



# Therapeutic Dilemmas in Young Patients with Early Stage Endometrial Cancer

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## Editorial

Nowadays, endometrial cancer (EC) is the 2<sup>nd</sup> most common tumor of the female reproductive system and the 5<sup>th</sup> most common cancer among female patients [1,2]. It is more frequent in wealthy and more developed countries (Northern and Western Europe, Northern America), while the mortality rate is considerably greater in less developed ones (Northern Africa, Melanesia)[1,2]. Despite the fact that the vast majority of EC patients are postmenopausal, approximately 14% of them are premenopausal and almost 4% are below 40 years of age [3-19]. It is widely believed that conservative management of those young patients with EC, represents a great challenge [3-19].

According to the most recent guidelines, systematic surgical staging plays a fundamental role in EC treatment [3-5,9-15,18,20-25]. This is mainly based on the fact that systematic surgical staging provides many advantages in diagnosis, treatment and prognosis for both types of EC [type I (endometrioid) or type II (serous, clear cell, undifferentiated)] [3-5,9-15,18,20-25]. Moreover, postoperative adjuvant treatment (radiotherapy, chemotherapy or a combination of both) plays a crucial role in EC patients with increased risk of recurrence or at advanced disease stage [3-5,9-15,26]. However, the extent of surgical staging and the type of postoperative adjuvant treatment should be thoroughly individualized based on disease stage, type of EC, fertility issues and patient's general performance status [3-5,9-16,18-15].

Based on the abovementioned, only young patients with FIGO stage IA, grade 1 and type I EC (endometrioid), are suitable for conservative therapeutic approach [3-5,7,16,27-30]. These patients should have intense desire for fertility preservation, informed consent and no contraindications for treatment with progestins [3,4,7,16,19]. Moreover, all of them should be referred to oncologic centres specialised in fertility sparing management [3,4,7,16,19].

It is worth noting, that patients should be informed that conservative approach does not represent the standard of care in EC treatment and the available data is very limited [3-5,7,16,19,27-30]. Furthermore, all patients should be thoroughly counselled about disease recurrence, future fertility and childbearing [3-5,7,16,19,27-30]. At the same time, a very close follow-up protocol should be accepted, for an extended time period [3-5,7,16,19,27-30]. In addition, they should be aware of the future need of systematic surgical staging in case of treatment failure or after childbearing [3-5,7,16,19,27-30].

At the beginning of the fertility sparing approach, an appropriate endometrial sample should be obtained from each patient, either with office endometrial biopsy, hysteroscopy or dilatation and curettage [3,4,7,16,19,31-36]. The main advantage of dilatation and curettage when compared with other methods, is the provision of a better quality specimen and this is the reason why it is more preferable [3,4,7,16,19,31-36]. Subsequently, the provided endometrial sample should be assessed by an expert pathologist, in order to make a precise diagnosis regarding grade and type of EC [3,4,7,16,19,34]. A thorough assessment of the entire specimen for hormone receptors (estrogen, progesterone) as well as for molecular prognostic markers (p53, Ki-67, HE-4), may provide additional data about nature and clinical behavior of the specific cancer [3,4,6,7,16,19,37]. The role of pathologist is of great importance when considering fertility sparing approach in EC, because based on their findings patients with aggressive types of EC should be excluded from any type of conservative management [3-5,7,16,19].

Apart from that, a detailed visualization of the entire abdomen should be obtained either with ultrasound, computerized tomography (CT) or magnetic resonance imaging (MRI), in order to evaluate the depth of myometrial invasion and identify any disease beyond uterus (ovaries, pelvic and para-aortic lymph nodes and omentum) [3,4,7,16,19,34,38-40]. The

main advantage of MRI when compared with other methods, is the better visualization of these anatomical structures and that is why it is more preferable [3,4,7,16,19,34,38-42]. The role of radiologist is really essential when considering fertility preservation in EC, because based on their findings patients with advanced stage disease should be excluded from any conservative approach [3,4,7,16,19,34,38-40].

Moreover, useful information regarding disease stage could be obtained with laparoscopy [3,7,16,19]. However, when considering fertility sparing management in patients with EC, the utilization of laparoscopy as an evaluation method still remains optional [3,7,16,19]. After completion of pre-treatment evaluation, the eligible patients [FIGO stage IA, grade 1 and type I EC (endometrioid)] could initiate the fertility sparing approach, which is mainly based on the use of oral progestin regimens [3-5,7,16,19,26,43,44]. The most commonly used progestins in daily practise, are medroxyprogesterone acetate (MPA) and megestrol acetate (MA) [3-5,7,14,19,26,34,43,44]. The recommended daily dosage of MPA is 400-600 mg, while that of MA is 160-320 mg [3-5,7,16,19,34,45]. The oral progestin regimens should be administered for a period of 6 months, as there are no evidence supporting prolonged treatment in order to achieve a late response [3-5,7,16,19,34,45-47]. However in the past, a lot of patients treated with oral progestins for extended time periods [3-5,7,16,19,34,45-47]. Apart from oral progestins, the administration of intrauterine devices releasing levonorgestrel with or without gonadotropin releasing hormone analogues (GnRH analogues) have shown promising results and could be considered as an alternative treatment option [4,5,16,19,34,43,48].

During fertility sparing approach with oral progestins, all patients should be routinely reassessed every 3 months with endometrial sampling, in order to evaluate the response to treatment [3,4,7,16,19,34,43,49]. The endometrial sample could be obtained either with hysteroscopy or dilatation and curettage [3,4,7,16,19,34,43,49]. After completion of the 6 month therapy with oral progestin regimens, all patients should be further assessed with MRI, in order to evaluate the overall response to treatment [3,4,7,16,19,34,39,49].

If the post-treatment assessment reveals no response to the fertility sparing approach, then systematic surgical staging should be performed in all patients according to the most recent guidelines for EC [3-5,7,9-16,18-21,24,25,34,46,47]. In this case, treatment with oral progestins should not be prolonged in order to achieve a late response, as there are no evidence to support that [3-5,7,16,19,34,45-47]. In contrast, if there is a complete response to the fertility sparing management, then patients should be further referred to a fertility centre in order to start an assisted conception protocol [3-5,7,16,19,50-53]. If they do not desire pregnancy at this time, then therapy with oral progestins should be continued and patients should be reassessed every 6 months [3,4,7,16,19,34,43,50].

Based on recently published data, the overall response rate in EC patients treated with oral progestin regimens is quite encouraging reaching almost 75% [3,4,7,16,19,29,34,50,54]. Moreover, there is evidence that pregnancy decreases the risk of EC recurrence [3,4,7,16,19,43,50]. After childbearing, systematic surgical staging should be performed in all these patients, because there is significant risk for disease recurrence and the overall recurrence rate is approximately 30-40% [3,4,7,16,19,34,50,54].

In conclusion, only young patients with FIGO stage IA, grade 1 and type I EC (endometrioid), are suitable for conservative therapeutic approach with oral progestin regimens [3-5,7,16,19,27-30,55]. All patients should be extensively counselled regarding disease recurrence, future fertility and childbearing and be aware of the future need of systematic surgical staging in case of treatment failure or after childbearing [3-5,7,16,19,27-30].

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