [19, 21, 27]); (7) normal serum levels of CA125 (<35 U/mL); (8) clinical stage IA [38] with absence of myometrial, cervical invasion, or extrauterine spread by some imaging criteria (vaginal ultrasound or computed tomography/magnetic resonance imaging [MRI]); and (9) should be reliable for follow-up.

Sometimes, patients of moderate, differentiated EC were treated with FST, where data were scanty but seemed unwarranted [39, 40]. Rose et al. reported a 39-year-old patient with grade 2 endometrial carcinoma with superficial myometrial invasion, whose lesions had been hysteroscopically resected with margins free and treated conservatively with megestrol acetate (MA). Pelvic recurrence occurred 2 years later despite a document of complete remission at 6 months of FST [39]. Brown et al. reported another 18-year-old grade 2 EC patients treated with levonorgestrel-releasing intrauterine device (IUD) and was without disease at 13 months [40].

Although method of assessment for myometrial invasion varied, the consensus of previous conservation treatments for EC was usually restricted to presumed stage IA disease without myometrial invasion. However, the accuracy of using imaging studies to evaluate the myometrial invasion remains equivocal. A meta-analysis showed that contrast-enhanced MRI was the most accurate modality for the pretreatment assessment of myometrial involvement, but detecting cervical extension was suboptimal [41]. Results of a recent study reported that fused T2-weighted and high-b-value diffusion-weighted images at 3 Tesla provided 90 %

accuracy for preoperative evaluation of myometrial involvement and 98 % accuracy for deep myometrial invasion [42]. Some used diagnostic laparoscopy to confirm negative ovarian neoplasms and peritoneal cytology [36•]; however, the benefits of invasive assessment were unproven. A deliberate family history and potential risk of progression should be conducted and genetic testing to rule out Lynch syndrome or Cowden syndrome may be indicated in cases with strong family history [16•].

Fertility-Preserving Treatment and Posttherapy Surveillance

In the literature, HT agents, dose/scheduling, and route of administration were highly variable (Table 1) [22, 25•, 27–35, 36•]. Most early series used progestins, either medroxyprogesterone (MPA) or MA [27, 28]. In our hospital, we achieved a first success case using MA 160 mg/day (D) plus tamoxifen 20 mg/D [43]. However, from 1997, the protocol of our hospital was amended that tamoxifen was optional [33] but always required a positive PgR. Studies did not require a positive PgR for enrollment into FST tended to find lower response rates (Table 1).

A progesterone-containing IUD releasing 65 µg of levonorgestrel daily was used to treat inoperable, early EC (age 60±16 years) with 75 % (8/12 patients) complete response [44]. However, the results of FST studies in young women showed that success of two studies was achieved by concurrently using gonadotrophin-releasing hormone analogs (GnRHa) [34] or MPA [35] in addition to IUD releasing 20 µg of levonorgestrel, whereas complete remission using levonorgestrel IUD was only documented in eight patients of another study [36•].

Selective ER modifiers, such as tamoxifen and arzoxifene or GnRHa, thought had definite activity as a single agent, but they were used only in advanced and recurrent EC [45–47]. Aromatase inhibitors have shown their potential to treat EC as single agent for advanced or recurrent EC or endometrial stromal sarcoma [7, 8, 48•], but only one report of two cases using anastrozole in combination with MA 160 mg/D has been reported in young women as FST [36•].

Live Birth Rates and Recurrences After FST

According to a recent systemic review of 32 studies (n=408) of EC women with FST, 76.2 % regressed and the live birth rate was 28 % [24•]. Because these women are frequent sub/fertility patients, assisted reproductive technology (ART) could be introduced for patients with a history of ovulation and fertility problems. Including patients with atypical complex hyperplasia and EC with FST, those who received ART had a 39.4 % live birth rate compared with 14.9 % of those who tried spontaneous conception [24•]. Concerns of ART ovulation induction agents might be

Table 1 Hormone therapy for fertility-sparing treatment in young women with early-stage endometrial cancer

Author	Year	No. of Patients	Prospective/retrospective	PgR+or ER+required	Agent/dose/schedule	CR rate	Comments
Progestins							
Ushijima [22]	2007	28	Prospective	NA	600 mg/D	55 %	8/14 (57 %) recurred with median PFI 47.9 mo (25–73); all Pts NED; 3 Pts with live birth
Perri [25•]	2011	27	Retrospective	NA	MA 160–320 mg/D	89 %	62 % recurrence; 2 developed ovarian carcinoma
Gotlieb [27]	2003	13	Retrospective	NA	MPA 200 mg-600 mg/D (2) or MA 160 mg/D (8) and other progestins (3)	100 %	5/13 (38.5 %) recurrent at 19–357 mo; mean duration of follow-up 82 mo; all Pts NED
Randall [28]	1997	12	Retrospective	NA	MA 40–400 mg/D (10) or oral contraceptive (1) or bromocriptine (1)	75 %	1/9 (11 %) recurrence; 2 developed ovarian carcinoma; mean duration of follow-up 40 mo; all Pts NED; 2 Pts with live birth
Niwa [29]	2005	12	Retrospective	NA	MPA 400–600 mg/D	100 %	8/9 (88.9 %) recurred in 9 Pts with >30 mo follow-up; all Pts NED; 5 Pts with live birth
Yamazawa [30]	2007	9	Prospective	PgR tested but not required for enrolment	MPA 400 mg/D	78 %	2/7 (28.6 %) recurred, these 2 Pts also had ovarian cancer; PgR expression related to response
Singnorelli [31]	2008	11	Prospective	NA	MPA 200 mg/D	54 %	Median 98 mo follow-up; all Pts NED; 4 Pts with 8 pregnancies
Kaku [32]	2001	12	Retrospective	NA	MPA 200–800 mg/D	75 %	2/9 (22.2 %) recurred; 1 Pt died at 69 months after the initial FST
Wang [33]	2002	9	Prospective	ER+and PR+	MA 160 mg/D plus tamoxifen 20 mg/D (8) MA 160 mg/D (1)	88.9 %	4/8 (50 %) recurred and 1 with ovarian cancer or metastasis; all Pts NED; 3 patients with live birth
Intrauterine progestins							
Minig [34]	2011	14	Prospective	NA	Levonorgestrel IUD, 20 µg/D for 1 year plus GnRHα 3.75 mg monthly for 6 months	57.1 %	4/8 (50 %) recurred; mean 29 mo follow-up; all Pts NED
Kim [35]	2011	5	Prospective	NA	Levonorgestrel 20 µg/D by IUD plus MPA 500 mg/D	80 %	No recurrence with mean follow-up 10.2 mo (range 6–16)
Laurelli [36•]	2011	14	Prospective	ER+and PR+	MA 160 mg/D (6) 52 mg Levonorgestrel IUD (8)	100 %	One recurred with median follow-up 40 mo (range 13–79)
Aromatase inhibitors							
Burnett [37]	2004	2	Retrospective	NA	Anastrozole 1 mg/D plus MPA 160 mg/D	100 %	NED with follow 6 mo and 19 mo

NA, not applicable; PgR, progesterone receptor; ER, estrogen receptor; MPA, medroxyprogesterone acetate; MA, megestrol acetate; GnRHα, gonadotrophin-releasing hormone analog; CR, complete response; PFI=progression free interval; D=day; mo=month(s); Pts, patients; NED, no evidence of disease; FST=fertility-sparing treatment; IUD=intrauterine device

associated with increasing the risk of EC recurrence; however, according to a large multicenter study [22], the relapse rate did not worsen from the hyperestrogenic state by ART.

Of the 29 studies, follow-up time was reported to range from 11 to 76.5 months, the pooled relapse rate was 40.6 % (95 % confidence interval (CI) 33.1–49.8 %) and only two cases with documented death [24•]. Many recurrences after FST were of short follow-up after salvage, therefore, mortality rate could be underreported. Such as the case of Kaku's series [32], the patient who relapsed and underwent hysterectomy and has a second relapse involving left

obturator node and vagina was free of disease at the time of publication [32]. This patient again had liver and brain metastases at 46 months, and partial resection of the liver was performed at 48 months; she died of disease at 69 months after the initial MPA therapy (personal communication, Profs T. Kaku and H. Yoshikawa) (Table 1).

Conservative treatment could be offered only to strictly selected patients who desire to preserve fertility and for whom close follow-up is possible during HT and continued surveillance after complete remission. These patients should be followed for as long as possible.

Maintenance and Consolidation Hysterectomy

For women who do not want pregnancy at the time being, a maintenance oral contraceptive agent or depo-Provera (MPA 150 mg intramuscular injection every 12 months) [22, 23, 33, 49] and periodical pelvic ultrasound and/or hysteroscopy [33] should be recommended. Consolidation hysterectomy when completing child-bearing often is advocated by many investigators. Recurrence rates after FST using HT after initial response are 22–67 % [24]. A case report of a 31-year-old grade 1, clinical stage I EC patient developed occult (asymptomatic) myometrial invasion with normal endometrium has been reported [50]. Therefore, routine pelvic MRI should be considered for follow-up of EC patients who determine to preserve their uterus after fertility-preservation is not a concern. In our hospital, we routinely recommend consolidation hysterectomy but preserving bilateral ovary is allowed if the patients receiving hysterectomy are in a state of sustained remission. However, we had two cases of late recurrences. One patient had left ovarian recurrence at 90 months after consolidation hysterectomy and bilateral salpingectomy with ovarian preservation at 47 months from FST. The other was treated with standard hysterectomy and bilateral salpingo-oophorectomy with lymph node dissection at the first relapse in the uterus (181 months after initial FST). The latter suffered a second relapse in the upper abdomen at 25 months after definitive surgery and a third relapse in the left lung 23 months later.

Investigations on Molecular Profiles Related to Outcomes

It is well known that response to progestin is closely related to progesterone receptor in clinical trials involving advanced and recurrent EC [7, 8]. Yamazawa et al. reported that the probability of complete response to MPA was related to positive expression of PgR in the setting of FST in young EC patients [30]. A multicenter trial investigated the efficacy of letrozole (an aromatase inhibitor) for advanced and recurrent EC, and the response had no correlation with biological markers analyzed [51]. Other in vitro investigations have not found consistent markers for reliable prediction to outcome of various HT for FST purpose [52–59].

Conclusions

When fertility preservation is not a concern, standard surgical staging and tailored adjuvant therapy regardless of age should be practiced. Current evidence cannot justify reliable selection criteria for ovarian preservation at the time of definitive surgery. High remission rates with subsequent pregnancies are seen in clinical stage IA without myometrial invasion and grade 1 EC of young women using oral high-

dose progestins as FST, yet late recurrences and death should be cautioned. Intrauterine progestins and aromatase inhibitors have limited data at present. Further investigations of molecular profiles for selecting candidates for preserving ovary or FST and whether to do a consolidation hysterectomy are necessary.

Acknowledgments Supported by grants from Chang Gung Medical Foundation (CMRPG391442) and the Department of Health, Taiwan (DOH100-TD-B-111-005 and DOH101-TD-B-111-005). Department of Health-Taiwan was not involved in the design of the study, collection, management, analysis or interpretation of the data, preparation, review, or approval of the manuscript. The authors thank Profs. Tsunehisa Kaku and Hiroyuki Yoshikawa for kindly providing updated information of long-term follow-up of their study.

Disclosures No conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC. <http://globocan.iarc.fr> (accessed November 10, 2012).
2. Siegel R, Naishdham D, Jemal A. Global cancer statistics. *CA Cancer J Clin.* 2012;62:10–29.
3. Cancer Registry Annual Report, 2008 Taiwan: Bureau of Health Promotion, Department of Health, The Executive Yuan, 2010.
4. • Lin CH, Chen YC, Chiang CJ, et al. The emerging epidemics of estrogen-related cancers in young women in a developing Asian country. *Int J Cancer.* 2011;130:2629–23637. *This study indicates that estrogen-related cancers increase rapidly in Taiwanese young women and that incidence rates are catching up with that of women living in the United States, which might also be true in other Asian countries.*
5. Ushijima K. Current status of gynecologic cancer in Japan. *J Gynecol Oncol.* 2009;20:67–71.
6. Purdie DM, Green AC. Epidemiology of endometrial cancer. *Best Pract Res Clin Obstet Gynaecol.* 2001;15:341–54.
7. Rose PG. Medical progress: endometrial carcinoma. *N Engl J Med.* 1996;335:640–8.
8. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. *Lancet.* 2005;366:491–505.
9. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Uterine neoplasms V.1.2012 at http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf (accessed on October 10, 2012)
10. Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. *Obstet Gynecol.* 2007;109:655–62.
11. Tran BN, Connell PP, Waggoner S, et al. Characteristics and outcome of endometrial carcinoma patients age 45 years and younger. *Am J Clin Oncol.* 2000;23:476–80.

12. Gitsch G, Hanzal E, Jensen D, et al. Endometrial cancer in premenopausal women 45 years and younger. *Obstet Gynecol.* 1995;85:504–8.
13. Duska LR, Garrett A, Rueda BR, et al. Endometrial cancer in women 40 years old or younger. *Gynecol Oncol.* 2001;83:388–93.
14. Chan JK, Sherman AE, Kapp DS, et al. Influence of gynecologic oncologists on the survival of patients with endometrial cancer. *J Clin Oncol.* 2011;29:832–8.
15. Wright JD, Buck AM, Shah M, et al. Safety of ovarian preservation in premenopausal women with endometrial cancer. *J Clin Oncol.* 2009;27:1214–9.
16. • Eskander RN, Randall LM, Berman ML, et al. Fertility preserving options in patients with gynecologic malignancies. *Am J Obstet Gynecol* 2011, 103–105. *This review provides a summary of fertility-sparing options for young women with gynecologic malignancies, with emphasis on appropriate patient selection, oncologic, and obstetrics outcome.*
17. Walsh C, Holschneider C, Hoang Y, et al. Coexisting ovarian malignancy in young women with endometrial cancer. *Obstet Gynecol.* 2005;106:693–9.
18. • Alhilli MM, Dowdy SC, Weaver AL, et al. Incidence and factors associated with synchronous ovarian and endometrial cancer: a population-based case-control study. *Gynecol Oncol.* 2012;125:109–13. *A population-based study provides synchronous ovarian malignancies found in endometrial cancer patients.*
19. Navarria I, Usel M, Rapiti E, et al. Young patients with endometrial cancer: How many could be eligible for fertility-sparing treatment? *Gynecol Oncol.* 2009;114:448–51.
20. Huang SY, Lai CH, Jung SM, et al. Ovarian metastasis in a nulliparous woman with endometrial adenocarcinoma failing conservative treatment: case report. *Gynecol Oncol.* 2005;97:652–5.
21. Shamshirsaz AA, Withiam-Leitch M, Odunsi K, 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;104:757–60.
22. Ushijima K, Yahata H, Yoshikawa H, 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;25:2798–803.
23. Lai CH, Huang HJ. The role of hormones for the treatment of endometrial hyperplasia and endometrial cancer. *Curr Opin Obstet Gynecol.* 2006;18:29–34.
24. • Gallos ID, Yap J, Rajkhowa M, et al. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systemic review and metaanalysis. *Am J Obstet Gynecol.* 2012;207:266.e1–12. *This recently published systemic review provides a well-rounded update of FST for endometrial cancer patients. Higher live birth rates were observed in those who received assisted reproductive technology.*
25. • Perri T, Korach J, Gotlieb WH, et al. Prolonged conservative treatment of endometrial cancer patients: more than 1 pregnancy can be achieved. *Int J Gynecol Cancer.* 2011;21:72–8. *A large, retrospective study showed a 89 % response rate using megestrol acetate 160–320 mg/D and high recurrence rate (62 %) in young endometrial cancer patients undergoing FST.*
26. Zivanovic O, Carter J, Kauff ND, Barakat RR. A review of the challenges faced in the conservative treatment of young women with endometrial carcinoma and risk of ovarian cancer. *Gynecol Oncol.* 2009;115:504–9.
27. Gotlieb WH, Beiner ME, Shalmon B, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. *Obstet Gynecol.* 2003;102:718–25.
28. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. *Obstet Gynecol.* 1997;90:434–40.
29. Niwa K, Tagami K, Lian Z, et al. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. *Br J Obstet Gynecol.* 2005;112:317–20.
30. Yamazawa K, Hirai M, Fujito A, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. *Hum Reprod.* 2007;22:1953–8.
31. Singnorelli M, Caspani C, Chiappa V, Mangioni C. Fertility-sparing treatment in young women with endometrial cancer or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. *BJOG.* 2009;116:114–8.
32. Kaku T, Yoshikawa H, Tsuda H, 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;167:39–48.
33. Wang CB, Wang CJ, Chou HH, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. *Cancer.* 2002;94:2192–8.
34. Minig L, Franchi D, Boveri S, 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;22:643–9.
35. Kim MK, Yoon BS, Park H, et al. Conservative treatment with medroxyprogesterone acetate plus levonorgestrel intrauterine system for early-stage endometrial cancer in young women. Pilot study. *Int J Gynecol Gynecol Cancer.* 2011;21:673–7.
36. • Laurelli G, Di Vagno G, Scaffa C, et al. Conservative treatment of early endometrial cancer: preliminary results of a pilot study. *Gynecol Oncol.* 2011;120:43–6. *This prospective study showed that using levonorgestrel alone achieved 100 % response rate for FST, although the case number was small (n=8) and follow-up was short.*
37. Burnett AF, Bahador A, Amezcua C. Anastrozole, an aromatase inhibitor, and medroxyprogesterone acetate therapy in premenopausal obese women with endometrial cancer: a report of two cases successfully treated without hysterectomy. *Gynecol Oncol.* 2004;94:832–4.
38. FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Obstet Gynecol.* 2009;105:103–4.
39. Rose PG, Mendelsohn G, Kornbluth I. Hysteroscopic dissemination of endometrial carcinoma. *Gynecol Oncol.* 1998;71:145–56.
40. Brown AJ, Westin SN, Broaddus RR, Schmeler K. Progestin intrauterine device in an adolescent with grade 2 endometrial cancer. *Obstet Gynecol.* 2012;119:423–6.
41. Kinkel K, Kaji Y, Yu KK, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. *Radiology.* 1999;212:711–8.
42. Lin G, Ng KK, Chang CJ, et al. Myometrial invasion in endometrial cancer: diagnostic accuracy of diffusion-weighted 3.0-T MR imaging—initial experience. *Radiology.* 2009;250:784–92.
43. Lai CH, Hsueh S, Chao AS, Soong YK. Successful pregnancy after tamoxifen and megestrol acetate therapy for endometrial carcinoma. *BJOG.* 1994;101:547–9.
44. Montz FJ, Bristow RE, Bovicelli A, Tomacruz R, Kurman RJ. Intrauterine progesterone treatment of early endometrial cancer. *Am J Obstet Gynecol.* 2002;186:651–7.
45. Thigpen T, Bradly MF, Homsley HD, et al. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2001;19:364–7.
46. McMeekin DS, Gorden A, Fowler J, et al. A phase II trial of arzoxifene, a selective receptor modulators, in patients with recurrent or advanced endometrial cancer. *Gynecol Oncol.* 2003;90:64–9.
47. Lhomme C, Callet VN, Lesimple T, et al. A multicenter phase II study with triptorelin (sustained-release LHRH agonist) in advanced or recurrent endometrial carcinoma: a French Anticancer Federation study. *Gynecol Oncol.* 1999;75:187–93.

48. • Steed HL, Chu QSC. Aromatase inhibition: a potential target for the management of recurrent or metastatic endometrial cancer by letrozole: more questions than answers? *Expert Opin Investig Drugs*. 2011;20:681–90. *This review summarized update of aromatase inhibition in the management of recurrent or metastatic endometrial cancer.*
49. Benshushan A. Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment. *Eur J Obstet Gynecol Reprod Biol*. 2004;117:132–7.
50. Hurst SA, Hartzfeld KM, Priore GD. Occult myometrial recurrence after progesterone therapy to preserve fertility in a young patient with endometrial cancer. *Fertil Steril*. 2008;89:724.e1–3.
51. Ma BB, Oza A, Eisenhauer E, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers: a study of the National Cancer Institute of Canada Clinical Trials Group. *Int J Gynecol Cancer*. 2004;14:650–8.
52. Yasuda M, Kotajima S, Kajiura H, et al. Loss of heterozygosity alterations associated with progesterone therapy in endometrial hyperplasia and adenocarcinoma. *Int J Gynecol Cancer*. 2005;15:155–62.
53. Vereide AB, Kaino T, Sager G, Orbo A. Scottish Gynaecological Clinical Trials Group. Bcl-2, BAX, and apoptosis in endometrial hyperplasia after high dose gestagen therapy: a comparison of responses in patients treated with intrauterine levonorgestrel and systemic medroxyprogesterone. *Gynecol Oncol*. 2005;97:740–50.
54. Vereide AB, Arnes M, Straume B, et al. Nuclear morphometric changes and therapy monitoring in patients with endometrial hyperplasia: a study comparing effects of intrauterine levonorgestrel and systemic medroxyprogesterone. *Gynecol Oncol*. 2003;91:526–33.
55. Kir G, Cetiner H, Gurbuz A, Karateke A. The value of epithelial membrane antigen overexpression in hyperplastic and malignant endometrium and its relationship with steroid hormone receptor expression. *Eur J Gynaecol Oncol*. 2004;25:502–5.
56. Chen D, Hackl W, Ortmann O, Treeck O. Effects of a combination of exemestane and paclitaxel on human tumor cells in vitro. *Anti-Cancer Drugs*. 2004;15:55–61.
57. Utsunomiya H, Suzuki T, Ito K, et al. The correlation between the response to progestogen treatment and the expression of progesterone receptor B and 17beta-hydroxysteroid dehydrogenase type 2 in human endometrial carcinoma. *Clin Endocrinol*. 2003;58:696–703.
58. Di Nezza LA, Jobling T, Salamonsen LA. Progestin suppresses matrix metalloproteinase production in endometrial cancer. *Gynecol Oncol*. 2003;89:325–33.
59. Bae J, Won M, Kim DY, et al. Identification of differentially expressed microRNAs in endometrial cancer cells after progesterone treatment. *Int J Gynecol Cancer*. 2012;22:561–5.