European Society of Gynecological Oncology Task Force for Fertility Preservation

Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients

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Abstract: Endometrial cancer (EC) in young women of reproductive age is a relatively rare diagnosis. However, since in the modern era women delay their childbearing for a variety of social reasons, more and more women in the near future will be nulliparous and have a diagnosis of EC at the same time. Hence, a more conservative approach of EC is desirable to preserve fertility of these women, without compromising their survival. Recently, the number of studies reporting encouraging results on fertility-sparing management of EC with high dose of progestins is increasing. It seems that preserving the uterus and the ovaries in a carefully selected patient with EC confers only a very small risk combined with an enormous benefit. Selection of women suitable for such a conservative approach, as well as method of treatment, follow-up, recurrence, obstetric outcomes, and survival rates are very important parameters when consulting women with EC wishing to preserve their fertility. In this article, we try to elucidate all the previously mentioned aspects and formulate clinical recommendations, based on published data, about the most proper approach and consultation of these patients.

Key Words: Fertility sparing, Endometrial cancer, Progestins, Recurrence, Obstetric outcomes

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Endometrial cancer (EC) is the commonest gynecological cancer in western countries with an increasing incidence trend.[1] Although it mainly affects postmenopausal women with a median age of 61 years, approximately 5% of the patients are younger than 40 years.[1,2] This combined with the fact that in the current era women delay their childbearing, a not insignificant number of premenopausal nulliparous women will be diagnosed with EC. Beside genetic predisposition (eg, Lynch syndrome), obesity, polycystic ovarian syndrome (PCOS), and anovulatory cycles, all causing a hyperestrogenic state, are the main predisposing factors for developing a type I (estrogen-dependent) EC. Because irregular bleeding is a quite common early symptom, most of these tumors (90%) are detected as well-differentiated (grade 1) endometrioid EC at a very early stage (International Federation of Gynecology and Obstetrics IA—either restricted to the endometrium or invading only superficially the myometrium).[3] The standard management with

hysterectomy, bilateral salpingoophorectomy with or without pelvic/para-aortic lymph node dissection confers an excellent 5-year overall survival rate of 93% and 99% disease-specific survival.[4] However, for these young women, the standard management is immensely affecting their quality of life as their chance of childbearing is lost. For this specific population, more conservative approaches using mainly medical treatment with high-dose oral progestins, that is, medroxyprogesterone acetate (MPA), megestrol acetate (MA), and more recently with levonorgestrel-release intrauterine devices (LNG-IUDs) have been reported.

Most of the series reported so far are retrospective, have recruited only a small number of patients, and have used different treatment methods and inclusion criteria, making the extraction of useful conclusions extremely difficult. Several reviews of the data have also been published.[5–9] The so far largest systematic review performed by Gallos et al,[7] in 2012 included 34 manuscripts reporting on overall 408 women with conservatively treated EC. Following this review, in 2013, a large series from Korea reported on 148 women managed conservatively.[10] These numbers emphasize on the rarity of the condition as well as the growing body of evidence and hence support the need for more information on how to treat these patients optimally.

The most important issues a treating physician has to consider before offering a conservative approach to women with EC are mainly divided in 2 categories: first, the assessment of the tumor's individual clinicopathological biology, that is, histological type, grade, myometrial invasion, and presence of lymphovascular space invasion; and second, choosing the optimal type, dose, and duration of medical treatment, as well as the proper follow-up.

In this article, we will try to elucidate all the aforementioned issues and constitute a guideline for gynecological oncologists treating women with EC with a strong desire to maintain their fertility. Although data are relatively scarce and the level of evidence is quite low, since the number of young women with EC who desire fertility preservation will increase in the future, we try to formulate clinical recommendations to improve both the counseling and management of these patients. The recommendations formed in this article were derived after reviewing the original papers on conservative management of EC (gathered from the references of the systematic reviews already published and not after systematic review of the literature) and reaching a consensus opinion between the members of the European Society of Gynecological Oncology task force.

Selection of the Right Patient: Establishing Stage 1A Grade 1 Endometrioid Carcinoma

All clinicians seem to agree that only women with anticipated stage 1A (without myometrial invasion) grade 1 endometrioid EC should be offered fertility-sparing treatment if desired. These patients seem to have a greater chance of responding to treatment with progestins and the likelihood of presenting with advanced disease in the future is really small. That means that persistent disease and/or a possible recurrence can still be salvaged with a simple hysterectomy, without compromising the excellent prognosis. However, we have to accept that there is no diagnostic tool to predict with absolute certainty the grade and even more the stage of EC, without performing a hysterectomy and hence we have to counsel our patients that some of them will receive a conservative treatment having only a moderate differentiated tumor and/or more advanced stage disease. Nevertheless, every effort should be made to exclude advanced disease and poor differentiation of the tumor before commencing fertility-sparing treatment with progestins.

From the large GOG studies from the mid 1980s, it was clearly shown that the most important prognostic factors for lymph node metastasis in patients with EC were the grade of the tumor and the depth of myometrial invasion. Specifically, it was shown that the risk of pelvic and/or para-aortic lymph node involvement when managing grade 1 tumors without myometrial invasion was less than 1%. Clearly, the prognosis of these patients was excellent with a 5-year progression-free survival that exceeded 95% when both these parameters were met.[3,11,12] However, establishing the correct grade and stage of the disease without performing a hysterectomy is not an easy task and will be discussed as follows.

Grade—Dilatation and Curettage vs Pipelle Biopsy

The differentiation of EC is the most important predictor of stage as well as response to treatment with progestins. Duska et al[13] reviewed women younger than 40 years with EC and showed that only grade 1 EC could predict stage 1 disease among them. In addition, Thigpen et al[14] was able to demonstrate that in advanced disease the response rate to MPA was 37% for grade 1 tumors compared with only 9% for grade 3 tumors.

Endometrial biopsy has been the cornerstone examination for the diagnosis of EC. Dilatation and curettage as well as pipelle biopsies are currently used to obtain endometrial tissue for histological diagnoses. In studies correlating the result of this initial diagnosis with the histological result of the final specimen after the patient had undergone hysterectomy, many authors have described a discrepancy of up to 20% either for performing a dilatation and curettage (D&C) or a pipelle biopsy.[15] When both techniques were compared, it appears that the D&C seems to be superior in terms of correlation with the final histological results. Specifically for grade 1 EC, Leitao et al[15] showed that by performing a D&C, only 8.7% of the patients were upgraded in the final specimen as compared to 17.4% of the patients that had a pipelle biopsy, a statistically significant difference ($P = 0.007$). In addition, a D&C is more likely to remove the tumor completely, hence reducing the tumor burden and facilitating the therapeutic effect of progestins, although this has not been examined in a prospective trial.[16]

Recommendation: A D&C is the preferred method to obtain histology.

Histopathologic Difficulties in Diagnosing and Grading Type I EC

In a study performed by Kaku et al,[17] only 19 of 39 cases of either endometrial hyperplasia or EC were confirmed correctly after a thorough histological review performed by

3 different pathologists. The remaining 20 cases were either upgraded or downgraded. In addition, in the phase 2 study from Japan among 47 patients 7 discrepancies in histological diagnosis between its center and the central review were identified.[18] Specifically, in 5 patients, the diagnosis was downgraded from grade 1 EC to atypical hyperplasia, whereas 2 cases were upgraded from grade 1 to grade 2. This further emphasizes the difficulties in comparing and/or interpreting the studies on conservative management of EC, especially when most of the studies available did not perform a central pathologic review of the initial diagnosis. Therefore, some presumed cases of endometrial carcinomas were included in the analysis showing excellent response rates, which could have been only cases of atypical hyperplasia where higher response rates are expected. This highlights the need for review of the initial pathology from more than one experienced histopathologist to improve the accuracy of the final histological diagnosis.

Recommendation: All specimens should be examined by 2 pathologists. In cases where a pathologist is working alone or in isolation, digital image transfer of photomicrographs should be used for a second opinion.

Stage—Myometrial Invasion According to Imaging

Myometrial invasion is the second most important prognostic factor for advanced disease in patients with EC.[3,19] In patients with superficial myometrial invasion, the 5-year overall survival is reported to range between 80% and 90%. This percentage falls to 60% when deep myometrial invasion is identified.[20] For that reason, being able to identify myometrial invasion is crucial when managing EC patients conservatively. Transvaginal ultrasound scan (TVUS), computed tomographic scan, and magnetic resonance imaging (MRI) scan have all been studied quite thoroughly and various sensitivities and specificities have been reported.[20,21] Most seem to agree that enhanced MRI scan is the most accurate method to diagnose myometrial invasion preoperatively and this was also summarized in a meta-analysis.[22] According to another meta-analysis from the same group, the authors reported a post-MRI probability of myometrial invasion of less than 1% in grade 1 tumors if the MRI scan was negative.[23]

TVUS has also yielded promising results in identifying degrees of myometrial invasion when performed by experienced and dedicated sonographers. In a prospective study, TVUS showed comparable efficiency to MRI scan and could be possible used in centers with difficult access to MRI scan to define myometrial invasion.[24]

However, we have to emphasize that a method for predicting whether the myometrium is invaded with an accuracy of 100% does not exist. A minor percentage of patients that will undergo fertility-preserving management for EC will have some degree of myometrial invasion that cannot be detected with the available imaging modalities. For example, in the trial by Kaku et al, all 12 patients treated conservatively were presumed to have no myometrial invasion. However, in 2 cases, when hysterectomy was performed as those tumors did not respond to progestin treatment, early myometrial invasion was detected in the final histology. In both cases, the hysterectomy was performed only 1 month after the initial diagnosis.[19] In the prospective trial conducted by the same group, 19 of 45 patients underwent hysterectomy either for recurrent disease or because they failed to achieve complete response. In 7 (36.8%) of them, early myometrial invasion was identified in the hysterectomy specimens.[18]

Recommendation: Enhanced MRI scan is the preferred option for establishing the depth of myometrial invasion.

Selection of Medication, Dose, Length of Treatment, and Follow-up

MPA or MA and the Role of LNG-IUD

Many different medical treatment regimens for fertility-sparing management of EC have been described in the literature. Most have used either MPA or MA; however, other medications have also been used like GnRH analogs, hydroprogesterone, letrozole, tamoxifen, oral contraceptives, and LNG-IUDs. In addition, few reports have used hysteroscopic resection of the tumor combined with oral progestins.[25] However, there is no prospective study so far comparing the efficacy of all the previously mentioned regimens.

Data comparing MPA and MA are conflicting. According to a meta-analysis, the use of other medical therapies (including MPA) was associated with a higher risk of recurrence when compared with MA.[9] In contrast, the so far largest series, which had not been included in the previously mentioned meta-analysis, did demonstrate—although the complete response rate was similar between patients receiving MPA and MA—that the former was significantly correlated with a reduced risk of recurrence.[10]

A few preliminary reports so far have documented that the use of LNG-IUD seems to be equally effective compared to oral progestins in terms of response rates in patients with EC.[26] Also, in a prospective observational study for the conservative management of 14 women with EC, only intrauterine progesterone releasing device and GnRH analog were used. Their results were comparable to studies using either MPA or MA with complete remission rate of 57% and recurrence rate of 25%.[27] Because those first results are encouraging, the Korean Gynaecological Oncology Group is currently running a prospective multicenter trial (KGOG2009) to analyze the value of adding an LNG-IUD to oral progestins in those patients.[28]

Recommendation: Either MPA or MA should be used. More trials are needed to further elucidate the role of LNG-IUD in this setting. Preliminary results are encouraging.

Dose of Progestins

Although it is generally accepted that administration of progestins is the mainstay of conservative management in young patients with EC, the optimal dose has not yet been determined. In several studies, different doses have been used of either MPA ranging from 100 to 1200 mg/d or MA ranging from 40 to 600 mg/d. However, most of the series were small, of retrospective nature, and due to their inherent heterogeneity, definitive conclusions cannot be drawn. According to a

GOG study in advanced or recurrent EC, a dose escalation (200 vs 1.000 mg) of oral MPA did not confer a significant benefit for the patients.[14]

In contrast, for MA, Eftekhar et al were able to demonstrate a benefit for increasing the dosage in a small series including 21 patients. Although the initial response rate after 3 months for 160 mg/d of MA orally was only 28%, doubling the dosage led to 56% additional responders after 6 months of treatment. Whether this additional effect was related to doubling the dosage or the prolonged duration of treatment is unclear.[29]

Most of the studies report no significant toxicity among the patients treated with high-dose progestins. However, in the Japanese study, there were 3 patients demonstrating grade 3 toxicity, that is, weight gain in 2 and liver dysfunction in one of them.[18] There is no thromboembolism or death related to the treatment reported in any of the studies.

Recommendation: According to most of the reports, we recommend to use MPA at a dose of 400 to 600 mg/d or alternatively MA at a dose of 160 to 320 mg/d.

Duration of Treatment

The optimal duration of treatment with progestins has also not been determined so far. In one review of the literature summarizing 231 cases, 47% of them received treatment with progestins for a period of 6 months or less, 17% between 7 and 9 months, whereas 13% longer than 9 months (in 23% of the patients, the duration was not reported in the original publication).[6] In the retrospective cohort from Korea, the mean duration of treatment with progestins was 8 months (range, 2–31 months) and the median time to achieve complete response was 18 weeks (range, 8–55 weeks).[10] In the prospective study from Japan, the therapy with progestins was given for 26 weeks. Among 12 complete responders, only 6 achieved complete response at 8 weeks (50%), whereas 11 achieved complete response at 16 weeks of treatment (91%).[18] Koskas et al[9] showed that most of the patients will respond within 6 months of treatment (72.4%) with only a small additional benefit for prolongation of treatment after that (78% at 12 months). Due to the heterogeneity of treatment protocols used, it is quite difficult to agree on the optimal duration of treatment with progestins. However, most of the studies seem to agree that the treatment should continue for at least 6 months.

Recommendation: It seems to be reasonable to try to achieve response by continuing with progestins for at least 6 months. Evidence to support treatment longer than 6 months to achieve a "late response" is weak.

Follow-up During Therapy and After Response

In the largest retrospective cohort as well as prospective cohort, complete response was defined as absence of any form of hyperplasia.[10,18] Those publications have described follow-up intervals between 2 and 6 months. However, both studies showed that all patients had no evidence of progressive disease within these first 6 months while all patients were on treatment. Hence, it seems that an earlier follow-up might not be necessary.

So far, no definitive method of follow-up has been established. Obviously, to prove complete response, histology—either by an office endometrial biopsy using the pipelle device or alternatively by a D&C—must be obtained. In this respect, it is of note, that according to a small prospective observational study, follow-up by endometrial aspiration biopsy seems to be less reliable in comparison to conventional D&C.[30]

In case of complete response, it is advisable to pursue pregnancy earlier rather than later because the rate of recurrence is up to 40% (see section on recurrent disease later).[7] There are no data regarding the right time for that, but it seems reasonable to start even the first month after complete response has been established. Until pregnancy is achieved, close follow-up of the patient in terms of symptoms and endometrial sampling with a pipelle biopsy every 6 months is also advisable to detect an early recurrence.

After completion of family planning, many authors have suggested that a definitive treatment with hysterectomy with or without bilateral salpingoophorectomy should be offered as long-term recurrences have been observed.[17] This is further emphasized by the fact that the predisposing factors of unopposed estrogens leading to EC (anovulatory cycles, PCOS, etc) have not been corrected. In any case, the possibility to proceed with hysterectomy after family planning completion should be discussed with the patient individually and informed consent should be obtained.

For patients not willing to conceive immediately, maintenance treatment with low-dose cyclic progestin or a progestin-containing IUD should be offered. The latter one has also the advantage to assure treatment compliance. The analysis of the Korean study showed that maintenance treatment with the previously mentioned regimens after complete response was significantly associated with a lower rate of recurrence.[10]

Recommendation: Perform the first D&C to check for response 6 months after initiation of treatment and not before. Maintenance treatment is advisable if immediate pregnancy is not pursued. Due to a high recurrence rate, hysterectomy is advisable once family planning has been completed.

Special Issues or Dilemmas

Check for Progesterone Receptor

Some of the studies have tried to identify whether the presence of estrogen and/or progesterone receptors (PgRs) in EC can be a reliable factor to predict success of endocrine treatment. Duska et al[13] showed that estrogen and PgR positivity or negativity was comparable between responders and nonresponders. However, other studies suggested that response to progesterone was significantly associated with the presence or absence of PgRs. In detail, Ehrlich et al[31] examined advanced and recurrent EC cases treated with progesterone and found out that 60% of PgR-positive patients responded well compared to only 18% of PgR-negative patients. Accordingly, Ingram et al[32] identified the absence of PgRs to be the most important prognostic factor for recurrence. Finally, in a small prospective study including 9 patients, Yamazawa et al[33] showed that all patients with complete response expressed PgRs compared with only 50% of PgR-negative patients.

Recommendation: There is no need to check for PgR expression routinely. Although PgR expression seems to be a reasonable predictive factor for response to treatment, it is feasible to try endocrine treatment in PgR-negative patients, as a significant number of them will respond.

Synchronous or Metastatic Ovarian Tumours

Synchronous or metastatic ovarian cancer in young patients presenting with EC is a relatively uncommon, but important issue when considering fertility-preserving management.[34] A multicenter retrospective study found that among 102 young women with EC, a synchronous or metastatic ovarian carcinoma was identified in 25%.[35] However, this percentage accounts for all stages and grades of EC. In 26 women who were treated conservatively (presumed grade 1 and no myometrial invasion), only 1 (3.8%) synchronous ovarian carcinoma was identified after treatment failure. In another similar study, 4 synchronous ovarian malignancies were identified among 37 young women with EC (11%).[36] However, again no stratification according to grade and stage was reported and for that reason it is difficult to calculate the incidence of synchronous or metastatic ovarian carcinomas in stage 1A (no myometrial invasion) grade 1 EC. In a multicenter retrospective study, among 471 young patients with EC managed surgically, no synchronous ovarian tumor was identified.[37]

Signorelli et al reported that staging laparoscopy is routinely performed in all cases of conservative management in EC in their institute to exclude the presence of synchronous ovarian tumors. Among the 21 patients, despite intensive screening with MRI scan, U/S scan and diagnostic laparoscopy, 2 (9.5%) patients with intraparenchymal ovarian carcinomas (15 and 12 mm) were identified soon after failure of conservative management.[38] Laurelli et al[39] also adopted the use of laparoscopy to exclude synchronous ovarian carcinomas in their series of patients treated conservatively; however, so far no ovarian tumor has been identified. Finally, Yamazawa et al reported that 2 patients who developed recurrent EC after complete initial response with MPA were found to have a synchronous ovarian cancer at the time of hysterectomy. In one of these cases, the size of the lesion was only 1 cm.[32]

Recommendation: Excluding suspicious ovarian lesions with imaging modalities like MRI scan or TVUS is mandatory. The possibility of a diagnostic laparoscopy should be discussed with the patient; however, no strong evidence exists to support its routine use.

Nonresponders–Partial Responders

Patients with EC managed conservatively are likely to respond within the first 6 months of treatment with either MPA or MA.

Recommendation: Patients with persistent disease proven by D&C should be counseled for a hysterectomy as the definitive treatment. The need for bilateral salpingoophorectomy in this young age should be discussed with each individual patient and informed decision should be made, especially in view of the risk for synchronous or metastatic ovarian tumor. Patients who after 6 months of treatment have a partial response (complex atypical hyperplasia) could be offered continuation of treatment with medroxyprogesterone for another 3 to 6 months.

Recurrence

The recurrence rate of EC after conservative management is consistently reported between 30% and 40%, while the median time to recurrence is 15 months ranging from 4 to 66 months.[5–7,10] In addition, the recent meta-analysis by Koska et al[9] showed that the probability of recurrence was increasing in relation to time for at least 5 years. All the above mean that a significant amount of women will recur soon after their remission and before having completed their family planning.

There are some encouraging data for re-treatment with progestins for recurrent EC. In a study of 27 patients by Perri et al, 15 of 24 complete responders experienced a recurrence after initial treatment with progestins. Eleven of them were re-treated with progestins and all of them responded again with 3 subsequent pregnancies.[40] In addition, Park et al, showed that among 33 patients that were re-treated with progestins after recurrence of their initial complete response. Five patients delivered six healthy babies. After a follow-up of 51 months, none of the patient had died of disease.[41]

Recommendation: In case of recurrent disease in initial complete responders re-treatment with progestins seems to be efficient and hence can be offered.

Success Rates and Pregnancy Outcomes

All the reviews published to date on conservative management of EC seem to agree that the percentage of women that will respond to progestin treatment is around 75%. Gallos et al's meta-analysis showed a pooled regression rate of 76.2% (95% confidence interval, 68%–85.3%) was reported.[7] In another review, a 12-month regression rate of 78% has been reported.[9] These numbers are comparable with the Korean series reporting a response rate of 77.7%.[10]

Women who wish to become pregnant should start trying to conceive as soon as complete regression of their disease has been achieved. This is further emphasized by the fact that, in the Korean study, pregnancy itself was significantly associated with a reduced risk for recurrence.[42] It seems that pregnancy stops the vicious cycle of unopposed estrogen stimulation that could trigger a recurrence. Gallos et al showed that among 325 women treated with progestins, 75 managed to achieve at least one live birth, resulting in a pooled live birth rate of 28% (95% confidence interval, 21.6–36.3). In the same meta-analysis, the live birth rate among women trying to conceive reached 39.4% when assisted reproduction was used compared to only 14.9% with spontaneous conception.[7]

Regarding the question whether assisted reproduction is safe, in conservatively treated EC patients after complete response, preliminary data seem to be promising.

In this respect, Park et al[42] reported comparable 5-year disease-free survival rates between women receiving fertility drugs and women trying to conceive spontaneously. In addition, they reported that disease-free survival was improved

significantly among patients who achieved at least one pregnancy compared with those who did not. Ichinose et al also documented the beneficial effect of pregnancy. In this study, all women who achieved a live birth after conservative treatment of EC had a lower chance of recurrence compared to those not achieving pregnancy. Moreover, this difference remained irrespective of whether ovulation drugs had been used or not.[43]

Recommendation: Complete response rates are up to 75%. Patients should be encouraged to pursue pregnancy very soon after complete remission of their disease has been confirmed histologically. Patients with previous history of infertility or with risk factors for infertility (obesity, PCOS, diabetes, anovulatory syndrome) should be promptly referred and encouraged regarding the use of assisted reproductive techniques.

Final Considerations/Future Directions

More and more women in the near future, experiencing EC, will be asking for fertility-sparing options. The gynecological oncology society needs to reach a consensus on how to manage these women conservatively without compromising their survival outcome. However, this is not an easy task as EC in young nulliparous women of reproductive age is a rare event. Consequently, only a small number of patients with EC require conservative management and the extraction of useful guiding conclusions from published studies becomes difficult. The use of progestins seems to offer very good results in treating early stage EC and allowing young women to pursue a pregnancy.

The mortality associated with conservative treatment of EC is extremely low despite the fact that the rate of recurrence is very high. This is attributed to the fact that in this setting most of recurrences were salvageable with hysterectomy only. Only 2 deaths attributed to conservatively treated EC were reported among 408 women.[7] The first one was due to diagnosis of a synchronous endometrial, ovarian, and primary peritoneal cancer after repeated recurrences and the second one due to an ovarian carcinoma on a patient who on recurrence underwent only a hysterectomy without bilateral salpingoophorectomy, as she wanted to avoid menopausal symptoms. Hence, the mortality rate is very low and can be considered acceptable; however, there is always the possibility that more deaths have occurred without being reported or published.

Translation research in EC cell lines has very recently yielded very interesting results regarding the use of the antidiabetic drug metformin and its effect on EC cells. These studies have shown that metformin suppresses EC cell growth and exhibits an antiproliferative effect in women with EC and insulin resistance.[44–47] Albeit small, these preliminary reports may shift the future of conservative management of EC and provide more targeted ways of treatment, especially for patients with PCOS and insulin resistance. A prospective phase II study is announced (feMME) and hopefully will further elucidate the role of metformin in combination to progesterone and active weight management for the treatment of early stage EC in the future.[48]

Young women with EC should always be carefully consulted about the need for a genetic test for detection of Lynch syndrome, depending either on their family history of cancer[49] or depending on testing for mismatch repair protein expression using microsatellite instability testing and immunohistochemistry analysis.[50] This will alert and identify patients with Lynch syndrome who need a very close monitoring and tailored consultation about their further follow-up and management. It is debatable whether a patient with Lynch syndrome should be offered conservative management and this becomes even more complicated in cases where hyperestrogenic state is also identified as a possible cause of an early EC.

Extensive counseling of the patient is the integral part of the management. The detailed information about all aspects and risks of conservative treatment has to be provided and informed consent obtained, before initiation of the treatment. All the previous recommendations should be interpreted with cautious because the studies upon which they are based provide mainly retrospective low-quality evidence. They should provide guidance for managing conservatively young patients with EC, but should never replace the basic rule of individualization of care as each patient has different characteristics as well as different needs and expectations.

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