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Potential of molecular classification to guide fertility-sparing management among young patients with endometrial cancer

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Abstract

The traditional histological classification system for endometrial carcinoma falls short in addressing the disease"s molecular heterogeneity, prompting the need for alternative stratification methods. Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) has emerged as a clinically efficient tool to categorize endometrial cancers according to mismatch repair deficiency, POLE exonuclease domain mutations, and p53 expression. However, the application of this classification to fertility-sparing treatments remains unexplored, and current guidelines lack specificity in how it should be used. In this review, we summarize the available literature and establish the framework for future investigations focused on molecular profiling–based risk assessment of endometrial cancer, with the goal of utilizing precision medicine to optimally counsel patients seeking fertility-sparing treatment. While the available evidence is limited and of low quality, it does provide insights and frames future perspectives for managing fertility-sparing approaches on the basis of molecular subtypes. Evidence suggests that mismatch repair–deficient tumors are likely to recur despite progestin therapy, emphasizing the need for alternative treatments, with targeted therapies being a new landscape that still needs to be explored. Tumors with POLE mutations exhibit a favorable prognosis, but the safety of hysteroscopic resection alone requires further investigation. p53 abnormal tumors have an unfavorable prognosis, raising questions about their suitability for fertility-sparing treatment. Lastly, the no specific molecular profile (or p53 wild-type) tumors, while having a relatively good prognosis, are heterogeneous and require more precise biomarkers to effectively guide therapy for those with poorer prognoses. Addressing these research gaps will lead to more precise guidelines to ensure optimal selection for fertility-sparing treatment.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with over 66,000 new cases estimated in 2023.[1,2] While only 6% of patients are diagnosed before age 45 years,[3] the diagnosis and treatment can be devastating for patients who have yet to fulfill their family-building goals. Recognizing the importance of fertility-sparing treatment, national guidelines describe appropriate candidates as those with well-differentiated tumors,

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no evidence of myometrial invasion, absence of metastatic disease, no contraindications for medical management (or pregnancy), and an explicit understanding that fertility preservation is not standard oncologic treatment.[4,5] This understanding is crucial as while most patients experience a response to progestins[6], the mainstay of fertility-sparing management, there is no consensus regarding the optimal duration of treatment or the regimen., Unfortunately, over a third of patients will experience a recurrence after an initial response,[6,7] and the long-term survival data are conflicting.[7,8]

It has become evident over the past decade that histologic classification of endometrial carcinomas is subpar to molecular classification, per The Cancer Genome Atlas (TCGA),, a joint effort of the National Cancer Institute and the National Human Genome Research Institute that utilizes genomic sequencing to uncover and catalogue genomic alterations in human cancer and create an “atlas” of cancer genome profiles [9,10] This may also be extrapolated to fertility-sparing management, where hormonal therapy may be universally offered without consideration of the molecular landscape of the tumor. The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) is a validated and clinically feasible approximation of TCGA categories that may be applied to and aid in individualizing care.[11] Understanding how this novel molecular classification system may be used to describe the response to fertility-sparing treatments will aid in selecting young patients who are eligible for fertility-sparing management while ensuring their oncological safety.

In this review, we summarize the available literature on and establish the framework for future investigations focused on molecular profiling–based risk assessment, with the goal of utilizing precision medicine to optimally counsel patients with endometrial cancer who are seeking fertility preservation.

2. Histologic vs molecular classification

The original histomorphologic classification system described by Bokhman in 1983[12] defined two pathogenetic types of endometrial cancer, with type 1 representing the more common estrogen-driven, typically low-grade endometrioid endometrial cancer and type 2 encompassing all rare and high-risk histologic subtypes, which are known to be more clinically aggressive. This dichotomy is the simplified basis for the 2023 FIGO staging definitions for type 1 and type 2 histological types.[13] In clinical practice, fertility-sparing treatment is considered acceptable primarily for the type 1 subtypes. With an increasing understanding of the molecular pathogenesis of endometrial cancer, however, it is now clear that these broad categories over-generalize and that four distinct molecular subtypes, as described by the TCGA, offer improved risk stratification. The application of these subtypes, however, proved complex and costly in clinical practice.[11,14]

Kommoss and colleagues developed and validated a practical molecular classification tool, ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer), that only requires formalin-fixed, paraffin-embedded material using methods that can be easily adopted in pathology laboratories at most cancer centers.[15] The methodology utilizes single gene sequencing of POLE and protein expression analysis via immunohistochemistry and identifies molecular subtypes that are analogous to the genomic subtypes described in

TCGA. In a study by Britton and colleagues that included 257 women younger than age 50 with endometrial cancer,[16] the ProMisE subtypes were strongly associated with all survival outcomes (overall, disease-specific, and progression-free). It is important to note that in their 2023 guidelines, the European Society of Gynecologic Oncology encourages using ProMisE molecular classifications in all young patients with grade 1, low-stage endometrial carcinoma who wish to preserve fertility, but they also note limited available evidence and clinical applicability.[17]

2.1. DNA polymerase epsilon mutation–mutated (ultramutated)

The ultramutated polymerase epsilon (POLE) mutants are copy number–stable endometrial cancers that are characterized by mutations in the exonuclease domain of DNA POLE. POLE-mutated endometrial cancers account for approximately 6%−13% of endometrial cancers.[18,19] These tumors typically exhibit an excellent prognosis and are predominantly endometrioid histology, with a high frequency of high-risk features, such as high grade and lymphovascular space invasion. Some studies have also identified that patients with POLE mutations are more likely to be diagnosed at a younger age.[20]

2.2. Mismatch repair deficiency (hypermutated)

MMR-deficiency (MMRd) is observed in 20%−30% of endometrial cancers.[21–24] MMRd subtypes lack the expression of one or more MMR proteins that are critical for DNA repair, such as MLH1, PMS2, MSH6, and PMS2. These tumors typically exhibit an intermediate prognosis and are predominantly endometrioid, with a high frequency of high-grade histology. Although most of these mutations result from sporadic causes, approximately 10% of microsatellite-unstable endometrial carcinomas are linked to germline mutations that cause Lynch syndrome.[25] Therefore, women with MMRd tumors should undergo testing for Lynch syndrome, as they may carry pathological MMRd gene variants.[26]–Therefore, women with MMRd tumors, particularly those without MLH1 promotor hypermethylation, are often referred for testing for Lynch syndrome, as they may carry MMRd germline pathologic variants.

2.3. p53 abnormal (copy number–high)

The p53 abnormal (p53abn) subgroup is characterized by aberrant p53 immunohistochemical staining, corresponding to the copy number–high subtype. While accounting for only 15% of endometrial cancers, p53abn tumors carry the worst prognosis and are responsible for 50%−70% of endometrial cancer deaths.[27] Patients with p53abn tumors are diagnosed at an older age, with a lower BMI; they mostly exhibit serous histology and are most commonly diagnosed at a high stage and grade, often presenting with features such as myometrial invasion, positive lymph nodes, and lymphovascular space invasion.[22]

2.4. p53 wild-type (copy number–low)/no specific molecular profile

The no specific molecular profile (NSMP) subgroup, which accounts for the majority of endometrial cancer cases, is characterized by the absence of POLE-mut, p53abn, or MMRd. It is the most heterogeneous and molecularly diverse group of carcinomas and

is characterized by predominantly low-grade endometroid histology; however, given its heterogeneity, it has intermediate outcomes.[21] For example, NSMP tumors with CTNNB1 mutations have been associated with an increased risk of recurrence in patients with low-stage, low-grade endometrial cancer.[28] Efforts are underway to develop subclassifications within this group to further risk-stratify patients harboring these mutations.

2.5. Multiple classifiers

A small percentage of tumors harbor more than one molecular subtype and are often referred to as "multiple classifiers." *The data suggest that TP53 variants in MMRd or POLE-mutated endometrial cancers should not be considered as a driver subtype as they are likely passenger events, not influencing the tumor's molecular landscape, and occur as later events without impacting the molecular phenotype. In triple-classifier endometrial cancers with one of the 11 pathogenic POLE variants mutation,*[29] *the primary driver is considered to be the POLE mutation.*[5 29–31]

3. Feasibility of molecular classification in patients not undergoing hysterectomy

While among patients undergoing definitive surgery for endometrial cancer an endometrial biopsy with a pipelle is sufficient, hysteroscopy and directed endometrial biopsy are preferred [5,26]. This is particularly important when considering fertility sparing management, as blind techniques may miss more than 50% of the endometrial cavity and therefore miss endometrial lesions. Molecular analyses have been shown to be successful on pre-operative endometrial biopsies and endometrial curettings, with high concordance with hysterectomy specimens.[32,33] For example, Britton and colleagues applied ProMisE to preoperative samples from 257 women younger than 50 years who had been diagnosed with endometrial cancer and found just 3 discordant results among those who ultimately underwent a hysterectomy.[16] Moreover, Kommoss and colleagues reported excellent concordance metrics (accuracy = 0.92, κ statistic = 0.88 [95% CI = 0.79–0.94]) between pre- and post-surgical staging specimens in their validation of molecular classification.[15]

4. Available literature

Currently, the mainstay of fertility-sparing management involves continuous high doses of oral progestins or a levonorgestrel intra-uterine device.[5] Recent studies and guidelines suggest that a combined approach involving hysteroscopic tumor resection and progestin is the most effective method of fertility preservation, irrespective of the molecular profile.[26,34–37] Several reports have assessed different genetic and molecular prognostic biomarkers that are associated with pathways that may be involved in a favorable response or resistance to progestin therapies.[38] However, it has only been relatively recently that research groups began reporting their experience employing ProMisE molecular classification among patients undergoing fertility-sparing treatment.[16,39,40] These studies are primarily analyses of small retrospective cohorts of young women with endometrial cancer (or atypical hyperplasia), some of whom received fertility-sparing management, primarily to demonstrate the feasibility of the ProMisE molecular classification.

Table 1 summarizes studies applying molecular classifiers to patients with endometrial cancer who underwent fertility-sparing treatment. Two studies included populations receiving intrauterine device with Levonogestrel (LNG-IUD), patients receiving the same type of fertility-sparing treatment. Puchel et al included all patients treated from 2013–2018 with a levonorgestrel intra-uterine device for endometrial cancer or endometrial intraepithelial neoplasia with the goal of determining whether molecular classification, via ProMisE, prognosticated response.[39] They found that most patients (44 of 58) had p53 wild-type, followed by 6 MMRd, 4 p53abn, and 4 POLE-mutated tumors. Patients with p53abn tumors had the shortest time to progression or definitive therapy, less than 6 months, and had the highest proportion (50%) of patients requiring definitive treatment. The patients with POLE-mutated and MMRd tumors had the longest median time to progression or definitive therapy, at 21.4 or 20.9 months, respectively. The authors concluded that patients with TP53 abnormalities were best served by definitive treatments, despite having what would otherwise be described as low-grade and indolent tumors. Similarly, Falcone and colleagues demonstrated that the ProMisE molecular classification is feasible.[40] They included patients who underwent a hysteroscopic resection, followed by an intrauterine device. The molecular classification could only be applied to 15 of 25 patients, primarily due to the very low tumor volume among women included in the study where 7 out 15 total patients had MMR deficiency at IHC analysis. Of these patients 3 out 7 had disease persistence, progression, and/or relapse. Of the 8 patients with no mutation (or POLE mutations) 2 had relapse of their disease.

Other investigations reported on patients who received a variety of different fertility-sparing management techniques.[41,42] Chung and colleagues included 57 patients with endometrial cancer and reported that 79% had p53 wild-type and 16% had MMRd, while only 2% had p53abn expression and 4% had POLE mutations. They demonstrated that patients with MMRd tumors were significantly less likely to experience a response to hormonal therapy than were those with p53 wild-type tumors (44% vs 82%). Interestingly, of the patients who ultimately had definitive treatment, patients with MMRd tumors had higher rates of upstaging in their final pathologic findings than did those with p53 wild-type tumors (75.0% vs 18.2%). Zhang et al included patients with endometrial cancer and endometrial intraepithelial neoplasia.[42] They found that the majority of patients who were eligible for fertility-sparing management had p53 wild-type tumors and that p53abn tumors were associated with the worst prognosis.

Finally, one study by Britton and colleagues did not focus on patients who received fertility-sparing treatment but included young patients who in theory could be interested in fertility-sparing treatment on the basis of their age, a higher-risk population of 257 women younger than age 50 with endometrial cancer.[16] They found that p53 wild-type cancers were primarily low grade (78% grade 1), low stage (85% uterine-confined), and of endometrioid histology (97%), whereas patients with p53abn and MMRd cancers were more likely to present with advanced-stage disease and high-risk features.

5. Application of molecular classification to fertility-sparing treatment

5.1. MMRd

MMRd tumors tend to have a higher likelihood of recurrence after initial regression with progestin treatment than do other molecular subtypes.[42–45] However, given a higher stage at presentation, the evidence is based on very small sample size studies, ranging from 3 to 9 patients,[42–48] limiting the ability to draw definitive conclusions. Some studies have suggested that these tumors are less responsive to progestin therapy.[43,45] However, it is worth noting that these studies did not include hysteroscopic resection, which could enhance regression rates compared to progestins alone.[44] Nonetheless, there appears to be a consistent pattern of worse prognosis, mainly due to higher recurrence rates.[43–45]

It has also been hypothesized that worse outcomes could be related to the elevated mutational load and that this may activate alternative pathways that are less dependent on hormone receptors.[45,49] Exploring the use of targeted therapies, such as immune checkpoint inhibitors, may be an opportunity for fertility-sparing management in these women. However, their potential impact on fertility potential has not been thoroughly evaluated, particularly in early-stage patients seeking conservative treatment.[50]

5.2. POLE mutated

POLE-mutated tumors appear to be associated with highly favorable outcomes, regardless of treatment approach. However, as these mutations typically present as high-grade cancer, a contraindication to conservative treatment, limited studies have evaluated POLE mutations in relation to fertility-sparing treatment. Relapses of this subtype exhibit the longest median time to progression or definitive therapy compared to other subgroups.[43,46] The current literature is based on a very small number of studies and patients, with sample sizes ranging from 1 to 4.[42,43,46–48] All of these factors contribute to the ongoing uncertainty regarding the treatment choice for POLE-mutated carcinomas in the conservative setting. Given the excellent prognosis associated with this mutation, the possibility of solely observing this group in stage I endometrial cancer among patients undergoing definitive surgery has been proposed, but further investigation is needed.[51]

5.3. p53abn

p53 mutation is described as one of the most important molecular factors that is predictive of prognosis in early-stage endometrial cancer. It is associated with an unfavorable outcome due to rapid tumor progression and invasion and is most often found in high-grade tumors such as serous and clear cell carcinomas. Studies have demonstrated that patients with p53 mutations exhibit a worse prognosis with fertility-sparing treatment,[42] with a shorter time to disease progression or definitive treatment.[44,46] Furthermore, ESGO guidelines[26] indicate that conservative therapy is likely inappropriate.

5.4. p53 wild-type/NSMP

p53 wild-type/NSMP is the most common molecular subtype among fertility-sparing patients, representing 70%−80% of published cases. The study sample sizes range from 3 to 44 patients.[42,46–48] NSMP cases have a more favorable prognosis, in terms of complete

response and recurrence rates, than do MMRd and p53abn cases. The optimal treatment approach for NSMP endometrial cancer, even in the definitive treatment setting, remains uncertain due to a lack of specific guidelines, and new biomarkers are still needed for prognosis and treatment guidance, considering the heterogeneity exhibited in this group. The PORTEC-4a trial[51] is designed to address this issue by incorporating two new biomarkers into prognostic classifiers: L1-CAM and CTNNB1 mutations. L1-CAM is an independent risk factor that is associated with both locoregional and distant spread. It is a transmembrane protein that is critical to cell migration and adhesion. Moreover, CTNNB1, the gene that encodes the beta-catenin protein, plays a critical role in various cellular processes, including cell proliferation, migration, and differentiation. CTNNB1 exon 3 mutations indicate a higher risk of recurrence.[11,52,53] Notably, this stratification is particularly important within the NSMP group, where the presence of L1CAM and CTNNB1 offers a less favorable prognosis.

Exploration of other molecules implicated in endometrial carcinogenesis, including the co-existence of PTEN and ARID1A, has also been reported to be of interest.[54–56] Unfortunately, there is sparse information regarding these new potential biomarkers and their utility in guiding fertility treatment decisions.[54,56]

6. Challenges and future directions

In the rapidly transforming field of endometrial cancer, molecular insights are fundamentally reshaping our understanding of the disease and its therapeutic approaches. Particularly within the cohort of patients who are initially classified as having low-risk early-stage endometrial cancer, a subset remains vulnerable to disease recurrence and progression–; however it is difficult to predict who these patients are at the time of diagnosis. Consequently, there arises an imperative to adapt treatment recommendations and strategies, a need that is further underscored by the recent introduction of the updated FIGO 2023 staging system,[57] which relies on molecular classification for the first time. This adaptation should be guided by emerging evidence based on the latest molecular knowledge, while minimizing the impact on healthcare costs and prioritizing patient well-being. The ESGO/ESHRE/ESGE guidelines[26] for fertility-sparing treatment represent an initial step in introducing new molecular knowledge in management recommendations; however, there is a need for further refinement and individualization of these recommendations.

As we consider the future of endometrial cancer treatment, various areas demand attention and require further exploration. For example, exploring the potential use of molecular therapies for MMRd tumors is a reasonable consideration. Immunotherapy with an immune checkpoint inhibitor, such as PD-1 inhibitors, or a multitarget tyrosine kinase inhibitor is a promising approach for advanced-stage or recurrent cancers, as addressed by recent landmark trials.[58–61] Unfortunately, there is no supporting evidence for the use of immune checkpoint or multitarget tyrosine kinase inhibitors in fertility-sparing treatments. However, while the effects of immunotherapy on ovarian and uterine toxicity have not yet been fully elucidated, case reports suggest that pregnancy following immunotherapy is possible.[62] Moreover, POLE-mutated tumors offer a great opportunity for assessing conservative management, in particular, extending its application beyond stage IA without

myometrial invasion. For patients with p53abn tumors, conservative therapy might not be an optimal recommendation, even if it is within the context of a histologically low-grade tumor.[26] Lastly, NSMP tumors lack a specific surrogate biomarker and are characterized by significant heterogeneity, underscoring the need for future research into high-risk markers such as PTEN and CTNN1 that can help tailor more personalized management strategies and guide treatment.

Positive estrogen receptor and progesterone receptor status has also been used as a marker and may be associated with better outcomes in patients with type I endometrial carcinoma.[63] However, pre-treatment assessment has shown that it has limited accuracy in predicting treatment response, highlighting the need for future research and its impact depending on the molecular subtype group.[44,64,65]

Lastly, molecular classification can contribute to the diagnostic and prognostic assessment of patients with atypical endometrial hyperplasia, reducing the risk of tissue misinterpretation and enhancing the detection of concurrent neoplasia. The molecular classification may not distinguish between atypical hyperplasia and endometrial cancer, but may serve as a promising avenue for exploration given that up to 40% of atypical hyperplasia_coexist with endometrial cancer.,[42,66,67] The value of molecular data could help understanding the factors that influence disease progression and may also raise suspicions of potentially missing invasive neoplasias that are not visualized in the sample. Some recent publications suggest the use of immunohistochemical markers such as PTEN, PAX2, ARID1A, or β-catenin to improve the identification of endometrial hyperplasia and enhance inter-observer agreement. However, the diagnostic utility of these markers remains a topic of debate, with current guidelines discouraging their use for diagnostic purposes due to a lack of strong evidence.[26]

These challenges and future directions underscore the dynamic nature of endometrial cancer care, where the intersection of molecular insights and clinical practice requires thoughtful adaptation and innovation.

7. Limitations in the literature

The role of molecular classification in fertility-sparing treatment for early-stage endometrial cancer remains a subject with limited and low-quality evidence, influenced by numerous biases and challenges. Studies in this context are primarily retrospective cohort studies, with inherent limitations, such as missing data and unmeasured confounding, and low sample size. Furthermore, the few available studies have primarily analyzed patients who underwent a variety of treatment regimens, which complicates data interpretation. It is important to acknowledge that despite its high accuracy, the ProMisE classification can still misclassify some patients.[40] Additionally, various other markers have been described with no clear impacts on clinical practice or outcomes. Therefore, future prospective evidence is essential to establish the role of molecular classification in fertility-sparing treatment for early-stage endometrial cancer. However, the low prevalence of the disease among young individuals who wish to become pregnant may present challenges.

8. Conclusions

Standard endometrial cancer management is undergoing notable changes due to emerging molecular insights. The ProMisE classification system may offer the potential to enhance assessment and treatment strategies for young women seeking fertility-sparing treatment options, aligning with the prognosis seen in patients undergoing definitive treatment. However, the current evidence for incorporating molecular classification into clinical practice in this context is still limited, and several challenges persist among the different molecular groups creating the opportunity for robust research in the future..

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Table 1.

Summary of studies applying molecular classifiers to patients with endometrial cancer who underwent fertility-preserving treatment

Study	Characteristic		MMRd (%)	POLE mutated (%)	p53abn (%)	p53wt (%)	Total (%)
Chung et al.	n (EC)		9 (16)	2 (4)	1 (2)	45 (79)	57
	Age at diagnosis (years)		33 (26–40)	27, 34	33	31 (19–45)	33 (19–45)
	Treatment		Oral MPA, MA or LNG-IUD plus MPA concurrently				
	Follow-up, median (range), months		38.4 (2.9–163.5)				
	CR rate		4 (44)	1 (50)	1 (100)	37 (82)	43 (75)
	PR		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SD/PD		5 (55)	1 (50)	0	8 (18)	14 (25)
	Recurrence after CR		1 (25)	1 (100)	1 (100)	16 (43)	19 (44)
Falcone et al.	n (EC)		7 (47)	1 (7)	0 (0)	7 (47)	15
	Age at diagnosis (years)		38 (28–39)	36		37 (25–40)	37 (25–40)
	Treatment		Hysteroscopic resection + LNG-IUD				
	Follow-up, median (range), months		106 (24–134)				
	CR rate		5 (71)	1 (100)	–	7 (100)	13 (87)
	PR		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SD/PD		2 (29)	0 (0)	0	0 (0)	2
	Recurrence after CR		1 (14)	0	–	2 (29)	3 (23)
Puechl et al. [a]	n (EC/EIN/EAH)		6[b]	4	4	44[c]	58
	Age at diagnosis		71.7 (51.9–86.8)	55.5 (52.1–68.3)	67.0 (48.1–89.0)	53.1 (24.3–91.1)	56.4 (24.3–91.1)
	Diagnosis	ECC	4 (67)	0 (0)	1 (25)	17 (39)	22 (38)
		EAH/EIN	2 (33)	4 (100)	3 (75)	27 (61)	36 (62)
	Treatment		LNG-IUD +/− MA, MPA or leuprolide				
	Follow-up, median (range), months		28.8 (3.3–141.5)				
	CR rate		2 (33)	3 (75)	2 (50)	20 (56)	27 (54)
	PR		1 (17)	0	0	6 (14)	7 (12)
	SD/PD		2 (33)	1 (25)	2 (50)	10 (23)	15 (26)
	Recurrence after CR		1 (50.0)	0 (0)	0 (0)	1 (5.0)	2 (7.4)

Study	Characteristic		MMRd (%)	POLE mutated (%)	p53abn (%)	p53wt (%)	Total (%)
Zhang et al.[d]	n (EC/EIN/EAH)		4	3	3	49	59
	Age at diagnosis, years (mean ± SD)		31.4 ± 2.9	33.1 ± 5.1	33.5 ± 3.0	31.5 ± 3.1	33.4 ± 1.1
	Diagnosis	ECC	3	2	1	33	39
		EAH/EIN	1	1	2	16	20
	Treatment		High-dose progestin (500 mg daily)				
	Follow-up, median (range), months		16.8 (4–104)				
Ran et al.	n (EC/EIN/EAH)		3 (25)	0	1 (8)	8 (67)	12
	Age at diagnosis (years)		35 (31–37)	-	34	29 (23–33)	30 (23–37)
	Diagnosis	ECC	3 (100)	-	1 (100)	8 (100)	12
		EAH/EIN	0	-	0	0	0
	Treatment		MA, MPA, Goserelin acetate, or LNG-IUD				
	Follow-up, median (range), months		46 (13–138)				
	CR rate		2 (67)	-	0	6 (75)	8 (67)
	PR		0	0	0	0	0
	SD/PD		1 (33)	-	1 (100)	2 (25)	4 (33)
	Recurrence after CR		0	-	0	1 (16)	1 (8)

numbers displayed are n (%) unless otherwise noted

[a]This study is not specifically focus for fertility sparing treatment, but rather on conservative hormonal treatment.

[b]Data on 1 patient not included due to lack of follow-up.

[c]Data on 8 patients were not included as they underwent definitive treatment before follow up biopsy or had no follow-up data.

[d]Raw numbers not provided

Abbreviations: EC, endometrial carcinoma; EIN, endometrial intraepithelial neoplasia; EAH, endometrial atypical hyperplasia; MPA, medroxyprogesterone acetate; MA, megestrol acetate; LNG-IUD, Levonorgestrel-releasing intrauterine device; MMRd, mismatch repair-deficient; CR, Complete Response; PR, partial response; SD, stable disease; PD, progressive disease; sd, standard deviation