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Review Article

Hormone therapy for younger patients with endometrial cancer

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Abstract

The relationship between hormones and endometrial cancer is well known because disease states, such as chronic anovulation and endogenous estrogen production from hormone-secreting tumors (for example, granulosa cell tumor of the ovary), are related to excess estrogen, and unopposed estrogen use might lead to endometrial overgrowth, hyperplasia, and subsequent development of endometrial carcinoma. Therefore, the possibility of using antihormone therapy in endometrial carcinoma and/or its precancer lesions, such as simple hyperplasia with and without atypia and complex hyperplasia with and without atypia, is always supposed, as in the management of breast cancer. In addition, if women in whom endometrial cancer is diagnosed are very young, some critical issues should be considered, including the possibility of ovary preservation-partial preservation of fertility and the possibility of both ovary and uterus preservation-complete preservation of fertility. Other factors are also important to consider and include oncologic risk, appropriateness of candidates for treatment, type of hormone use, response rate of hormonal therapy, appropriate surveillance, and additional counseling for issues such as anxiety about relapse and metastasis, distress about side effects, advice of the family, advice of the medical staff, and economic burden.

This review will be focused on updated information and recent knowledge of the use of hormones in the management of younger women with endometrial cancer who want fertility preservation.

Keywords: endometrial cancer; estrogen; fertility preservation; progesterone

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Introduction

Uterine corpus cancer, with an estimated 606,910 cases (8% of gynecologic cancers) in the United States, second only to breast cancer (n = 2,971,610; 41%), is common among women who have survived endometrial cancer [1]; therefore, it is a concern in gynecologic oncology. Although the incidence of uterine corpus cancer is still lower in developing countries than in developed countries, there has been a significantly increasing trend toward a greater number of endometrial cancer cases in recent years in Taiwan and other Asian countries [2], suggesting that many more gynecologic oncologists in Taiwan might be interested in this topic. Uterine corpus cancer can be classified into two major distinguishing tumors: endometrial cancer or uterine sarcoma. On the basis of biologic and histopathologic variables, endometrial cancer can be further broken down into two major types—one is strongly associated with unopposed estrogen (Type I), but the other may be relatively unrelated to the overproduction of estrogen (Type II) [3–6]. In the 2007 issue of the Taiwanese Journal of Obstetrics and Gynecology, Liu [7] reviewed the characteristics of endometrial cancer extensively and focused on the molecular carcinogenesis of endometrial cancer. In this article, additional updated information is provided and hormone therapy in endometrial cancer is discussed.

Type I and Type II endometrial cancer

Types I and II endometrial cancers have distinct biologic and histopathologic differences (Table 1).

Type I endometrial cancers account for more than 80% of cases with favorable outcomes, and are frequently associated with unopposed estrogen or hyperestrogenic environments; they are usually an endometrioid type [7]. A series of carcinogenic changes in Type I endometrial cancers are often found in the pathologic review. The severity can be initiated from endometrial hyperplasia without atypia and upgraded to a more severe status; for example, complex endometrial hyperplasia with atypia (atypical complex hyperplasia, ACH) or well-differentiated (Grade 1) endometrial cancer. In addition, the histologic type of Type I endometrial cancer is often endometrioid, and is of a low grade (Grade 1 or 2), with frequently positive immunohistochemical staining for the phosphatase and tensin homolog (*PTEN*) gene (approximately 50–80%), or microsatellite instability (approximately 20–45%), K-ras mutation (approximately 10–30%) or β-catenin (20%), and hormone receptors, such as estrogen receptors, progesterone receptors, or androgen receptors (ARs) [7,8]. The sources of unopposed estrogen exposure can be exogenous, including hormone replacement therapy (HRT) in postmenopausal women [9–11], or endogenous, such as obesity or anovulation status [12]. Obesity contributes to an increased rate of endometrial cancer, although endogenous estrogen is always considered the most important factor. However, there is no doubt that some endocrines, paracrines, cytokines, and growth factors related to obesity might further influence this result. For example, insulin resistance, hyperglycemia, and hyperinsulinemia can significantly increase insulin growth factor bioavailability, which promotes endometrial proliferation by insulin growth factor-1 receptor signaling [6,13]. Type I endometrial cancer is the most common extracolonic malignancy if endometrial carcinomas occur in familial penetration (approximately 2–5% of all endometrial cancer in Western countries) in multiorgan cancer syndrome, such as hereditary nonpolyposis colorectal carcinoma (HNPCC)/Lynch syndrome; the lifetime risk of endometrial cancer varies between 32% and 60% in Lynch syndrome compared with 1% in the general population [14].

Type II endometrial cancer is often related to age. For example, it frequently occurs in older postmenopausal women, without dependence on estrogen stimulation, and often arises in an atrophic environment. The histology includes papillary serous, clear cell, and poorly differentiated carcinomas with a tendency to invade the lymphatic and vascular spaces, metastasize to lymph nodes, and microscopically involve other intraperitoneal structures despite minimal or no invasion within the

Table 1
The characteristics of Type I and Type II endometrial cancers.

	Type I	Type II
Incidence	≥80%	≤20%
Age	Premenopause, perimenopause, and postmenopause	Postmenopause
Histologic subtype	Endometrioid	Serous, clear, (MMMT?)
Grade	Low	High
Clinical behavior	Indolent	Aggressive
Estrogen-related	Strong	Weak
Obesity	Often	Rare
Parity	Frequently nulliparous	Rarely nulliparous
Presence of precursor lesion	Often and frequent	Arguable
	EIN or hyperplasia with/without atypia	EIC
Immunohistochemical staining	*PTEN* gene: approximately 50–80%	p53 mutations: 90%
	MSI: approximately 20–45%	E-cadherin: approximately 80–90%
	K-ras mutation: approximately 10–30%	HER-2/neu overexpression: approximately 45–80%
	β-catenin: 20%	p16 mutation
	Frequent positive to hormone receptors, such as ER, PR, or AR	

AR = androgen receptor; EIC = endometrial intraepithelial carcinoma; EIN = endometrial intraepithelial neoplasia; ER = estrogen receptor, MMMT = malignant mixed mullerian tumor; MSI = microsatellite instability; PR = progesterone receptor; PTEN = phosphatase and tensin homolog.

uterine cavity, and leading to advanced stage, high recurrence rates, and a poor prognosis. Immunohistochemical staining is often positive for p53 mutations (90%), E-cadherin alteration (approximately 80–90%), and HER-2/neu overexpression (approximately 45–80%), and of most importance, is frequently negative for hormone receptors, such as ERs or PRs [7].

Staging and standard treatment for younger women with endometrial cancer

Endometrial cancers commonly present in an early stage and are staged surgically according to the 2009 French Federation Internationale de Gynecologie et d'Obstetrique (FIGO) staging system, a revision of the 1988 FIGO staging system [15,16]. The major differences between the 1988 and 2009 FIGO staging systems for endometrial cancers include the following: (1) the 1988 FIGO IA and IB are combined into the 2009 FIGO IA, and the 1988 FIGO IC is now the 2009 FIGO IB; (2) Stage II no longer has a subset A and B, and endocervical glandular invasion is considered as Stage I; (3) positive cytology no longer is part of Stage III; and (4) pelvic and para-aortic lymph node invasion is classified as Stage IIIC, based on the poor prognosis [15].

Because endometrial cancer has a surgicopathologic staging system (FIGO) and most cases are estrogen-related, the standard treatment for endometrial cancer includes cytology, total hysterectomy (TH), and bilateral salpingo-oophorectomy (BSO) with/without the requirement of lymph node sampling and lymph node dissection, although some argue that the 2009 FIGO recommendations still fail to adequately address the controversies in surgical staging [17]. Hysterectomy results in the loss of fertility and is often an unacceptable treatment for women of childbearing age [18–21].

In younger women with endometrial cancer who want to preserve fertility, two strategies can be used: partial preservation of fertility or complete preservation of fertility.

Partial preservation of fertility can be achieved by TH alone without BSO in selected patients with disease confined to the uterus, based on the concept that ovarian preservation in young women with early-stage endometrial cancers [22] and HRT in women with early-stage endometrial cancer after TH and BSO [23,24] might be safe. Partial preservation of fertility is clearly demonstrated in the data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) study, which showed that ovarian preservation had no effect on either cancer-specific or overall survival in these younger and/or premenopausal women with early-stage endometrial cancer [22]. Complete preservation of fertility is mediated through dilation and curettage with or without hysteroscopy to remove endometrial lesions only and followed by various types of hormone therapy, especially progestins, to offer the opportunity to preserve both the uterus and ovaries, based on promising data from a recent review showing that 77.7% of patients demonstrated a response to hormonal therapy and 53.2% had a durable complete response [25]. However, before considering the possibility of fertility preservation, some important issues should be considered.

The incidence and 5-year survival rate of endometrial cancer diagnosed in women younger than 40 years

According to the most recent cancer statistics in the United States [1], an estimated 47,130 new cases of endometrial cancer will be diagnosed in 2012; more than 90% of these cancers develop in the endometrium and 68% are diagnosed at an early stage. The 5-year survival rate is 95.8% for localized disease in the United States [1] and 99.0%, 98.6%, and 98.7% for 1988 FIGO IA, 1988 FIGO IB, and 2009 FIGO IA, respectively, at Taipei Veterans General Hospital [16]. Because it is reported that 5% of patients with endometrial cancer are younger than 40 years, and of most importance, the prognosis of this population is excellent (most of these cases are relatively well-differentiated Type I endometrioid cancers or diagnosed as ACH), a strategy of partial or total fertility preservation in these younger women might be possible. In addition, these prognosis-favorable endometrial cancers often occur in nonfertile women [26], suggesting that many younger women in whom endometrial cancers are diagnosed have not completed childbearing, and the need to preserve fertility is high.

Partial preservation of fertility

As mentioned previously, the standard treatment for endometrial cancers is TH and BSO. BSO is typically performed in conjunction with TH to exclude occult ovarian metastases and to decrease estrogen production, which might be beneficial in endometrioid cancer treatment because this type of cancer is an estrogen-responsive tumor. Despite the theoretical benefits of oophorectomy during endometrial cancer treatment, this procedure results in complete loss of fertility and surgical menopause with the subsequently increasing risk of long-term sequelae of estrogen deprivation, such as cardiovascular disease or osteoporosis [27–29].

Although ovarian preservation offers the potential for future oocyte retrieval as a family-building option and would also avoid the immediate consequences of estrogen deprivation, as mentioned previously, this strategy may lead to the potentially fatal risk of overlooking occult ovarian metastases and coexisting synchronous ovarian primary tumors and the potential risk of endocrine stimulation of residual microscopic endometrial cancers [30,31]. A large study conducted by the Gynecologic Oncology Group (GOG), enrolling 621 patients with Stage I endometrial cancers, showed that an appreciable number of patients (22%, 144 of 621) with Stage I endometrial cancers and undergoing complete surgical staging have disease outside of the uterus (lymph node metastasis, adnexal disease, intraperitoneal spread, and/or malignant cells in peritoneal washing) [32]. In addition, although most reports showed that clinical Stage I endometrial cancer with metastasis to the ovary is rare, the incidence of any stage of endometrial cancer with a synchronous ovarian malignancy is as

high as 10–29.4%, which is at least fivefold greater than the incidence in women older than 45 years with endometrial cancer [33]. It is fortunate that premenopausal women with concomitant ovarian and endometrial cancers often had Stage I ovarian cancers, and that women with Grade I tumors of each type of cancer had an excellent prognosis after surgical management [33]. However, many recent studies have failed to support this concept.

For example, a retrospective study of 976 women in China with clinical Stage I endometrial cancer showed that the incidence of coexisting ovarian cancer in clinical Stage I endometrial cancer was low (2.05%; 1.74% with ovarian metastases and 0.31% with synchronous ovarian primary cancer) [34]. Among these patients, 50% (10 of 20) had microscopic ovarian involvement, with an incidence of 1.3%. However, these data should be used with caution because many risk factors could be identified that contributed to these unusual findings, including 40% of patients (8 of 20) identified as Grade 3, 15% (3 of 20) as nonendometrioid type, and 45% (11 of 20) as cervical invasion. The authors found that cervical invasion (2009 FIGO Stage II), uterine serosa extension (2009 FIGO Stage IIIA), and fallopian tube involvement (2009 FIGO Stage IIIA) were independent high-risk factors for ovarian metastases in clinical Stage I endometrial cancer [34], suggesting that patients with 2009 FIGO Stage I are still a low-risk population for ovarian metastases.

A Korean report of 260 patients with early-stage endometrial cancer, including 204 2009 FIGO Stage I patients (78.5%) showed that 7.31% of patients (19 of 260) had coexisting ovarian malignancy (12 metastatic and 7 synchronous primary malignancies), and identified the independent risk factors, such as intraoperative extrauterine disease, nonendometrioid histology, lymph node metastasis, and patient age, for those with coexisting ovarian cancers [35]. In addition, of the 206 patients without any evidence of intraoperative extrauterine disease, the coexisting ovarian cancer rate was 0.97% (2 of 206), and none were younger than 45 years [35]. The Korean Gynecologic Oncology Group (KGOG) performed a nationwide study to determine whether ovarian preservation is feasible in younger patients with endometrial cancer with a median follow-up of 55 months [36]. Although seven of the 175 patients (4.0%) had documented recurrence, no recurrences were observed in Stage I patients with endometrioid histology, suggesting that ovarian preservation does not adversely affect the recurrence of early-stage endometrial cancer [36]. In a Yale University (USA) study enrolling 251 patients with endometrial cancer who were younger than 45 years, including 189 patients (75.3%) with FIGO Stage I disease, 58.2% of patients (146 of 251) underwent an adequately surgically staged procedure and no difference in survival was found between clinically or surgically staged patients in the group of Stage I patients who underwent TH and BSO and those who underwent TH only, and there was no statistically significant difference in overall survival in the group of Stage I patients with or without BSO [37]. In addition, ovarian preservation had no significant influence on disease-free survival in patients with Grade 1 disease [37].

The data of the SEER study, including 402 patients (12%) who had ovarian preservation out of a total of 3269 women 45 years of age or younger with Stage I endometrial cancers, showed that 5-year survival was similar between the patients who received TH with and without the ovarian preservation, and 5-year survival was 98% for patients with 1988 FIGO IA endometrial cancers, regardless of whether the ovaries were preserved or moved [22]. Among patients with 1988 FIGO IC (2009 FIGO IB) endometrial cancer, survival was 89% [95% confidence interval (CI) = approximately 83–96%] in women who underwent BSO, compared with 86% (95% CI = approximately 63–100%) in those who had ovarian preservation. Multivariate Cox proportional hazards models of survival based on performance of BSO showed that ovarian preservation had no effect on either cancer-specific [hazard ratio (HR) = 0.58; 95% CI = 0.14–2.44] or overall (HR = 0.68; 95% CI = approximately 0.34–1.35) survival, suggesting that ovarian preservation in these younger and/or premenopausal women with early-stage endometrial cancer may be safe and not increase cancer-related mortality [22].

The concern regarding ovarian preservation is that continued ovarian estrogen production might increase the risk of endometrial cancer recurrence. Although the previously mentioned studies [22,34–37] showed that overall survival rate was similar between the patients with TH with and without BSOs, other prospective trials, which were designed for the evaluation of the risk of HRT in endometrial cancer survivors [38,39], might strengthen the concept of the safety of ovarian preservation in endometrial cancer survivors. The GOG study was designed to determine the effect of estrogen replacement therapy on the recurrence rate and survival of 1236 women who had undergone surgery for Stage I or II endometrial cancer [38]. With a median follow-up of 35.7 months, the absolute recurrence rate in the estrogen-treated arm was 2.3% compared with 1.9% in the placebo arm, which contributed to 0.8% mortality in the estrogen-treated patients (5 of 618) and 0.6% mortality in the placebo arm (4 of 618). These results supported the safety of exogenous estrogen with regard to the risk of endometrial recurrence, although this study was not complete [38]. A prospective randomized study aimed to evaluate the effect of immediate estrogen plus progestin therapy on the oncologic outcome of patients with endometrial cancers. Fifty patients received therapy and showed that immediate postoperative use of HRT did not increase recurrence or death in a median follow-up of 49.1 months [39].

Ovarian preservation might be safe in situations in which patients with endometrial cancer are younger than 45 years; have 2009 FIGO Stage I endometrial cancer; Grade 1 or Grade 2 cancer; endometrioid type cancer; and no grossly extrauterine tumors. Other situations could be individualized based on a careful calculation of the risk-benefit ratio when the patients decide in favor of ovarian preservation.

Total preservation of fertility

Although ovarian preservation can provide women with the opportunity of future fertility, it is still a major ethical and

social problem because surrogate motherhood is not always accepted in some countries or societies. In addition to preservation of the ovary, an additional preservation of the uterus seems to be more reasonable for most patients who want to preserve their fertility. However, this attempt is really more challenging than preserving the ovary alone and sacrificing the uterus. It is a major challenge not only for the patients but also for the doctors. The main concern is the risk of persistent tumors, tumor recurrence, and tumor-associated morbidity or mortality. The patients with endometrial cancer who want uterus preservation can present with two distinguishing clinical conditions. One is that the tumor confined to the uterine cavity has been removed completely and the other is that rescue therapy can eradicate the residual tumors completely. In addition, the use of effective rescue treatment without further compromising fertility is a key step toward success in the conservative management of women with endometrial cancer. To achieve this goal, several concerns should be addressed. A recent review from Kesterson and Fanning [40] tried to respond to these six major concerns: oncologic risk, appropriate candidates, response rate of hormonal therapy, type of hormone use, appropriate surveillance, and additional counseling. The concerns and possible explanations (Table 2) are presented in detail in the next paragraphs.

Kitamura [41] has tried to clarify the criteria that cancer patients use to set priorities in their treatment choices using the analytic hierarchy process, a mathematical decision-making method that includes the alternatives "to receive treatment" and "to not receive treatment," and five criteria: anxiety about relapse and metastasis, distress about side effects, advice of the family, advice of the medical staff, and economic burden. The author found that anxiety about relapse and metastasis and advice of the medical staff were the most important factors in making a treatment choice [41]. This finding can be used to respond to the concerns of women with early-stage endometrial cancer and a desire to preserve their fertility.

Table 2
Fertility-sparing treatment of endometrial cancers or endometrial precursor lesions: questions and possible answers.

Questions	Possible answers
Oncologic risk	1. Persistent or progressive: approximately 14.4–25.4% 2. Complete response with recurrence: approximately 23.2–35.4%
Good candidate	1. Younger than 40 y 2. Has a desire to preserve fertility 3. Has a need to give birth 4. Has the ability to give birth 5. Can become pregnant immediately after tumor regression 6. Endometrioid endometrial carcinoma 7. Severity less than or equal to Grade 1 on experts' review 8. Diseases limited to 2009 FIGO IA by imaging (diagnostic tools, including MRI, laparoscopy, if required); the best is 1988 FIGO IA 9. Good compliance 10. No contraindication for high-dose progestin or other hormone therapies
Response rate	1. Initial response: approximately 74.6–85.6% 2. Complete response: approximately 48.2–65.8%
Hormone type	MPA Megestrol Progestin intrauterine device LNG-IUD plus GnRH agonist
Hormone dosage	Approximately 200–800 mg MPA Approximately 80–320 mg megestrol
Surveillance	Every 2–6 months
Reproductive outcome	Approximately 34.8–41%
Counseling	A team effort

FIGO = International Federation of Gynecology and Obstetrics; GnRH agonist = gonadotropin-releasing hormone agonist; LNG-IUD = levonorgestrel-release intrauterine device; MPA = medroxyprogesterone; MRI = magnetic resonance imaging.

Oncologic risk

The oncologic risk may be the most important concern, but there are many controversial issues. As shown previously, one is the possible presence of extrauterine diseases related to Stage I endometrial cancers, and that conservative treatment might miss these lethal conditions. For example, an earlier study from the GOG Study Group in 1987 showed that 22% of patients with Stage I endometrial cancer might have diseases outside of the uterus [32]. The same study showed grade and depth of invasion as independent risk factors related to extrauterine disease [32].

In addition, the risk of coexistence of synchronous ovarian cancer, especially an endometrioid type, might be high, particularly in younger women with endometrial cancer [35,42–44]. In general, the phenomenon of synchronously arising malignancies of the female genital tract appears to be more common in the younger group than in the older group [44]. One report evaluating 1365 patients with endometrial cancers, with 44 women younger than 45 years and 1321 older than 45 years, found synchronous ovarian malignancies occurred in six patients (14%, 6 of 44) in the young group compared with 23 (2%, 23 of 1321) in the older group [44]. The authors still concluded that a conservative approach is a meaningful quality of life goal for patients with cancer, but suitable only for a limited number of patients. For example, eight patients (18%, 8 of 44) in the young group had FIFO Stage IA, Grade 1 disease and may have been eligible for fertility-sparing treatment, corresponding to an incidence rate of 0.3/100,000 [44].

All above-mentioned oncologic risks, such as probably coexistence of diseases outside of the uterus, or coexistence of synchronous ovarian cancer in these early-stage endometrial cancers, questioned the acceptability of conservative treatment for endometrial cancer. Therefore, oncologic risk can be minimized if patients with endometrial cancer have disease limited to a low grade (the best is Grade 1) and minimal muscular invasion or no myometrial invasion [the best is 1988 FIGO IA and endometrial intraepithelial neoplasia (EIN), but not endometrial intraepithelial carcinoma].

Appropriate candidates

What types of patients with endometrial cancer are appropriate candidates for fertility preservation? To respond to this question, the following factors should be considered: the desire to preserve fertility in the presence of endometrial cancer; the need to bear children (and of most importance, the ability to give birth); and the desire to become pregnant immediately after tumor regression. Therefore, younger age might be one of the most critical factors because fertility declines with increasing age [12,45,46].

Other important factors include confirmation of the severity of disease by experts, diseases limited to a low grade and minimal myometrial invasion (as discussed previously), absence of extrauterine spread, good compliance, and absence of a contraindication to medical treatment.

Confirmation of disease severity includes grade diagnosis and myometrial invasion of the disease by experts; however, the consistency (pathological diagnosis-agreement between the different experts or different evaluation time) is still questionable. For example, pathologic experts are required for grade and differential diagnosis. ACH harbors a broad spectrum of differential diagnoses [47]. All forms of hyperplasia may share specific morphologic features, including an increase in the gland-stroma ratio, irregularities in gland shape, and variation in gland size and shape [47]. Morphologic features of atypical hyperplasia can be evaluated in three parts, including nuclei (stratification with loss of polarity, enlarged and rounded with irregular shapes, coarsening of chromatin creating a vesicular appearance, prominent nucleoli, mitotic activity), varied amount of cytoplasm (eosinophilia, diffuse or focal), and appearance of glands (often markedly increased gland-stroma ratio) [48]. However, sometimes hyperplasia is difficult to distinguish from benign abnormalities or more severe forms of endometrial cancer. Cytologic changes in atypia might be confused with cytoplasmic changes in metaplasia [48].

ACH can be considered an immediate precursor of EIN. EIN, a monoclonal endometrial preinvasive glandular proliferation, is the immediate pathologic precursor of endometrioid endometrial adenocarcinoma, with a long-term cancer risk 45-fold greater than that of its benign endometrial hyperplasia counterparts, although this classification cannot replace the recent World Health Organization (WHO) classification [49]. Diagnostic features of EIN must fulfill the following: for architectural evaluation, including that the area of the glands exceeds that of the stroma (glands/stroma > 1) and the lesion is composed of individual glands and may branch slightly and vary in shape; for cytology, including that nuclear and/or cytoplasmic features of the epithelial cells differ between glands with abnormal architecture and those with a normal background, and may include change in nuclear polarity, nuclear pleomorphism, or altered cytoplasmic differentiation, and the presence of a highly abnormal cytology if no normal comparison glands are present; for size, that they should not exceed 1 mm in maximum linear dimension, after excluding the mimic lesion, including benign or cancer statuses, such as benign conditions with overlapping criteria: disordered proliferative, basalis, secretory, polyps, repair, etc.; and carcinoma, if maze-like glands, solid areas, or significant cribriforming is present [49].

Sometimes ACH might be missed or associated with well-differentiated adenocarcinoma because patients undergoing a hysterectomy soon after the biopsy/curettage diagnosis of ACH have a final diagnosis of endometrioid carcinoma, with an incidence ranging from 17% to 43% of cases [50–52], even though well-differentiated adenocarcinoma can be diagnosed when one of three essential criteria is met, including a confluent gland pattern, an extensive papillary pattern, and a desmoplastic stroma response [48]. A multicenter European study was designed to assess intraobserver and interobserver agreement in the diagnosis of endometrial lesions by five expert European gynecologic pathologists, and found a lack of agreement in the diagnoses of ACH and lack of reproducibility in the recognition of the histologic features of stromal alterations to differentiate ACH from well-differentiated adenocarcinoma in endometrial biopsy or curettage specimens [50].

Radiologic experts and good imaging studies such as magnetic resonance imaging (MRI) are needed to evaluate myometrial invasion or extrauterine involvement. A recent KGOG study showed that using the CA-125 blood test and MRI as criteria provided accurate differentiation of a low-risk group from a lymph node metastasis group among patients with endometrial cancer, because the false- negative rate was 1.4% in the validation cohort (43% of 360 patients) with good discrimination (area under the receiver operator curve = 0.85) [53]. In addition, the native likelihood ratio of the low-risk criteria was 0.11 (95% CI = 0.04–0.29), and the false-negative rate was 1.3% (95% CI = 0.5–3.3%) at the assumed prevalence of nodal metastasis of 10% [53].

The use of 3.0 T MRI to evaluate the depth of myometrial invasion by endometrial cancer, and whether there is myometrial invasion, has high diagnostic accuracy, with 95% sensitivity, approximately 60–70% specificity, 91–93% positive predictive value, 75–78% negative predictive value, and a total accuracy of 88–90% [54]. In distinguishing cases of no and superficial myometrial invasion from cases of deep myometrial invasion, 3.0 T MRI had 88–94% sensitivity, 94–97% specificity, 83–93% positive predictive value, 94–97% negative predictive value, and 92–94% accuracy [54].

Good compliance without a contraindication for high-dose hormonal therapy, mainly progestins, is also an important selection criterion for good candidates. Good compliance is a basic requirement not only for the treatment of many chronic diseases or surgical illnesses [55–58] but also for women with endometrial cancer who wish to preserve their fertility, because compliance with follow-up and the taking of long-term medication is important. A repeat follow-up examination including a surgical approach (for example, dilation and curettage or laparoscopy examination) might sometimes pose problems for some patients, but it is needed because of the oncologic risk inherent in these patients. Therefore, if the patients are not able to have good compliance, the possibility of fertility preservation should not be suggested. Finally,

fertility preservation is not possible in women intolerable of or with a contraindication for hormonal therapy. The treatment for endometrial cancer is often a hormone-like agent, which may involve the hepatic metabolism and affect hemostasis or mood change. However, there are no specialized reports addressing the absolute contraindications for frequently used agents for hormonal therapy in endometrial cancer. Therefore, the labeling guidance text for progestin-only oral contraceptives can be used a reference. A Category 3 or 4 contraindication for progestin treatment includes a history of or current breast cancer, liver disease (i.e., severe cirrhosis) or liver tumors (hepatocellular adenoma or hepatoma), and use of medications to treat seizures or tuberculosis (i.e., phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, or rifampicin) [59]. Less common side effects of high-dose progestins include headaches, tender breasts, nausea, dizziness, weight gain, acne, thrombosis, and extra hair on the face and body [60]. In a recent self-screening survey for the use of progestin-only oral contraceptive pills, only 1.6% of women were identified as having at least one contraindication for progestin-only oral contraceptive pills, with a sensitivity rate of 75% (95% CI = approximately 50.6–90.4%), and 0.6% of women in a prospective study of oral contraceptive use reported having a contraindication for progestin-only oral contraceptives [59], which emphasizes again that the advice of medical staff is one of the most important factors in treatment choice.

Type of hormone use

How to select an appropriate conservative treatment agent for women with endometrial cancer is also an important issue. A Web-based survey of all United Kingdom consultant gynecologists ($n = 338$) from the Royal College of Obstetricians and Gynecologists showed that the most popular choices for managing complex endometrial hyperplasia were oral progestins (33.2%, 109 of 338) and the levonorgestrel intrauterine system (LNG-IUS) (52.1%, 171 of 338); most gynecologists (52.6%) would explore two conservative choices before attempting to perform a hysterectomy for this condition [61]. By contrast, for ACH, more than 80% of gynecologists (83.2%, 273 of 338) would perform a hysterectomy and would only consider LNG-IUS or oral progestins as a second or third option [61]. It is interesting that more gynecologists (57.6%, 155 of 269) favored the use of LNG-IUS as a secondary choice in the management of women with ACH [61].

The published data on the conservative treatment of women with endometrial ACH or endometrial cancer seem to differ from those of the above survey. A recent systematic review summarized 45 studies with 391 women (median age of 31.7 years, ranging from approximately 19 years to 80 years), including 111 patients in whom a diagnosis of ACH was made and 280 patients in whom a diagnosis of endometrial cancer was made [25]. The study data and recommendations are presented later in this paragraph, and only the types of hormones are discussed in this section. Progestin agents included medroxyprogesterone acetate (MPA), megestrol acetate, LNG-IUS, intramuscular 17-hydroxyprogesterone, oral contraceptives, norethisterone, dihydrogesterone, natural progesterone, and combinations of two agents [25]. Of the progestins used to treat these patients, most (49%) were MPAs; 25%, megestrol acetates; 19%, LNG-IUS; 5.3%, natural progesterones; 0.8%, intramuscular progesterone treatment; and the remaining were nonspecified treatments [25]. The dosage use for these patients with ACH or endometrial cancer varied greatly: MPA ranged from 200 mg to 800 mg, and megestrol acetate ranged from 40 mg to 320 mg.

Some gynecologists have favored the use of LNG-IUS in the management of patients with ACH or endometrial cancer [62]. Of 12 patients who had a 36-month follow-up with LNG-IUS treatment, the endometrial biopsy results were negative in seven of 11 (63.6%) at 6 months and in six of eight (75%) at 12 months, suggesting that LNG-IUS can eradicate some cases of presumed Stage IA, Grade 1 endometrioid cancer in women at high risk for perioperative morbidity [62]. In addition, a small prospective observational study showed that 16 of 19 patients with ACH had regression within 12 months of LNG-IUS treatment, and only two patients were treated with TH due to persistent disease [63]. However, a systematic review investigating the efficacy of LNG-IUS for endometrial protection was less confident in its support for recommending LNG-IUS as the treatment of choice for hyperplasia. In addition, there was no evidence to adequately support the use of LNG-IUS as chemoprevention in women with a risk factor for future endometrial cancer, such as HNPCC syndrome or obesity, although its use might be of benefit in reducing the risk of endometrial polyps and hyperplasia in tamoxifen users [64], who are often survivors of breast cancer, and be significantly risky for patients with endometrial cancer [65–69]. Experience with the sole use of LNG-IUS in the setting of endometrial cancer is still limited, and evidence is needed. Therefore, oral progestin or other hormone therapy, for example, gonadotropin-releasing hormone agonist (GnRH agonist) [70–73], antiprogestins [73], selective progesterone receptor modulators (SPRMs) [74,75], estrogen receptor antagonists, such as fulvestrant [76], aromatase inhibitors [75], or new-generation progestin [77], should be added in patients treated with LNG-IUS [25,78].

Response rate with hormonal therapy

The overall response rate with hormone therapy in patients with ACH and endometrial cancer, when the uterus is preserved, has been described earlier (staging and standard treatment for younger women with endometrial cancer section) (Table 2). In the meta-analysis of 45 studies cited in the previous section, including 391 patients (the median age of 31.7 years, ranging from 19 years to 80 years), Gunderson et al [25] summarized the reports from 111 women in whom a diagnosis of ACH was made and 280 women in whom a diagnosis of endometrial cancer was made [25]. The median follow-up time was 39 months, ranging from 2 months to 138 months, with a complete response in 304 women (77.7%) [25]. Median time to complete response in 226 patients was

6 months, ranging from 1 month to 18 months. Two hundred and eight women (53.2%) had a complete response with no evidence of recurrence; 96 women (24.6%) had an initial response, but finally had recurrence with a median time to recurrence of 24 months, ranging from 4 months to 72 months; 87 women (22.2%) failed to respond to hormonal therapy [25].

The safety of fertility preservation in women seems to be much more acceptable for those with ACH, because these patients not only need little time to achieve complete remission but also have a higher percentage of complete remissions. Durable response and initial response rates for ACH (65.8% and 85.6%) were significantly higher than for endometrial carcinoma (48.2% and 74.6%), respectively [25].

Appropriate surveillance

Appropriate and close surveillance is of the most importance for these patients because oncologic risks are always present and any delay in adequate treatment may result in a fatal outcome for these patients. In addition, the potential risk of hormone treatment should be emphasized. For example, thrombosis is a serious adverse reaction to high-dose progestin, caused by the high-dose progestin's inhibitory activity against plasminogen activators, which might result in cerebral infarction, myocardial infarction, and pulmonary embolism; therefore, monthly checks of the clotting system are suggested, and treatment with high-dose progestin needs to be discontinued upon detection of any abnormality in the clotting system [77]. Furthermore, cancer tissue susceptibility to hormone treatment is important in avoiding the potential risk of cancer persistence and progression. It has been shown that the susceptibility of ACH and endometrial cancer to hormone therapy varies among individual cases, with responses more likely to appear in cases of ACH and less likely in cases of endometrial cancer, especially in higher grade tumors, such as Grade 2 or more. Therefore, the surveillance of patients undergoing fertility preservation might differ between those with ACH and endometrial cancer. A meta-analysis review that reported the need for a minimum of 3 months of progestin therapy for ACH patients before assessing response and longer for patients with endometrial cancer, the danger of concomitant adnexal malignancy, and the considerable risk of disease recurrence all mandate close follow-up and definitive surgical therapy if needed [25]. Although most patients with endometrial cancer who can be managed with conservative treatment are predicted to have a response to hormone therapy, a thinning of the endometrium on transvaginal ultrasound is associated with an increased chance of responding to progestin therapy [78]. However, the predictive value cannot be considered as an alternative to endometrial sampling or repeat dilation and curettage. There is no agreement yet on a checkup list for patients with endometrial cancer with uterus preservation. Therefore, the following suggestions may need further validation. First, regular transvaginal ultrasound and/or Pap smear every 3 months are recommended, and the thickness of the endometrium should be less than 5 mm. Second, repeat endometrial sampling and/or Pap smear should be performed every 3–6 months because the Pap smear sometimes can detect abnormal cells from the extracervix [79,80]. Third, MRI or laparoscopy can be performed annually or semiannually if indicated [81,82]. Fourth, childbearing should be planned as soon as possible, and if there is no immediate attempt to become pregnant, continuing hormonal therapy is highly recommended. Fifth, more definite therapy should be sought in case of any suspicion of nonresponders during follow-up.

Additional counseling

Although almost all endometrial cancer is sporadic, there is no doubt that genetics plays a role in the pathogenesis. For example, Lynch syndrome or HNPCC—a disorder of hereditary mutation in DNA mismatched repair genes— presents a relatively high lifetime risk for endometrial cancer (27–71% compared with 3% in the general population). Not only is there a high risk of endometrial cancer in patients with Lynch syndrome, but also a high risk of colon, ovarian, genitourinary, and gastrointestinal carcinomas. Another syndrome with *PTEN* mutations is Cowden syndrome, an autosomal-dominant inherited disorder that results in breast, endometrial, thyroid, kidney, and colorectal cancers, as well as dermatologic conditions, including hamartomas. Patients with these hereditary disorders, similar to a *BRCA1* mutation, should be referred for genetic counseling. Identification of patients with this genetic

Table 3
Domestic experience in the management of young women with endometrial atypical complex hyperplasia or cancer who underwent uterus preservation.

Authors (y)	Patients	Hormone	CR rate	Recurrent rate	Birth	TH	FU
Kung [88] (1997)	22 y/o	M, T, Oral pills	100%	NA	NA	NA	12 mo
Wang [89] (2002) (n = 9)	32 y/o (30–39)	M, T, GnRH-a	88.9% (8/9)	50% (4/8)	22.2% (2/9)	66.7% (6/9)	69 mo (25–113 mo)
Huang [89] (2005)	36 y/o		100%	100%	100%	100%	4 mo
Chang [91] (2006) (n = 2)	35 y/o 35 y/o	MPA Oral pills					
Wu [92] (2008)	35 y/o	M	100%	100%	NA	NA	24 mo
Chao [93] (2011) (n = 3)	30 y/o 31 y/o 32 y/o	M + T M	100%	0%	100 (3/3)	100%	11 y (8–16 y)

CR = complete remission; FU = follow-up; GnRH-a = gonadotropin releasing hormone agonist; M = megestrol acetate; mo = months; n = number; y/o = years old; MPA = medroxyprogesterone; T = tamoxifen; TH = total hysterectomy.

predisposition allows the patient and her relatives to undertake additional cancer prevention strategies. Finally, because anxiety about relapse and metastasis and advice of the medical staff are the most important factors for treatment choice in cancer patients [41], a team [83], including special gynecologic oncologists [84], psychosocial experts [85], cytogenetic experts [86], and reproductive endocrinologists [87], etc., should be included in consultations for these early endometrial cancer patients who need fertility preservation.

The Taiwan experience

Six reports can be found with domestic data [88–93] (Table 3). As early as 1997, Kung et al [88] reported a 22-year-old nulliparous woman with concomitant early-stage endometrial cancer and polycystic ovary syndrome who was treated with multimodality and sequential treatment, including repeat endometrial curettage, a 6-month megestrol acetate and tamoxifen treatment, a combination of contraceptive pills, hysteroscopy, and laparoscopy, with a successful preservation of the uterus [88]. The largest series, from Chang Gung Memorial Hospital, supported the feasibility of an active and multimodal treatment strategy in nulliparous young patients with well-selected Stage I, Grade 1 endometrial cancers [89], although almost all patients finally needed TH for definite therapy, even those patients without clinically evident disease [93].

Conclusion

Fertility preservation therapy for young women with ACH or endometrial cancer is still not a standard therapy, although it is a reasonable choice. Before attempting this approach certain concerns should be adequately explored between the patient and physician, including the choice of either complete or partial preservation of fertility. Other concerns include the high oncologic risk, even in patients with a high response rate. Careful counseling for anxiety about relapse and metastasis, distress about side effects, advice of the family, advice of the medical staff (teamwork), and the economic burden should be included in the decision-making process.

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