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Improving response to progestin treatment of low-grade endometrial cancer

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Précis

Biomarkers can be used to identify women with low-grade endometrial cancer who may benefit from progestin treatment.

Abstract

Objectives: This review will examine how response rates to progestin treatment of low-grade endometrial cancer can be improved. In addition to providing a brief overview of the pathogenesis of low-grade endometrial cancer, we discuss limitations in the current classification of endometrial cancer and how stratification may be refined using molecular markers to reproducibly identify 'low-risk' cancers which may represent the best candidates for progestin therapy. We also discuss constraints in current approaches to progestin treatment of low-grade endometrial cancer and perform a systematic review of predictive biomarkers.

Methods: PubMed, ClinicalTrials.gov and Cochrane Library were searched for studies reporting pre-treatment biomarkers associated with outcome in women with low-grade endometrial cancer or endometrial hyperplasia with an intact uterus who received progestin treatment. Studies of fewer than 50 women were excluded. The study protocol was registered in PROSPERO (ID 152374). A descriptive synthesis of pre-treatment predictive biomarkers reported in the included studies was conducted.

Results: Of 1,908 records reviewed, 19 studies were included. Clinical features such as age or body mass index (BMI) cannot predict progestin response. Lesions defined as 'low-risk' by FIGO criteria (stage 1A, grade 1) can respond well, however the reproducibility and prognostic ability of the current histopathological classification system is sub-optimal. Molecular markers can be reproducibly assessed, have been validated as prognostic biomarkers and may inform patient selection for progestin treatment. POLE-ultramutated tumors and a subset of p53 wild-type or MMR-deficient tumors with 'low-risk' features (eg. progesterone and estrogen receptor-positive) may have improved response rates, though this needs to be validated.

Discussion: Molecular markers can identify cases which may be candidates for progestin treatment. More work is needed to validate these biomarkers and potentially identify new

ones. Predictive biomarkers are anticipated to inform future research into progestin treatment of low-grade endometrial cancer and ultimately improve patient outcomes.

Introduction

Endometrial cancer is the most common gynecological cancer, and the fourth most common cancer among women in Western countries. There are approximately 382,000 new cases and 90,000 deaths annually worldwide [(1)]. Caucasian women have the highest incidence rates of endometrial cancer, though the majority of these tumors are low-grade and these patients generally have a favorable prognosis. Conversely, African-American women have the highest incidence rates of advanced disease with poorer survival [(2)]. At least 41% of endometrial cancers have been attributed to obesity (BMI >30 kg/m^2), with each 5 kg/m^2 increase in BMI being associated with a 62% increase in risk of endometrial cancer [(3)]. Conversely, sustained weight loss reduces this risk [(4-8)].

Standard of care intervention for women with endometrial cancer involves a hysterectomy and bilateral salpingo-oophorectomy with or without surgical staging, as well as lymph node sampling and additional biopsies, although node dissection is not pursued for low-grade tumors in some areas of the world. Surgery is generally effective, however obesity increases the risk of surgical complications and patients often have concomitant comorbidities contributing to their perioperative risk [(9-13)]. Reassessing therapeutic options in the increasingly common situation of medically complex, morbidly obese patients with endometrial cancer [(14)] and identifying conservative treatment options for these patients has been designated a research priority [(15)]. Hysterectomy also results in irrevocable loss of fertility in young women who may wish to retain childbearing capacity. The estimated proportion of new cases of endometrial cancer in premenopausal women in 2018 varies worldwide, ranging from approximately 10% of all cases of endometrial cancer in North America, Europe and Oceania, to 20% in Africa and Latin America and 28% in Asia [(16)].

Progestins have been tested as a treatment option mostly in case series of women with low-grade endometrial cancer or hyperplasia who are high-risk surgical candidates due to

obesity and/or medical comorbidities, or those who wish to retain fertility. To date, different types, doses and duration of progestins have been used, furthermore the patient selection process was often *ad hoc.* Meta-analyses indicate that 72-76% of tumors respond to progestins and 20-41% recur after an initial complete response [17, 18]. Reproducible stratification of tumors and biomarkers of progestin response are urgently required to identify tumors with intrinsic or emergent progestin resistance. Women who are unlikely to respond to progestins should have surgery and/or radiotherapy. This cohort also provides an opportunity to evaluate agents which might be employed to overcome endocrine therapy resistance. Identifying which patients will or will not benefit from progestin-based therapy was raised as one of the top ten unanswered research questions in a consensus engagement of endometrial cancer survivors, physicians and researchers [19].

This review will examine how response rates to progestin treatment of low-grade endometrial cancer may be improved. We will discuss how molecular markers can be used to reproducibly identify 'low-risk' tumors which may represent the best candidates for progestin treatment and perform a systematic review of pre-treatment biomarkers associated with progestin response.

Pathogenesis of low-grade endometrial cancer

The single biggest risk factors for endometrial cancer are obesity and metabolic dysfunction [3, 20]. In young women with endometrial cancer, 49-58% are obese and 8-18% have Lynch syndrome, another known risk factor for endometrial cancer [21-24]. Young women are also frequently nulliparous and anovulatory and their tumors are typically considered to be in a hyperestrogenic state.

Obesity is particularly associated with low-grade endometrial cancer [25, 26], however the mechanisms underlying this are poorly understood. A report from the International Agency for Research on Cancer concluded that there was strong evidence for sex hormone metabolism and chronic inflammation mediating the relationship between obesity and

cancer, and the evidence for insulin and insulin-growth factor (IGF) signaling was moderate [26]. Non-steroidal anti-inflammatory drugs have been associated with a reduced risk of endometrial cancer, particularly in obese women, implying a causative role for inflammation in obesity-related endometrial cancer [27-29].

Endometrial hyperplasia is a common precursor of low-grade endometrial cancer and typically arises from chronic unopposed estrogen signaling. While hyperplasia without atypia is considered benign with a low risk of proceeding to carcinoma (RR 1.01–1.03), hyperplasia with atypia (also known as Endometrial Intraepithelial Neoplasia; EIN) has a high risk of proceeding to carcinoma (RR 14–45) [30]. Numerous driver mutations have been identified, the most frequently mutated genes in low-grade endometrial cancer are *PTEN* (phosphatase and tensin homolog), *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), *CTNNB1* (catenin beta 1), *ARID1A* (AT-rich interaction domain 1A) and *PIK3R1* (phosphoinositide-3-kinase regulatory subunit 1) [31]. Mutations in *PTEN* are found in the majority of low-grade endometrial tumors as well as in premalignant lesions, leading to the assumption that they are an initiating event in tumorigenesis [32, 33]. Mutations in *CTNNB1* exon 3 are particularly prevalent in young, obese women without Lynch syndrome [34]; however, the mechanism of action of these mutations is poorly understood.

Classification of endometrial cancer and its limitations

Endometrial cancers are classified according to histopathologic assessment of tumor type and grade, as well as surgical staging according to the International Federation of Gynecology and Obstetrics (FIGO) criteria [35]. Tumors that are stage I, grade 1 or 2 with no or superficial myometrial invasion are deemed ‘low-risk’ and are not routinely offered adjuvant therapy. Approximately 5% of all recurrences occur in these patients [36], highlighting the need to reproducibly identify ‘low-risk’ tumors.

It is now recognized that the current pathological classification and grading system of endometrial carcinomas are limited in both reproducibility and prognostic ability. Lack of

consensus on histologic subtype diagnosis is seen in at least one-third of cases [37-39]. Furthermore, only a modest correlation between preoperative endometrial sampling and final pathology grading is seen with grade being upgraded in 15-20% of cases and high-risk pathology being identified in 19-29% of cases on final pathology [40-43]. A new binary grading system that discriminates between low (grade 1-2) and high-grade (grade 3) tumors has been proposed which has superior prognostic significance for survival and greater inter-observer reproducibility than current FIGO criteria [44-46]. However, this may not be appropriate in a conservative therapeutic approach as only grade 1 tumors are generally considered suitable [47].

In early-stage endometrial cancer, the European Society for Medical Oncology-modified classification, which includes uterine factors such as histological subtype, grade, myometrial invasion and lympho-vascular space invasion, has been demonstrated to have the highest power of discrimination for stratifying the risk of recurrence or nodal metastases, however it does not show high accuracy with a concordance index of only 0.73 [48].

More recently, The Cancer Genome Atlas (TCGA) classified endometrial cancers into four prognostically distinct subtypes based on genomic features [31]. Subsequently, other research teams sought to recapitulate these molecular subtypes using clinically-applicable methods on standard formalin-fixed paraffin-embedded material. POLE (DNA polymerase epsilon)-ultramutated tumors are associated with excellent prognosis, followed by p53 wild-type (also referred to as No Specific Molecular Profile; NSMP) and DNA mismatch repair (MMR)-deficient tumors with intermediate prognosis. p53-abnormal tumors have the worst prognosis [49-52]. In young women (<50 years of age), p53 wild-type/NSMP tumors are the most frequent (64% of cases), followed by MMR-deficient (19%) and POLE-ultramutated (13%) tumors. p53-abnormal tumors are the least frequent (4%). The majority of obese women (82%) also have p53 wild-type/NSMP tumors [53].

Approximately 3% of endometrial tumors have more than one of these four molecular features suggesting they are currently unclassifiable. Preliminary studies suggest that the

POLE-ultramutated phenotype predominates in tumors with pathogenic *POLE* exonuclease domain mutations that are also p53-abnormal or MMR-deficient, and the MMR-deficient phenotype predominates in MMR-deficient tumors that are also p53-abnormal or have non-pathogenic *POLE* mutations, although these findings remain to be validated and standardized criteria developed for interpreting *POLE* variants [49, 50, 54-56].

Marked inter-tumor and intra-tumor molecular heterogeneity have been reported in low-grade endometrial tumors [57-59]. Intra-tumor heterogeneity may vary between molecular markers as one study reported >95% concordance between three tumor blocks for *POLE* and *CTNNB1* mutation status and MMR protein expression, whilst concordance for p53 and L1CAM (L1 cell adhesion molecule) protein expression was 91-94%, supporting the use of select biomarkers in clinical decision-making [60]. Refinement of molecular classifiers that can reproducibly be assessed on diagnostic specimens is thus required to identify tumors that are 'low-risk' and may safely be managed conservatively. From a practical point of view, the assessment of molecular markers such as *POLE* mutation testing and immunohistochemistry for MMR proteins and p53 are not currently feasible in all facilities, spurring the need for the development of low-cost technologies that can easily be implemented within existing diagnostic workflows.

Molecular markers of 'low-risk' endometrial cancer

Improved endometrial cancer stratification is necessary to enable study of treatment efficacy within biologically similar tumors, ultimately improving patient outcomes. There is now increasing evidence that molecular markers will help achieve this, providing reproducible categorization, prognostic information and suggestion of predictive biomarkers for both conventional and targeted therapies. For example, women with MMR-deficient endometrial tumors have improved disease-specific survival after adjuvant radiotherapy compared to women with MMR-proficient tumors [61]. MMR-deficiency also predicts clinical benefit of immune checkpoint blockade [62, 63].

Progestins can be offered to women with low-grade tumors, although as discussed earlier,

reproducible identification of these tumors can be problematic. Stratification using molecular markers, possibly in combination with histopathological features, is predicted to reproducibly identify 'low-risk' tumors that may represent women who will benefit from progestins. Low-grade endometrioid tumors are largely p53 wild-type/NSMP (60%), although some are MMR-deficient (29%) and a minority are POLE-ultramutated (6%) or p53-abnormal (5%) [31]. Molecular features thus do not entirely correlate with grade. It has been postulated that FIGO grading is most appropriate in p53 wild-type/NSMP and MMR-deficient tumors, as these mostly correspond to endometrioid subtype [64]. Molecular markers could also be used to refine stratification of these subtypes in order to reproducibly identify 'low-risk' tumors.

Both estrogen (ER) and progesterone (PR) receptors have been recognized as independent prognostic biomarkers in early-stage endometrial cancer for many decades [65, 66]. ER is generally expressed in p53 wild-type/NSMP, POLE-ultramutated and MMR-deficient tumors, whilst PR expression is increased only in p53 wild-type/NSMP tumors [31, 67]. Within p53 wild-type/NSMP tumors, *CCND1* (cyclin D1) C-terminal mutation, *CTNNB1* exon 3 mutation, 1q32.1 amplification, L1CAM overexpression, loss of ER and PR and high DNA damage have all been identified as poor prognostic markers [34, 54, 68-72], indicating that further molecular stratification within this subtype is possible.

Although MMR-deficient tumors represent a significant proportion of low-grade endometrioid tumors, they have clinical features associated with poor outcomes [49-51, 53, 73]. A recent study of stage 1, grade 1 endometrioid tumors indicated that MMR-deficiency was associated with increased risk of recurrence [74], questioning whether this subtype can be considered 'low-risk' and therefore may not benefit from progestin therapy. Further stratification within MMR-deficient tumors could potentially be applied as tumors with *CCND1* C-terminal mutation [69] and methylated *PTEN* [75] have been associated with worse prognosis. Furthermore, up to one-quarter of young women with Lynch syndrome who have endometrial cancer have synchronous ovarian cancer [24], suggesting that women with MMR-deficient tumors, and particularly those with Lynch syndrome, require careful evaluation by both molecular and

imaging methods for improved risk assignment and may require close monitoring if offered progestin therapy.

The excellent prognosis of POLE-ultramutated tumors appears to be irrespective of adjuvant treatment [76, 77], suggesting that early-stage POLE-ultramutated tumors could benefit from conservative management [67]. Conversely, p53-abnormal tumors have the worst prognosis and low-grade tumors with overexpression of p53 have increased risk of relapse and decreased survival [78, 79], suggesting that women with these tumors should not be offered conservative treatment. However, it should not be excluded that *TP53* variants may be passenger events, as evidenced by subclonal p53 overexpression in tumors with concomitant pathogenic *POLE* exonuclease domain mutations or MMR-deficiency, as was discussed earlier [55].

It thus appears that three molecular subtypes potentially represent tumors that are 'low-risk': 1) POLE-ultramutated tumors; 2) p53 wild-type/NSMP tumors with wild-type *CCND1* and *CTNNB1,* are ER and PR-positive, lack 1q32.1 amplification and with low L1CAM expression and DNA damage; and 3) MMR-deficient tumors with wild-type *CCND1,* are ER- and PR-positive, lack *PTEN* methylation and without Lynch syndrome (Figure 1). Further studies are required to validate these molecular markers of 'low-risk' endometrial cancer, compare them to conventional criteria for risk assignment in terms of both patient outcomes and cost-effectiveness, and evaluate whether they represent the best candidates for conservative therapy and specifically progestin treatment.

A risk prediction model that identifies individuals at high risk of endometrial cancer was recently proposed [80]. The model is based on genetic, insulin, reproductive and obesity risk scores. Inflammation is not currently directly incorporated as it is not known which inflammatory factors should be assessed. The model remains to be validated but could potentially be adapted to identify 'low-risk' cases of endometrial cancer that could benefit from conservative treatment. Furthermore, a recent study concluded that L1CAM <1% and nuclear PR >85% assessed by immunohistochemistry on presurgical samples and

myometrial invasion <50% correctly determined 'low-risk' patients in 80% (56/70) of cases [81], highlighting the need to combine clinical and molecular features in diagnostics.

L1CAM overexpression has been demonstrated to be an independent poor prognostic marker [82-84], others include overexpression of HER-2/*neu* (human epidermal growth factor receptor 2) [85], STMN1 (stathmin 1) [86], CD133 [87] or MCT1 (monocarboxylate transporter 1) [88]; loss of ASRGL1 (asparaginase and isoaspartyl peptidase 1) [89, 90] or E-cadherin [91]; aneuploidy [92] or few intraepithelial $CD8^+$ T lymphocytes at the invasive border [93]. Blood-based biomarkers such as CA-125 (cancer antigen 125), CA 15-3 (cancer antigen 15-3), HE4 (human epididymis protein 4) and more recently, metabolites and steroids, have also been reported to identify endometrial cancers at high risk of recurrence [94-99]. High visceral fat percentage, as quantified by computed tomography, has also been associated with poor outcome in endometrial cancer [97, 100]. Finally, genetic polymorphisms, notably the G allele in rs13222385 in EGFR (epidermal growth factor receptor), have also been associated with worse overall survival [101]. The prevalence of these markers and their utility in stratification within the four prognostic molecular subtypes described earlier remain to be assessed.

Progestin treatment of endometrial cancer

The progestins megestrol acetate and medroxyprogesterone acetate are approved by the US Food and Drug Administration as adjunctive or palliative treatment of advanced, recurrent or metastatic endometrial cancer. Various randomized and non-randomized clinical trials have offered progestins to young women with low-grade, early-stage disease who desire to retain childbearing capacity, as well as obese women and women with comorbidities at high risk of surgical complications. For young women who are successfully managed with progestins, subsequent pregnancy is not uncommon (12-83% live birth rate) though assisted reproduction technology is advised to maximize chances of a live birth [18, 102-106] and hysterectomy is often recommended once childbearing has been completed [47, 107]. Most studies completed to date used the oral progestins megestrol acetate or medroxyprogesterone acetate at various doses, whilst intrauterine progestins are now

increasingly utilized, sometimes in combination with oral progestins, though treatment duration varies. It has been reported that intrauterine progestins achieve a higher rate of pathological complete response than oral progestins [17, 108], possibly due to improved patient compliance and increased progestin concentration in the endometrium [109].

Meta-analyses have indicated that in women with early-stage endometrial cancer, progestins are associated with a 72% to 76% response rate; however, 20% to 41% of patients relapse after having developed a complete pathological response [17, 18]. The age range in these meta-analyses varies considerably, including women up to 88 years of age, although the mean age was under 40 years. A meta-analysis including only studies with women under 44 years of age with atypical hyperplasia (EIN) or early-stage endometrial cancer who desired fertility, reported that remission reached a plateau of approximately 80% 12 months after commencing treatment; however, recurrence probability increased continually with time, being 17% at 12 months and 29% at 24 months [110]. Prospective studies of Asian women under 40 years of age with early-stage endometrial cancer, most of whom were nulliparous, have reported much lower response rates after six months treatment. A Japanese study of 45 women reported a complete response rate of 55% and a recurrence rate of 57% with oral progestins and low-dose aspirin [103], whilst a recent Korean study of 35 women reported a complete response rate of only 37% with combined oral and intrauterine progestins [111]. These studies raise the question of whether ethnicity affects response to progestins. Asian women present younger at diagnosis and with higher stage disease than Caucasians, suggesting differences in risk factors such as obesity [112]. Asian women reportedly have a higher body fat percentage with greater abdominal adiposity and higher rates of metabolic syndrome than Caucasian women [113]. The Cancer Genome Atlas (TCGA) data indicated tumors from Asian women have an increased mutation load and frequency of somatic MMR mutations versus tumors from Caucasian women [114]. It should be noted that there were only 20 tumors from Asian women in TCGA, highlighting the need for more extensive molecular

and clinical profiling of tumors from non-Caucasian women to better understand potential confounding factors.

Current prospective trials exploring progestin treatment of low-grade endometrial cancer are reviewed in Supplementary File 1. Inclusion criteria are based on clinicopathological features with three trials limiting inclusion to PR-positive tumors (NCT02990728, NCT03463252 and NCT03538704). Only one trial involves a follow-up time exceeding 36 months (NCT02397083), limiting the ability to comprehensively assess women whose tumors may recur. Three trials have a formal aim of identifying predictive biomarkers (NCT01686126, NCT02990728 and NCT03567655), two of which include the addition of either weight loss or metformin to intrauterine progestin, either of which are proposed to increase pathological complete response. Sustained weight loss, either by surgical [7, 115-118] or non-surgical methods [4-6], is associated with reduced risk for endometrial cancer, highlighting that the relationship between obesity and endometrial cancer is reversible. Multiple meta-analyses have indicated that prior metformin use is associated with improved survival in endometrial cancer patients [119-122].

Current guidelines stipulate that conservative treatment of endometrial cancer should only be considered in women desiring to retain fertility and patients should be counselled for hysterectomy as definitive treatment once childbearing has been completed, or those with persistent or progressive disease. The National Comprehensive Cancer Network [47] and European Society of Gynaecological Oncology (ESGO) [107] guidelines both state that stage IA, grade 1 endometrioid adenocarcinomas can be considered for fertility-sparing treatment. Formal dilatation and curettage (D&C) instead of pipelle biopsy is the preferred method to obtain histology, demonstrating a higher correlation with the final histological results, and specimens should be examined by at least one pathologist. Pelvic MRI scan is the preferred method to establish myometrial invasion, though transvaginal ultrasound scan can be used if MRI is contraindicated or not available. ESGO guidelines also stipulate that hysteroscopy may be performed in combination with D&C and there is no need to routinely assess PR

status, although the authors acknowledged that the recommendations should be interpreted with caution due to the lack of prospective high-quality studies [107]. A recent survey of European clinicians indicated that, despite the majority believing that grade 1 endometrial cancer without myometrial invasion could be offered progestins, most centers treated few patients conservatively. There was no consensus on whether PR status should be examined prior to commencing conservative treatment, or whether patients with Lynch syndrome could be considered [123], highlighting the need for predictive biomarkers that are validated in large, prospective studies.

Systematic review of biomarkers of progestin response

The objective of this systematic review was to identify pre-treatment biomarkers of progestin response in low-grade endometrial cancer. Endometrial hyperplasia was also included as it is a precursor lesion and many studies include both endometrial cancer and hyperplasia. Previous systematic reviews of predictive biomarkers have only assessed immunohistochemical markers and included all studies regardless of participant numbers, resulting in the inclusion of some very small sample sizes [124-126]. We sought to provide an assessment of clinical, histopathological and molecular markers associated with progestin response in larger studies (≥50 women) in order to focus on predictive biomarkers with higher quality evidence for future validation. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID 152374).

Sources: PubMed, ClinicalTrials.gov and Cochrane Library were searched for studies reporting pre-treatment biomarkers of progestin response in women with low-grade endometrial cancer or endometrial hyperplasia and with an intact uterus. Search terms included: “endometrial cancer”, “endometrioid adenocarcinoma”, “uterine cancer”, “uterine adenocarcinoma” or “endometrial hyperplasia” AND “progest*”, “levonorgestrel”, “LNG”, “IUD”, “MPA”, “medroxyprogesterone”, “megestrol” or “gestagen” AND “predictive”, “*marker” or “response”. All studies published in English until 1st October 2019 were included.

Study Selection: Titles and/or abstracts were retrieved and screened against the inclusion and exclusion criteria. Full-text articles of potentially eligible studies were assessed. Additional studies manually curated were also considered. Only studies assessing pre-treatment biomarkers associated with outcome in women with low-grade endometrial cancer or hyperplasia treated with progestins were included. Studies had to include at least 50 women. Progestin treatment could be of any type, dose or duration and could be administered in combination with another form of conservative therapy. Treatment outcomes were evaluated as disease regression or recurrence. Studies reporting predictive biomarkers in advanced or recurrent endometrial cancer or women without an intact uterus were excluded. Reviews, editorials, commentaries and conference abstracts were also excluded. Risk of bias was not assessed. For each included study, data extracted included the study type, population, treatment, outcome and biomarker assessed. A descriptive synthesis of predictive biomarkers reported in the included studies was conducted.

Results: A total of 1,908 unique records were reviewed and 19 studies were included (Figure 2). Details of all the included studies can be seen in Supplementary File 2. 12 of these studies were retrospective and 7 were prospective. Age, BMI, ethnicity, menopause status, progestin type, dose and duration as well as outcome measured varied between studies.

Reports on clinical factors associated with outcome are conflicting (Table 1). Many studies investigating BMI reported that obesity was associated with failure to achieve disease regression and increased recurrence [105, 127-130]. However, a recent study of Japanese women reported that lower BMI was associated with increased recurrence [131], whilst numerous studies have reported no association between BMI and outcome [132-137]. The association between age or menopause status and outcome are also conflicting, with two studies reporting younger age or premenopausal status were associated with disease regression or reduced recurrence [127, 132], whilst another reported younger age was associated with increased recurrence [136]. Multiple studies have reported no association between age or menopause status and outcome [105, 128-131, 133-135, 137]. A thinner endometrium

has been associated with disease regression or reduced recurrence in one study each of women with endometrial hyperplasia [128, 134]. Diabetes has been associated with increased recurrence in one study [128] but not in other studies [127, 129, 130, 137]. Numerous other clinical factors including gravidity [127, 129, 134], parity [105, 127-130, 134-137], polycystic ovarian syndrome [105, 127, 129, 131], smoking [129, 133, 134], family history of cancer [127, 133] and hypertension [128, 130, 137] have been investigated in multiple studies, but none has shown an association with outcome.

Studies on histopathological features as predictors of progestin response are generally in agreement with each other (Table 2). Lower nuclear or histological grade have been associated with improved histological response or survival respectively [138, 139]. Lesion type has been associated with disease regression and reduced recurrence as hyperplastic lesions without atypia have improved outcome compared to hyperplastic lesions with atypia (EIN), which in turn have improved outcome compared to cancer [128, 129, 132, 136]. However, numerous studies have reported similar outcomes between lesion types [127, 131, 133, 135]. Low mitotic index and tumor volume have also been associated with improved histological response and survival respectively in one study each [138, 139].

PR is the most studied molecular marker associated with progestin response (Table 3). Multiple studies have shown that PR expression is associated with disease regression, though PR-negative lesions can benefit from progestins [129, 137, 139, 140]. Isoform-specific studies are conflicting: high PRβ has been associated with disease regression in one study [141], whilst other studies have reported no association with outcome [139, 142]. PRα has not been associated with disease regression in any study [141, 142]. PR location has also not been associated with disease regression [142], but low stromal PRα and high glandular PRβ have been associated with increased recurrence [135, 136].

ER expression has also been associated with disease regression, though similar to PR, ER-negative lesions can benefit from progestins [129, 139, 140, 142].

Conversely, biomarkers of resistance to progestin treatment are relatively understudied with small numbers of cases. MMR-deficient lesions have been associated with failure to achieve disease regression in one study [132]. Overexpression of HSPA5/GRP78 (heat shock protein family A member 5) [143] and p53 [137] have also been associated with failure to achieve disease regression in one study each of women with endometrial hyperplasia. One study also reported that high Ki67 was associated with failure to achieve disease regression [139], though another study reported no association with outcome [129].

Other molecular markers that have no association with outcome are AR (androgen receptor) [142], BAX (BCL2 associated X) [135], BCL2 (B-cell lymphoma 2) [135, 137, 139-141], cleaved caspase [139], COX2 (cytochrome c oxidase subunit II) [140], MLH1 (mutL homolog 1) [140], PAX2 (paired box 2) and PTEN [135, 141, 144]. Finally, only two studies have investigated blood-based biomarkers and neither levels of CA-125 [134] nor estradiol [136] were associated with outcome.

Discussion: Multiple factors have been investigated as potential markers of progestin response in endometrial hyperplasia and low-grade endometrial cancer. Many of the studies conducted include small sample sizes with either few cases or numbers of non-responders, potentially resulting in biased conclusions. Systematic reviews of predictive biomarkers conducted to date have only assessed immunohistochemical markers and included all studies regardless of participant numbers [124-126]. We included all predictive biomarkers in this systematic review regardless of how they were assessed, but were more selective by only including studies with a minimum of 50 women. The reason for this was to focus on markers with higher quality evidence for future validation, though this did result in the exclusion of multiple studies which either explored novel predictive biomarkers or provided further evidence supporting biomarkers reviewed here (predominantly PR). Many studies include both endometrial cancer and precursor lesions, and the inability to separate between lesion types is a limitation of this study.

Reports on clinical factors associated with progestin response are conflicting. More studies

have reported the lack of an association between BMI and outcome [132-137] than the number of studies that have reported an association [105, 127-130], with one conflicting study [131]. Similarly, for age or menopause status, more studies have reported the lack of an association with outcome [105, 128-131, 133-135, 137] than the number of studies that have reported an association and even then, results are conflicting [127, 132, 136]. A thinner endometrium has been associated with disease regression and decreased recurrence in one study each [128, 134], however the cut-off values for assessing endometrial thickness used in either study varied. Diabetes has been associated with increased recurrence in one study [128] but not in other studies [127, 129, 130, 137]. Therefore, there do not appear to be any clinical factors that could be used to select women who could benefit from progestin treatment.

Reports on histopathological features associated with progestin response are relatively consistent with less aggressive, lower grade lesions being more likely to respond. Whether hyperplastic lesions, either with (EIN) or without atypia, have improved outcomes to cancer is conflicting, indicating that lesion type is not a basis for offering progestin treatment.

Numerous predictive molecular markers have been proposed and ER, and especially PR, are the most reported to date, though most studies have only been conducted in women with endometrial hyperplasia. There are numerous sources of evidence for PR being the best biomarker for progestin response to date, however it is not required for response as PR-negative lesions can benefit from progestins [129, 137, 139, 140]. A recent meta-analysis of immunohistochemical biomarkers for progestin response in women with endometrial hyperplasia or early endometrial cancer concluded that PR was a predictive biomarker only when intrauterine and not oral progestins were used, although the accuracy of intrauterine progestins was too low to be considered determining for clinical practice [124]. It should be noted that only two studies of intrauterine progestins were included in this meta-analysis. Large studies assessing PR isoforms are limited with one study indicating PRβ was associated with disease regression [141]. A recent systematic review of immunohistochemical markers concluded that PRβ was the most promising predictive biomarker, however this was

based on only two studies reporting a significant association, whilst a third study reported no association [126]. However, glandular PRβ, as well as PRα, have also been associated with increased recurrence [135, 136]. PRβ expression correlates with activated PR, which has been proposed to reflect active PR signaling [145]. The PR antagonist onapristone has demonstrated clinical benefit in recurrent or metastatic endometrial tumors expressing activated PR [146], though whether activated PR is also a predictive biomarker for PR agonists remains to be seen. As most low-grade endometrioid tumors are PR-positive, the clinical utility of PR as a predictive biomarker needs to be validated; furthermore, the role of the activated form of the receptor as well as expression levels and location remain to be clarified. Studies in mice indicated that stromal PR was required for response to progestins [147, 148], however this remains to be validated in humans [142].

Expression of PTEN [135, 141, 144] has not been associated with outcome in multiple studies. A recent meta-analysis of seven studies, only two of which included at least 40 women, indicated that loss of PTEN had no significant impact on response to progestins, though the authors suggested that combined assessment of PTEN with other markers may be useful [125]. MMR-deficiency has been associated with failure to achieve disease regression in one study, however, this study only had six cases with abnormal MMR staining, three of which had germline MMR mutations. These women were older, had lower BMI and a higher incidence of endometrial cancer than women with tumors with normal MMR staining [132]. Overexpression of HSPA5/GRP78 [143] or p53 [137] have also been associated with failure to achieve disease regression in one study each, though cut-off values for either biomarker were not established. More studies with larger numbers of cases are needed to independently assess and validate these potential biomarkers of resistance to progestin therapy.

Current guidelines state that conservative management of endometrial cancer should only be considered in women with stage IA, grade 1 endometrioid adenocarcinomas who desire to retain fertility [47, 107]. However, progestins have also successfully been given to women at

high risk of surgical complications due to obesity and/or comorbidities. Clinical and pathological phenotypes vary between these populations and establishing which women will respond to progestins is essential to improve patient outcomes and reduce healthcare costs. As discussed here, there is some evidence that molecular markers may assist in reproducibly identifying these women, though none have yet been validated. Of the four prognostic molecular subtypes described earlier, progestin therapy has been documented as conservative management in a subset of young women with predominantly p53 wild-type/NSMP tumors and a small proportion of MMR-deficient or POLE-ultramutated tumors, but not in p53-abnormal tumors; however the outcomes of these women in unclear due to missing data [53]. p53 wild-type/NSMP tumors are the most frequent subtype amongst young and obese women [53] and are predicted to respond best to progestins [31, 67]; however, no study to date has assessed whether this molecular subtype has improved response rates. A small retrospective study in women <40 years of age undergoing hysteroscopic resection followed by progestin therapy indicated that 7/7 PR-positive grade 1 endometrioid tumors that were p53 wild-type/NSMP had complete response at 6 months; however, two women were subsequently diagnosed with ovarian cancer [59]. This same study also reported that 5/7 MMR-deficient tumors had complete response at 6 months; however, two women, both of whom had germline MMR mutations, were subsequently diagnosed with a second cancer. Two tumors were POLE-ultramutated, one of which had concomitant MMR-deficiency; only the tumor that was MMR-proficient had a complete response at 6 months and this woman continued to do well after 86 months follow-up. Finally, one tumor was p53-abnormal but it also had concomitant germline MMR-deficiency. Although this woman had a complete response at 6 months, she was subsequently diagnosed with a second cancer. Although this study by Falcone *et al.* [59] was small, it supports the hypothesis that molecular subtypes could inform patient selection for progestin therapy, though further stratification is required to identify 'low-risk' tumors. Whether POLE-ultramutated tumors and a subset of p53 wild-type/NSMP or MMR-deficient tumors with 'low-risk' features (summarized in Figure 1), have improved response rates versus current histopathological selection methods needs to be

assessed. Larger studies, including women with a range of ages and BMI and different ethnicities, are required to validate this hypothesis, as well as establish which markers further refine stratification to a level that both improves patient outcomes and is clinically feasible.

Taken together, these studies indicate that patients and lesions with certain features may exhibit the best progestin response and prognosis. Importantly, there are no clinical features associated with progestin response. Whilst reports on histopathological features associated with progestin response are relatively consistent, reproducibly classifying lesions is problematic as was discussed earlier. Molecular markers can be identified and have been validated as prognostic biomarkers, though none has been validated as a predictive biomarker for progestin response. PR is the most studied predictive biomarker to date; however its clinical utility remains to be validated and a standardized scoring system needs to be developed if it is to be implemented into clinical practice. Combined assessment of PR with other biomarkers may have improved predictive ability. The association between MMR status and progestin response is unclear with only a small number of cases studied to date, as is the importance of the mechanism of MMR-deficiency, though the International Society of Gynecological Pathologists has proposed that universal MMR testing be performed in young women desiring fertility-sparing treatment [(64)]. Whether germline MMR-deficient women should be excluded from receiving progestins or monitored more closely remains to be determined. What is clear from available evidence is that women with p53-abnormal tumors should be excluded from receiving conservative treatment, though concomitant pathogenic *POLE* exonuclease domain mutations or MMR-deficiency need to be excluded as *TP53* variants occurring in these contexts are likely passenger and not driver mutations [(55)].

The heterogeneity in the type, dose and duration of progestin used, study type, population, number of participants, outcomes measured and cut-off values used for hormone receptor expression in studies to date highlight the need for large, prospective trials with consistent

parameters in order to provide high-quality evidence. Longer studies are also required in order to monitor recurrences and subsequent pregnancies and correlate these with pre-treatment biomarkers. Of note, successful pregnancy after progestin treatment has been associated with reduced recurrence in two studies with long-term follow-up [105, 127]. All assessments of molecular markers to date have been targeted, no study has performed an unbiased genome-wide assessment of the molecular features of endometrial lesions that do or do not respond to progestin therapy. Increasing the range of predictive biomarkers to include mutations in other genes, epigenetic modifications, gene and protein expression signatures and post-translational modifications is anticipated to identify novel predictive biomarkers as well as improve specificity and sensitivity. Ideally, separate analysis of both tumor and stroma would be conducted with the recognition that stromal factors may be predictive of response. Only two studies to date have investigated blood-based biomarkers (CA-125 and estradiol) and neither reported an association with outcome [134, 136], though other circulatory factors remain to be assessed. Other factors such as fat localization remain to be assessed. Finally, integrating molecular biomarkers with clinical and histopathological features as well as quality-of-life assessments will provide a more comprehensive assessment, enabling clinicians to provide their patients with options on whether they can safely delay or avoid standard of care without adversely affecting their cancer-related outcomes or quality-of-life.

To date, only three prospective trials have a formal aim of identifying biomarkers of progestin response and although they are important resources of samples, patient numbers are clearly insufficient to validate the biomarkers proposed to date. Samples collected in other trials, such as those reviewed in Supplementary File 1, could potentially be aggregated into an international biobank to obtain the statistical power needed to validate and potentially identify new predictive biomarkers as endometrial biopsies are typically collected at baseline as part of standard of care. A drawback of all cohorts to date is the lack of a control arm of women not treated with progestin for comparison, though the ethics of including untreated

women with a formal diagnosis of endometrial cancer is highly questionable. Most prospective studies also collect tumor and blood specimens every three months throughout treatment, potentially enabling a comprehensive picture to be established of how the molecular features of tumors and spectrum of circulating factors change as tumors respond or not to progestins, providing insights into tumorigenic processes and their reversibility. Understanding the mechanisms of the pathogenesis of low-grade endometrial cancer and its relationship with obesity will most likely result in the identification of novel targets for treatment as well as preventative strategies.

Conclusions

Molecular markers have been validated as prognostic factors in endometrial cancer in numerous studies, as well as predictive biomarkers for select treatments, paving the way for biomarkers to replace current histopathological grading and staging of tumors, reproducibly stratify tumors into risk groups and direct patients towards the optimal treatment strategy. However, there are currently no validated markers of response to progestin therapy, which would be of significant benefit to young women who wish to retain fertility as well as obese women and/or those with comorbidities who are at high risk of surgical complications. Key unanswered questions for women considering progestin therapy for their endometrial cancer are summarised in Table 4. To date, only three prospective studies include a formal outcome of identifying predictive biomarkers, however samples from other trials may be used for discovery and validation. Prospective clinical trials provide consistent progestin type, dose, duration, sampling times and assessment of response, enabling a high level of evidence-based recommendations to be generated. Predictive biomarkers are anticipated to improve response rates and guide further research into progestin treatment of endometrial cancer. Outcomes such as weight loss and subsequent pregnancy will also need to be considered in future trials as they can contribute to improved response and reduced recurrence respectively.

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Competing Interests

DGH is a founder and Chief Medical Officer of Contextual Genomics, a for profit company that provides genomic diagnostics and reporting to assist in cancer patient treatment.

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Tables

Table 1. Pre-treatment clinical features investigated for their association with disease regression and/or recurrence.

Clinical feature	*Regression*	*Recurrence*	*No association*
BMI	Non-obese [105, 127, 128, 130]	Non-obese [131] Obese [105, 127-129]	[132-137]
Age	Younger [132]	Younger [136] Older [127]	[105, 128-131, 133-135, 137]
Menopause status		Premenopausal [136]	[128]
Endometrial thickness	Thin [134]	Thick [128]	
Diabetic status		Diabetic [128]	[127, 129, 130, 137]
Gravidity			[127, 129, 134]
Parity			[105, 127-130, 134-137]
Polycystic ovarian syndrome			[105, 127, 129, 131]
Smoking			[129, 133, 134]
Family history of cancer			[127, 133]
Hypertension			[128, 130, 137]

Table 2. Pre-treatment histopathological features investigated for their association with disease regression and/or recurrence.

Histopathological feature	*Regression*	*Recurrence*	*No association*
Grade	Low [138]		[139]
Lesion type	Hyperplastic [128, 132]	Cancer [128, 129, 136]	[127, 131, 133, 135]
Tumor volume	Low [138]		
Mitotic index	Low [139]		
Nuclear grade	Low [139]		

Table 3. Pre-treatment molecular markers investigated for their association with disease regression and/or recurrence.

Molecular marker	*Regression*	*Recurrence*	*No association*
PR	High [137, 140]		[129, 139]
PRβ	High [141]		[139, 142]
Glandular PRβ		High [135, 136]	[142]
Stromal PRβ			[142]
Glandular PRα		Low [136]	[142]
Stromal PRα		Low [135, 136]	[142]
Glandular PRα:PRβ		≤1 [136]	
Stromal PRα:PRβ		≤1 [136]	
ERα	High [140]		[129, 135, 139, 142]
ERβ			[135, 142]
MMR status	Proficient [132]		
HSPA5/GRP78	Low [143]		
Ki67	Low [139]		[129]
p53	Low [137]		
AR			[142]
BAX			[135]
BCL2			[135, 137, 139-141]
Cleaved caspase			[139]
COX2			[140]
MLH1			[140]
PAX2			[135, 141, 144]
PTEN			[135, 141, 144]
CA-125			[134]
Estradiol			[136]

Table 4. Key unanswered questions for women considering progestin treatment for their endometrial cancer.

1.	Which tumors will have a complete pathological response?
2.	What are the optimum type, dose and duration of progestin treatment?
3.	What are the optimum duration and frequency of follow-up after achieving a pathological complete response?
4.	Should progestin treatment be continued after achieving a pathological complete response and if so, for how long?
5.	Should progestin treatment be continued after a partial or failed response and if so, for how long?
6.	What are the criteria for stopping progestin treatment?
7.	Is a hysterectomy necessary after completing childbearing?
8.	Should dual-agent therapy be administered (eg. metformin, weight loss, targeted therapy) and if so, which patients would benefit?
9.	Can MMR-deficient tumors due to germline MMR mutation(s) be treated similarly to tumors with somatic MMR modifications?
10.	How can emerging molecular data best be incorporated into patient management?

Figures

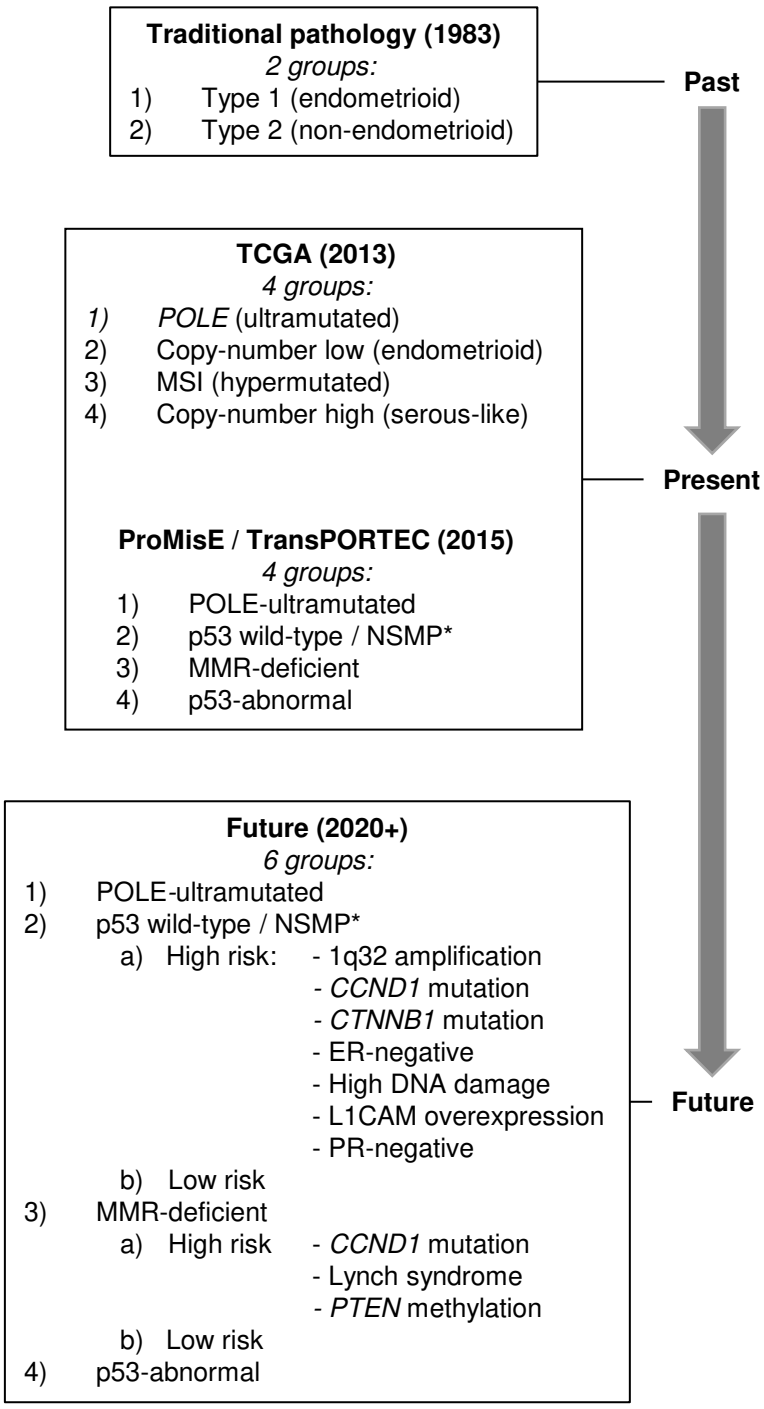
Figure 1. Evolution of the classification of endometrial cancer. Since TCGA classified endometrial cancers into four prognostically distinct molecular subtypes in 2013, stratification of tumors into risk groups using molecular markers has been and continues to be improved. *NSMP = No Specific Molecular Profile.

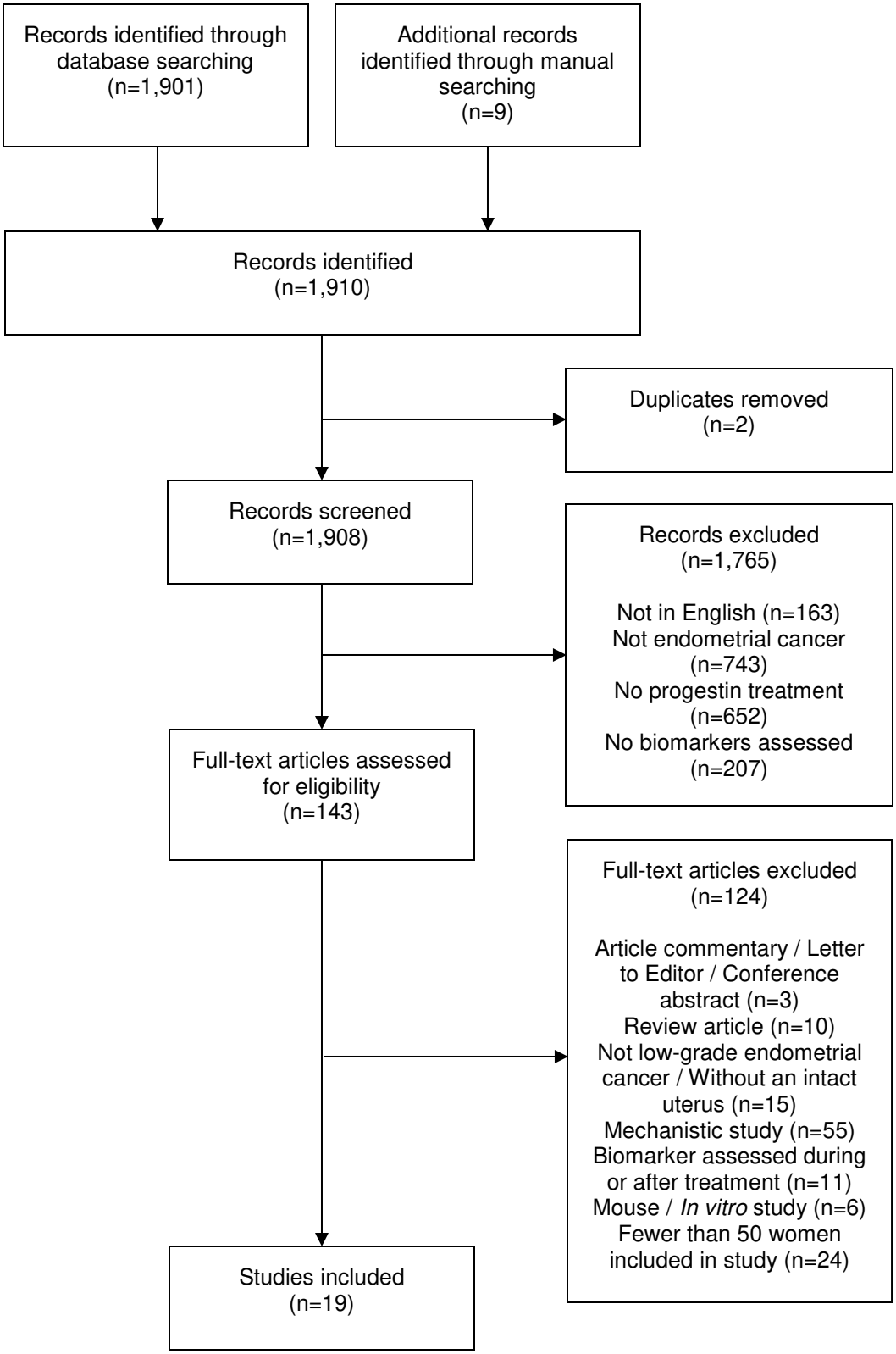
Figure 2. Flow diagram outlining study selection.

Supplementary Material

Supplementary File 1. Current prospective trials exploring progestin treatment of low-grade endometrial cancer. LNG-IUD = levonorgestrel-releasing intrauterine device. MA = megestrol acetate. MPA = medroxyprogesterone acetate.

Supplementary File 2. Overview of the included studies. EC = endometrial cancer. EH = endometrial hyperplasia. EIN = endometrial intraepithelial neoplasia. GnRH = gonadotrophin-releasing hormone. LNG-IUD = levonorgestrel-releasing intrauterine device. MA = megestrol acetate. MPA = medroxyprogesterone acetate.


Traditional pathology (1983)
2 groups:
1) Type 1 (endometrioid)
2) Type 2 (non-endometrioid)
Past
TCGA (2013)
4 groups:
1) POLE (ultramutated)
2) Copy-number low (endometrioid)
3) MSI (hypermutated)
4) Copy-number high (serous-like)
ProMisE / TransPORTEC (2015)
4 groups:
1) POLE-ultramutated
2) p53 wild-type / NSMP*
3) MMR-deficient
4) p53-abnormal
Present
Future (2020+)
6 groups:
1) POLE-ultramutated
2) p53 wild-type / NSMP*
a) High risk: - 1q32 amplification
- CCND1 mutation
- CTNNB1 mutation
- ER-negative
- High DNA damage
- L1CAM overexpression
- PR-negative
b) Low risk
3) MMR-deficient
a) High risk - CCND1 mutation
- Lynch syndrome
- PTEN methylation
b) Low risk
4) p53-abnormal
Future


Records identified through database searching (n=1,901)
Additional records identified through manual searching (n=9)
Records identified (n=1,910)
Duplicates removed (n=2)
Records screened (n=1,908)
Records excluded (n=1,765)
Not in English (n=163)
Not endometrial cancer (n=743)
No progestin treatment (n=652)
No biomarkers assessed (n=207)
Full-text articles assessed for eligibility (n=143)
Full-text articles excluded (n=124)
Article commentary / Letter to Editor / Conference abstract (n=3)
Review article (n=10)
Not low-grade endometrial cancer / Without an intact uterus (n=15)
Mechanistic study (n=55)
Biomarker assessed during or after treatment (n=11)
Mouse / *In vitro* study (n=6)
Fewer than 50 women included in study (n=24)
Studies included (n=19)

ClinicalTrials.gov ID	*Sponsor*	*Conditions*	*Interventions*	*Outcome measures*	*Samples collected*	*Estimated primary completion*
NCT00788671: A Phase II Study of the Levonorgestrel Intrauterine Device (Mirena) to Treat Complex Atypical Hyperplasia and Grade 1 Endometrioid Endometrial Carcinoma	MD Anderson Cancer Center, USA	50 women aged ≥18 years with complex atypical hyperplasia or grade 1 endometrioid endometrial cancer. Presence of one or more of the following: desire for future fertility, BMI >40kg/m^2, multiple comorbidities.	LNG-IUD (single-arm, multi-center)	Primary: Complete regression at 12 months.	Endometrial biopsies at baseline, 3, 6, 9 and 12 months	November 2019
NCT01686126: A Phase II Randomised Clinical Trial of Mirena® ± Metformin ± Weight Loss Intervention in Patients With Early Stage Cancer of the Endometrium	Queensland Centre for Gynaecological Cancer, Australia	165 women aged ≥18 years with endometrial hyperplasia with atypia or grade 1 endometrioid endometrial cancer. BMI >30kg/m^2 wishing to retain fertility or at high risk of surgical complications due to comorbidities or obesity.	LNG-IUD +/- Metformin or weight loss (randomized, multi-center)	Primary: Pathological complete response at 6 months. Secondary: Predict response to treatment and increase molecular understanding of the biological pathogenesis of early endometrial cancer.	Endometrial biopsies and blood at baseline, 3 months and 6 months	December 2019
NCT02035787: Metformin With the Levonorgestrel-Releasing Intrauterine Device for the Treatment of	UNC Lineberger Comprehensive Cancer Center, USA	30 women aged ≥18 years with complex atypical hyperplasia or grade 1 endometrial cancer. Non-surgical	LNG-IUD + Metformin (single-arm, single-center)	Primary: Response rate at 6 months. Secondary: Adverse events at 12 months. Exploratory: Explore	Endometrial tissue, blood and urine at baseline and 6 months	September 2019

ClinicalTrials.gov ID	*Sponsor*	*Conditions*	*Interventions*	*Outcome measures*	*Samples collected*	*Estimated primary completion*
Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients		candidates due to desire for fertility-preserving treatment or unacceptable surgical risk.		changes in cellular proliferation (Ki-67) from baseline to 6 months, association between the level of expression of the metformin transporter proteins and key targets of the metformin/mTOR signalling pathway and CR status at 6 months, metabolic profiling of serum, urine and tumor tissue pre- and post- 6 months of metformin treatment, association between metabolic factors and metformin concentration levels in tumor tissue/blood/urine and CR at 6 months.		
NCT02397083: Phase II Study of the Levonorgestrel Intrauterine Device	MD Anderson Cancer Center, USA	270 women aged ≥18 years with complex atypical hyperplasia or stage	LNG-IUD +/- everolimus (randomized, multi-center)	Primary: Response rate at 6 months. Secondary: Adverse events, progression-	Endometrial biopsies at baseline, 3 months and 6	September 2026

ClinicalTrials.gov ID	*Sponsor*	*Conditions*	*Interventions*	*Outcome measures*	*Samples collected*	*Estimated primary completion*
Alone or in Combination With the mTORC1 Inhibitor, Everolimus, for the Treatment of Complex Atypical Hyperplasia and Stage Ia Grade 1 Endometrial Cancer		IA grade 1 or focal grade 2 endometrioid endometrial cancer.		free survival and overall survival up to 11 years and response duration up to 4 weeks after completion of study treatment. Exploratory: Determine if response to therapy can be predicted based on the molecular profile of the tumor or by changes in gene expression after therapy.	months	
NCT02990728: Mirena® ± Metformin as Fertility-preserving Treatment for Young Asian Women With Early Endometrial Cancer	Chang Gung Memorial Hospital, Taiwan	120 women aged 20-40 years with grade 1 endometrioid endometrial cancer. Tumor expresses PR and ER. Desire for fertility preservations.	LNG-IUD +/- Metformin. Patients with poor response at first assessment (90-100 days after commening treatment) will receive additive oral progestin therapy (randomized, single-center)	Primary: Response at 6 months. Secondary: Discover tumor morphological and molecular changes before and after treatment, effectiveness of adding oral progestin to patients with poor response, compare systemic effects and rate of long-term success	Endometrial biopsies collected before, during and after treatment	March 2018

ClinicalTrials.gov ID	*Sponsor*	*Conditions*	*Interventions*	*Outcome measures*	*Samples collected*	*Estimated primary completion*
				(remission and pregnancy) between the two treatment groups, assess the expression of molecular markers (including PR, ER, PTEN, Ki-67, Bcl-2) before, during and after treatment.		
NCT03018249: A Randomized Surgical Window Pilot Investigation of the Relationship of Short-Term Medroxyprogesterone Acetate (NSC #26386) Compared to Medroxyprogesterone Acetate Plus Entinostat (NSC #706995) on the Morphologic, Biochemical, and Molecular Changes in Primary Endometrioid Adenocarcinoma of the Uterine Corpus	National Cancer Institute, USA	50 women aged ≥18 years with endometrioid endometrial adenocarcinoma.	MPA +/- entinostat ~3 weeks before hysterectomy (randomized, multi-center)	Primary: Mean post-treatment PR score. Secondary: Histologic response at 36 months, mean post-treatment Ki-67 score at 36 months and adverse events at 45 days post-surgery. Other: Mean post-treatment tumor ER score, co-expression of PR, Ki-67 and p21.	Endometrial biopsies before and at hysterectomy	December 2020
NCT03241914:	Fudan University,	40 women aged 18-	MA +/- LNG-IUD	Primary;	Blood at	July 2020

ClinicalTrials.gov ID	*Sponsor*	*Conditions*	*Interventions*	*Outcome measures*	*Samples collected*	*Estimated primary completion*
Megestrol Acetate Plus LNG-IUS to Megestrol Acetate in Young Women With Early Endometrial Cancer	China	45 years with endometrioid endometrial cancer. Desire for retaining reproductive function or uterus.	(randomized, single-center)	Pathological response rate up to 12 months. Secondary: Adverse events, relapse, pregnancy and compliance up to 24 months. Other: Economic benefit up to 12 months.	baseline	
NCT03463252: Value of Levonorgestrel-Releasing Intrauterine System (LNG-IUS) in the Fertility-preserving Treatment of Atypical Endometrial Hyperplasia and Early Endometrial Carcinoma	West China Second University Hospital, China	224 women aged ≤40 years with atypical endometrial hyperplasia or PR-positive stage IA grade 1 endometrioid endometrial cancer. Strong desire for fertility preservation.	Without contraindication of oral high-dose progesterone: MPA +/- LNG-IUD. With contraindication of oral high-dose progesterone: LNG-IUD +/- GnRH agonist (randomized, single-center)	Primary: Pathologic response at 6-9 months, pregnancy rate at 7-15 months and live birth rate at 16-24 months. Secondary: Side effects up to 9 months.	Endometrial biopsies every 3 months for 9 months	December 2019
NCT03538704: Effect of Fertility-sparing Therapy of Early Endometrial Cancer	Peking University People's Hospital, China	80 women aged 18-40 years with BMI ≥25kg/m^2 with PR and ER-positive stage Ia, grade 1 or 2 endometrial cancer or atypical hyperplasia.	MPA +/- metformin (randomized, multi-center)	Primary: Complete response until 12 months. Secondary: Pregnancy rate until 12 months. Other: Recurrence until 12 months.	Endometrial biopsies and blood every 3 months for 12 months	March 2020

ClinicalTrials.gov ID	*Sponsor*	*Conditions*	*Interventions*	*Outcome measures*	*Samples collected*	*Estimated primary completion*
		Strong desire for fertility preservation.				
NCT03567655: Study of Fertility-sparing Management Using High-dose Oral Progestin in Young Women With Stage I Endometrial Adenocarcinoma With Grade 2 Differentiation or Superficial Myomectomy Invasion	Korean Gynecologic Oncology Group, Korea	41 women aged 20-40 years with stage IA, grade 1 endometrioid adenocarcinoma with superficial myometrial invasion or grade 2 endometrioid adenocarcinoma that is presumably confined to the endometrium or with superficial myometrial invasion. Desire to preserve fertility.	MPA 500mg/day for 3-12 months (single-arm, multi-center)	Primary: Complete response rate at 12 months. Secondary: Disease-free survival, fertility outcomes, side effects, predictive and prognostic biomarkers and clinicopathological factors associated with response and recurrence, patient-reported outcomes.	Endometrial biopsies every 3 months for 12 months	October 2022
NCT03671811: Open-Label Randomized Phase II Trial of Megestrol Acetate With or Without Pterostilbene in Patients With Endometrial Cancer Scheduled for Hysterectomy	City of Hope Medical Center, USA	36 women aged ≥18 years with endometrial cancer.	MA +/- pterostilbene for 3 weeks prior to hysterectomy (randomized, single-center)	Primary: Tumor Ki67 proliferation index pre- and post-treatment up to 6 weeks. Secondary: Histologic response of gland cellularity, mitotic index, metaplasia and eosinophilic cytoplasm up to 6	Pre- and post-treatment up to 6 weeks endometrial samples	December 2020

ClinicalTrials.gov ID	*Sponsor*	*Conditions*	*Interventions*	*Outcome measures*	*Samples collected*	*Estimated primary completion*
				weeks and immunohistochemical expression of Bcl-2 and Casp3 pre- and post-treatment up to 6 weeks.		
NCT04008563: Bariatric Surgery for Fertility-Sparing Treatment of Atypical Hyperplasia and Grade 1 Cancer of the Endometrium	University Health Network Toronto, Canada	36 women aged 18-41 years with BMI ≥35kg/m^2 and complex atypical hyperplasia or stage 1, grade 1 endometrioid endometrial cancer. Desire for fertility preservation.	LNG-IUD +/- bariatric surgery (pilot randomized, multi-center)	Primary: Recruitment rate. Secondary: Completion of bariatric surgery, loss to follow-up, completion of patient-reported outcomes questionnaire and complete response rate at 15 months.	None	August 2022
NCT04046185: Programmed Death-1 (PD-1) Inhibitor Combined with Progesterone Treatment in Early Stage Endometrial Cancer Patients Who Want to Preserve Fertility	Shanghai First Maternity and Infant Hospital, China	60 women aged 18-45 years with grade 1 or 2 endometrioid endometrial cancer confined to the endometrium. Desire for fertility preservation.	MA 160mg/day +/- Toripalimab 240mg IV 4 times every 3 weeks (randomized, single-center)	Primary: Pathologic complete and partial remission at 6 months. Secondary: Adverse effects up to 1 year and pregnancy rate up to 2 years.	Unknown	October 2022

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
Chen *et al.* (2016) [127]	Retrospective (single-center)	53 Chinese women aged 20-42 years with PR-positive: - 16 complex EH - 37 grade 1 stage IA EC	MPA (250-500mg/day, oral) or MA (160-480mg/day, oral) +/- GnRH agonist (leuprolide acetate depot 3.75mg/28 days as one cycle for 3-6 cycles) or LNG-IUD for ≥2 months	Complete response	74% after median 6 months (range 3-24 months); 62% within 6 months	BMI <30kg/m^2	Abnormal menstruation Age Diabetes Family history of cancer Lesion type PCOS Previous pregnancy Progestin type	12 (23%) women had a BMI ≥30kg/m^2.
		39 Chinese women aged 20-42 years with PR-positive: - 12 complex EH - 27 grade 1 stage IA EC		Recurrence	26% after median 29 months (range 4-56 months)	Age ≥35 years BMI ≥30kg/m^2 Persistent infertility Time to complete response (>6 months)	Family history of cancer Lesion type PCOS Progestin type	10 (26%) women were aged ≥35 years. 4 (10%) women had a BMI ≥30kg/m^2.
Fawzy *et al.* (2016) [137]	Prospective (single-center)	50 premenopausal women with:	MPA (20mg/day for 20 days/cycle,	Regression	Overall: 76% EH without atypia: 77%	Low p53 PR	Age BCL2 BMI Diabetes	All women suffered from menometror

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
		- 43 EH without atypia - 7 EH with atypia (EIN)	oral) for 3-6 months		EH with atypia (EIN): 71%		Histology Hypertension Parity	rhagia and had a thick endometrium (≥14mm). PR-positive defined as immunoreactive score ≥2.
Gallos *et al.* (2013) [140]	Prospective (single-center)	174 women (predominantly Caucasian): - 155 complex EH - 19 atypical complex EH (EIN)	LNG-IUD for 5 years	Regression	77%	ER PR	BCL2 COX2 MLH1	Hormone receptor positive defined as ≥1% staining.
		152 women		Relapse	12% after median 32 months (IQR 11-58 months)		BCL2 COX2 ER MLH1 PR	
Gallos *et al.* (2013) [128]	Prospective (single-center)	344 women: - 310 complex EH without atypia - 34 complex EH with atypia (EIN)	LNG-IUD or oral progestin for ≥3 months	Regression	LNG-IUD: 95% Oral: 84%	BMI <35kg/m^2 Lesion type	Age Diabetes Endometrial thickness Ethnicity Hypertension Menopause Parity	Only significant in women with complex EH without atypia treated with LNG-IUD.

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
		219 women: - 202 complex EH without atypia - 17 complex EH with atypia (EIN)		Relapse	LNG-IUD: 14% Oral: 30%	BMI ≥35 kg/m^2 Diabetes Endometrial thickness >9mm Lesion type	Age Ethnicity Hypertension Menopause Parity	BMI, diabetes and endometrial thickness were only significantly associated with relapse in women with complex EH without atypia treated with LNG-IUD. Only BMI remained significant after multivariable analysis.
Mitsuhashi *et al.* (2019) (131)	Retrospective (single-center)	61 Japanese women aged ≤40 years: - 21 atypical EH (EIN) - 40 grade 1 endometrioid EC	MPA (400mg/day, oral) + metformin (750-2250mg/day, oral)	Relapse	13% after median 57 months (range 13-88 months)	BMI <25 kg/m^2	Abnormal glucose metabolism Age Insulin resistance Lesion type PCOS	48 (76%) women had a BMI ≥25 kg/m^2. 43 (68%) women had insulin resistance.

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
Ørbo *et al.* (2015) [144]	Retrospective (multi-center)	141 Norwegian women with EH	LNG-IUD or MPA (10mg for 10 days/cycle, oral) or MPA (10mg daily, oral) for 6 months	Resolution	87% after 6 months		PAX2 PTEN	All women treated with LNG-IUD had complete response.
Ozkaya *et al.* (2013) [134]	Prospective (single-center)	67 premenopausal women with simple EH without atypia	Cyclic MPA (10mg for 12 days/cycle, oral) for 3 months	Resolution	84% after 3 months	Endometrial thickness <16.5mm	Age BMI CA-125 Gravidity Menstrual cycle Ovarian cysts Parity Smoking Systemic disorders Uterine fibroids	
Park *et al.* (2013) [105]	Retrospective (multi-center)	148 Korean women aged ≤40 years with grade 1 stage IA endometrioid EC	MPA (30-1500mg/day, oral) or MA (40-240mg/day, oral) for ≥2 months	Complete response	78% after median 18 weeks (range 8-55 weeks)	BMI <25 kg/m^2	Age Medical co-morbidity Parity PCOS Progestin type Progestin dose	139 (94%) women were nulliparous.
		115 women		Recurrence	30% after	BMI ≥25 kg/	Age	

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
					median 15 months (range 4-61 months)	m^2 Persistent infertility Progestin type (MA)	Maintenance treatment after complete response Medical co-morbidity Parity PCOS Progestin dose Time interval to achieve complete response	
Podratz *et al.* (1985) [138]	Retrospective (single-center)	142 women: - 10 grade 1 EC - 63 grade 2 EC - 69 grade 3	Progestin (oral or intramuscular) for ≥2 months	Regression	Overall: 11% Grade 1: 40% Grade 2: 18% Grade 3: 2%	Histologic grade (1 and 2)	Progestin type	
				Survival	Overall five-year survival: 8% Grade 1: 20% Grade 2: 17% Grade 3: 0%	Histologic grade (1 and 2) Tumor volume (≤10cm^3)		
Rattanachai	Prospective	134 Thai	Cyclic	Complete	93%		Age	

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
yanont *et al.* (2005) [133]	(single-center)	women: - 116 simple EH - 18 complex EH	progestin for ≥6 months	response			Amenorrhoea BMI Family history of cancer Histology History of prior bleeding Infertility Lesion type Menstrual cycle Metabolic disease Pelvic pathology Progestin type Smoking	
Sletten *et al.* (2017) [135]	Retrospective (multi-center)	57 Norwegian women aged 30-70 years with EH	LNG-IUD or MPA (10mg for 10 days/cycle, oral) for 3 months	Regression	75% after 3 months	Progestin type (LNG-IUD)		
		43 Norwegian women aged 30-70 years:		Relapse	23% after median 6 months (range 2-130 months)	Low stromal PRα High glandular PRβ	Age BMI Lesion type Parity Progestin	Hormone receptor positive defined as >10%

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
		- 33 complex EH - 10 atypical EH (EIN)					type Glandular or stromal: BAX BCL2 ERα ERβ Glandular PRα Stromal PRβ Mutations in: PAX2 PTEN	staining.
Sletten *et al.* (2019) [136]	Retrospective (multi-center)	94 Norwegian women aged 30-70 years: - 12 simple EH - 73 complex EH - 9 atypical EH (EIN)	LNG-IUD (52mg) or MPA (10mg/day or 10mg for 10 days/cycle, oral) for 6 months	Relapse	43%	High glandular PRβ Lesion type (atypical EH) Low glandular PRα Low stromal PRα Premenopausal PRα:PRβ ≤1 (glands + stroma) Younger age	BMI Estradiol level Parity Stromal PRβ	Menopausal status and age were significantly associated with relapse in univariable analyses, but not in multivariable analysis.

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
Tierney *et al.* (2016) [143]	Retrospective (multi-center)	61 women with complex atypical EH (EIN)	LNG-IUD, MPA or MA for ≥3 months	Regression	41% after median 4 months (range 1-29 months)	Low GRP78		44 (72%) women were aged <40 years.
Upson *et al.* (2012) [141]	Retrospective (multi-center)	114 women aged >18 years (predominantly Caucasian): - 73 complex EH - 41 atypical EH (EIN)	Oral progestin for ≥2 months	Regression	71%	High PRβ	BCL2 PAX2 PRα PRα + PRβ PTEN	PR-high defined as >75% staining. Association only seen in atypical EH.
Vereide *et al.* (2006) [142]	Prospective (single-center)	50 Norwegian women aged 30-70 years: - 26 simple EH - 6 simple atypical EH - 11 complex EH - 7 complex atypical EH (EIN)	MPA (10mg for 10 days/cycle) or LNG-IUD (20µg/day) for 3 months	Complete response	Overall: 72% LNG-IUD: 100% MPA: 52%		Glandular/stromal: AR ERα ERβ PRα PRβ	Hormone receptor positive defined as >10% staining.
Yang *et al.* (2015) [129]	Retrospective (multi-center)	88 Chinese women aged <40	Oral or intrauterine progestin or	Regression	88% after median 6 months		Age BMI Diabetes	Hormone receptor positive

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
		years: - 37 complex atypical EH (EIN) - 51 well-differentiated endometrioid EC	combination for ≥5 months		(range 3-13 months)		ER Ki67 Lesion type Menometrorrhagia PCOS PR Previous pregnancy Prior OCP use Smoking status	defined as ≥10% staining. Ki67-positive defined as strong nuclear staining.
		71 Chinese women aged <40 years: - 32 complex atypical EH (EIN) - 39 well-differentiated endometrioid EC		Relapse	35% after median 39 months (range 8-71 months)	BMI ≥30 kg/m^2 Lesion type (EC)	Age Diabetes ER Ki67 Menometrorrhagia PCOS PR Previous pregnancy Prior OCP use Smoking status	Only BMI was significant after multivariate analysis.
Yang *et al.* (2018) [130]	Retrospective (single-center)	148 Chinese women aged <55 years with atypical EH	MA (160mg/day, oral) +/- metformin (1500mg/da	Complete response	95% after mean 7 months (range 1-15 months)	BMI <25 kg/m^2	Age Diabetes Hypertension Insulin	Women with insulin resistance had higher BMI and a

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
		(EIN)	y) for ≥6 months				resistance Metabolic syndrome Parity Progestin therapy	lower incidence of metabolic syndrome and diabetes than women without insulin resistance.
Zaino *et al.* (2014) [139]	Prospective (multi-center)	59 women (predominantly Caucasian) with endometrioid EC: - 31 grade 1 - 17 grade 2 - 9 grade 3 - 2 unknown	MPA (400mg, intramuscular) for 21-24 days	Histologic response (complete or partial)	Complete response: 2% Partial response: 63%	Low Ki67 Low mitotic index Nuclear grade <2	BCL2 Cleaved caspase ER Histologic grade Metaplasia (mucinous/squamous) Non-neoplastic endometrium (atrophy/decidua/hyper) Nucleoli Pale eosinophilic PR PRβ Secretion (atypical/lum	Hormone receptor positive defined as score >0.2.

Reference	*Study type*	*Population*	*Treatment*	*Outcome*	*Response / recurrence rate*	*Associated with outcome*	*Not associated with outcome*	*Comments*
							inal/subnuclear)	
Zakhour *et al.* (2017) [132]	Retrospective (multi-center)	84 women (majority Hispanic) aged ≤55 years: - 57 complex atypical EH (EIN) - 27 FIGO 1 EC	Progestin (oral, intrauterine or injectable, or any combination of these) for ≥3 months	Regression	Overall: 49% Complex atypical EH (EIN): 62% EC: 22%	Lesion type (EH) Normal MMR staining Younger age	BMI	24 (29%) women were aged >40 years. 0/6 (0%) tumors with abnormal MMR staining responded, 3 of these had germline MMR mutation. Women with abnormal MMR staining were older, had lower BMI and a higher incidence of FIGO 1 EC than women with normal MMR staining.