Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature

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ABSTRACT

Objectives: To investigate the efficacy of progestin treatment to achieve pathological complete response (pCR) in patients with complex atypical endometrial hyperplasia (CAH) or early endometrial adenocarcinoma (EC).

Methods: A systematic search identified 3245 potentially relevant citations. Studies containing less than ten eligible CAH or EC patients in either oral or intrauterine treatment arm were excluded. Only information from patients receiving six or more months of treatment and not receiving other treatments was included. Weighted proportions of patients achieving pCR were calculated using R software.

Results: Twelve studies met the selection criteria. Eleven studies reported treatment of patients with oral (219 patients, 117 with CAH, 102 with grade 1 Stage I EC) and one reported treatment of patients with intrauterine progestin (11 patients with grade 1 Stage IEC). Overall, 74% (95% confidence interval [CI] 65-81%) of patients with CAH and 72% (95% CI 62-80%) of patients with grade 1 Stage I EC achieved a pCR to oral progestin. Disease progression while on oral treatment was reported for 6/219 (2.7%), and relapse after initial complete response for 32/159 (20.1%) patients. The weighted mean pCR rate of patients with grade 1 Stage I EC treated with intrauterine progestin from one prospective pilot study and an unpublished retrospective case series from the Queensland Centre of Gynaecologic Oncology (QCGC) was 68% (95% CI 45- 86%).

Conclusions: There is a lack of high quality evidence for the efficacy of progestin in CAH or EC. The available evidence however suggests that treatment with oral or intrauterine progestin is similarly effective. The risk of progression during treatment is small but longer follow-up is required. Evidence from prospective controlled clinical trials is warranted to establish how the efficacy of progestin for the treatment of CAH and EC can be improved further.

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Key words: meta-analysis; endometrial cancer; hyperplasia with atypia; progestin; fertility-sparing

INTRODUCTION

Endometrial cancer is the most common gynaecological cancer in developed countries, with an estimated incidence per year of 23.5 per 100,000 in the US [1], 18.5 per 100,000 in Canada [2] and 16.5 per 100,000 in Australia [3]. In patients younger than 50 years of age the incidence of endometrial cancer is increasing by 1% per year [1].

Overall, 84% of all endometrial cancers are Type 1 endometrioid adenocarcinomas (EC) [4], which typically carry a good prognosis. Type 1 EC is associated with obesity, diabetes mellitus and hypertension. Increasing body mass index has been shown to be strongly associated with the development of EC[5-7]. It has been estimated that at least 16,000 new cases of EC in Europe in 2002 were caused by obesity (population attributable risk of 30.0; 95% CI 25.6 – 34.4) [8].

Complex atypical endometrial hyperplasia (CAH), a precursor lesion of EC, is also more common in obese patients, and is estimated to progress to EC in 15-75% of patients [9-16]. Invasive EC can already be found in approximately 30% of patients initially diagnosed with CAH [17].

The current standard treatment for CAH and endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy [18-21] with or without surgical staging [22]. While radical surgery offers good 5-year survival prospects of 75-90% [20], it also eliminates prospects of further fertility. Many patients carry a high burden of medical co-morbidities, which has been associated with a higher risk of surgical adverse events [23-26]. For example, wound infections are a frequent postoperative complication in obese patients [24].

It is thus accepted clinical practice to offer oral and/or intrauterine-delivered (IUD) progestin to selected patients diagnosed with CAH and EC. In particular, two groups of patients might

benefit most: a) young women diagnosed with CAH and EC who still wish to have children and b) patients with severe medical co-morbidities precluding (immediate) surgery [27-42].

No evidence from randomised controlled trials is available and no randomised controlled trials are currently underway on the efficacy of progestin treatment in achieving a pathological complete response. Although there are a number of previous, mostly small, systematic reviews or meta-analyses reporting outcomes of progestin therapy, none of these reviews restricted outcomes to pathological complete response, posed restrictions on the duration of treatment or detailed the response to either oral or intrauterine progestin separately for patients with CAH or EC [43-45].

METHODS

Search strategy

A systematic review was conducted to identify all articles published between January 1950 and February 2011 involving patients with CAH or grade 1, clinical Stage I EC treated with intrauterine or oral progestins. Systematic searches were performed using MEDLINE, Cochrane Library, ScienceDirect, DynaMed and MD Consult Australia. Database selection and search terms for use were formulated with the guidance of a subject librarian with expertise in the field. A combination of Medical Subject Headings (MeSH) and keyword searches were used. The number of search terms used was dependent on the number of terms allowed by each database. MEDLINE, which allowed the most tailored and extensive search, was used to generate two subsets of citations, for relevant participant and intervention type, which were combined with “AND”. Searches were limited to English literature and human studies. The keywords “endometrial”, “uterine”, “adenocarcinoma”, “carcinoma”, “cancer”,

"neoplasm" or MeSH term "Endometrial Hyperplasia" were used for participant type and "progestin", "progestogen", "progestagen", "progesterone", "gestogen", "levonorgestrel", "levonogestrel", "medroxyprogesterone", "megestrol", "noresthisterone", "dydrogesterone", "ethisterone", or "norgestrel" for intervention type. Keyword searches were performed on ScienceDirect and Cochrane Library using the terms "endometrial AND proges*". The topics "Endometrial Cancer" and "Endometrial Hyperplasia" were searched for relevant papers in DynaMed and MD Consult Australia. Reference lists of primary and review articles were scanned for other relevant studies not identified through electronic searches.

Selection of studies

Pre-defined inclusion and exclusion criteria for study selection were established prior to conducting the literature search. We included cohort studies, case series, comparative studies, controlled studies, and prospective studies, involving ten or more CAH patients receiving any single route of administration or ten or more EC patients receiving any single route of administration (either oral or IUD progestin treatment) and reporting pathological complete response rate as the primary outcome. Patients were eligible if aged eighteen years or older and treated for six months or longer with oral or intrauterine progestin and had pretreatment computed tomography or magnetic resonance imaging to confirm staging for EC patients. However, we decided to include one study where 6 of the 11 patients selected for review only had a transvaginal ultrasonography due to not being able to fit into MRI because of body habitus. This study was included as it was the only study available with 10 or more patients with EC treated with progestin by IUD [46]. We excluded studies that treated patients with progestin and simultaneously with additional treatment such as hysteroscopic ablation, radiotherapy, chemotherapy, other endocrine treatment (tamoxifen, bromocriptine), or other routes of administration of progestins (intramuscular, transdermal, vaginal).

A two-stage process was used to select relevant studies for the review (Figure 1). Two authors (J.B. and M.J.) independently examined titles and abstracts of all articles identified through electronic searches and excluded those not meeting the selection criteria. The second stage involved examination of full manuscripts and final decisions about inclusion and exclusion of studies. Where more than one article was found describing the same study, only the most recent or most complete publication was included. Full manuscripts were also obtained of review articles to allow identification of potentially eligible studies from reference lists.

Data extraction

Data extraction was performed by one author (J.B.) and entered into a predesigned spreadsheet. Where studies contained both patients that did and did not meet inclusion criteria but allowed distinction of outcomes, only information about patients fulfilling selection criteria was extracted. For studies where ambiguity existed about outcomes for a subset of participants fulfilling our criteria, authors were contacted with requests for clarification.

For each selected study, information was extracted about study design and number of patients treated for CAH or EC. We also summarised patients' mean age and age range, study setting and country, study period, actual and intended follow-up, dropout rates for prospective studies, route of progestin treatment, treatment duration, drug, dose and regimen, and rates of complete and partial pathological response, relapse, progression, pregnancies and live births. Fertility outcomes were only extracted from studies included in our analysis.

From our centre database (Queensland Centre of Gynaecological Cancer Series 2004-2011) we retrospectively extracted all patients with histological grade 1 and apparent Stage I EC based on CT scan of pelvis and abdomen and either a chest X-ray or CT scan of the chest, who were treated with a Mirena levonorgestrel-releasing intrauterine device (IUD) for at least

six months. Overall, eleven patients were identified, and data on pathological complete response, or evidence of persistent disease or progression was extracted.

Outcome measure

Our primary outcome measure of interest was pathological complete response, defined as histological regression to normal endometrium, including proliferative, secretory, inactive or atrophic endometrium. Histological regression to simple or complex endometrial hyperplasia without atypia was classified as a partial pathological response. Worsening of CAH to EC on histology or of grade 1 Stage I EC to a higher grade or stage on histology or surgical staging was classified as progression.

Statistical analyses

Using SAS software, for each study, the proportion of patients achieving pathological complete response with exact binomial 95% confidence intervals was computed [47]. Across studies, weighted proportions were then calculated, producing a pooled overall estimate and 95% confidence intervals. Chi-squared tests were used to assess statistical heterogeneity. Forest plots of sample size against proportion achieving pathological complete response were produced using R software and examined for publication bias.

To assess the effect of the inclusion criteria applied in the main analyses, two sensitivity analyses were conducted. We compared the pathological complete response rate obtained from the main analysis against:

Expanded analysis: Pathological complete response rate obtained when inclusion criteria were widened to include studies with three or more eligible CAH or EC patients in either treatment arm, treated for three months or more.

RESULTS

The electronic search strategy yielded a total of 3245 potentially relevant citations after removal of duplicates. The agreement between independent reviewers was 98% for selection of full manuscripts to be examined (Cohen's Kappa 0.65) and 100% for studies to be included. Overall, 3139 citations were excluded on the basis of title and abstract information (Figure 1). Examination of reference lists of review articles identified a further ten studies of potential relevance. Full manuscripts were thus obtained and examined for 116 articles, and 12 studies met selection criteria, of which 11 involved oral progestin treatment (6 retrospective case series, 2 prospective case series, 1 prospective cohort, 1 retrospective cohort, and 1 retrospective comparative study). In addition, weighted mean response rates for patients with grade 1 Stage I EC to intrauterine progestin treatment was estimated from one prospective pilot study by Montz and colleagues (11 patients) [46] and from our retrospective case series conducted at QCGC (11 patients). Four studies not previously included in reviews were identified [15, 28, 29, 39]. Characteristics of included studies are described in Table 1.

Oral Progestins: Meta-analysis of studies of oral progestin treatment involved a total of 219 patients, 117 with CAH and 102 with grade 1 Stage I EC; patients' age ranged from 19 to 77 years (mean age 36 years from nine studies that reported age for patients extracted for this meta-analysis, median value used for study by Hahn et al.). Follow-up ranged from 6 months to 23 years, with mean value of 45.8 months (median value used for study by Hahn et al.). The majority of patients (153/219, 70%) were treated with daily medroxyprogesterone acetate (MPA) 2.5–1500mg/day; 34/219 (15.5%) were treated with daily megestrol acetate 80–320mg/day; 12/219 (5.5%) were treated with cyclic MPA 10mg/day for 14 days of each

menstrual cycle, and 8/219 (4%) were treated with both MPA and megestrol. One study did not specify type of progestin used [48].

Overall, 86/117 (74%, 95% CI 65–81%) of patients with CAH and 73/102 (72%, 95% CI 66–78%) of patients with grade 1 Stage I EC achieved a pathological complete response with oral progestin treatment for six months or longer. Pathological complete response rates varied from 50-94% between CAH studies and 50-100% between EC studies. There was no evidence of heterogeneity between studies involving CAH patients (p=0.25), but heterogeneity was observed between studies involving EC patients (p=0.001).

Time taken to achieve pathological complete response ranged from 1 to 12 months with a mean of 5.9 months among the four studies that reported this (median value used for study by Hahn et al.). In addition, 18/219 (8.2%) patients achieved partial remission (range: 0–30% between studies). Non-responders (36/219, 16%) were reported to have undergone hysterectomy in five studies [28, 29, 32, 33, 35] .

Overall, 6/219 patients (2.7%) progressed from CAH to Stage I EC (grade 1 EC in five cases, grade 2 EC in one case) during oral progestin treatment. No patients with EC are reported to have progressed under treatment. Of the 159 patients who initially achieved a pathological complete response, 32/159 (20.1%) relapsed on longer follow-up. Reported relapse rates among responders varied from 0-50% between studies. Of 14 CAH patients who achieved pathological complete response and then relapsed, 8 had recurrence of CAH and 6 developed EC. Of 18 EC patients who achieved pathological complete response and then relapsed, 6 developed CAH and 12 had recurrence of EC. Time until relapse ranged from 4 months to 7 years after the completion of progestin treatment, with mean 27 months for seven studies that reported time until relapse (median value used for study by Hahn et al.). Six patients who

relapsed were reported to have been treated with a second course of oral progestin, of which three successfully achieved pathological complete response.

Of the nine studies that reported on fertility outcomes (187 patients) [28, 29, 32, 33, 35-37, 39, 42], 49 pregnancies and 35 live births were reported; 43% (44/103) patients who were reported to have been attempting to conceive after achieving pathological complete response were successful, the majority with fertility treatment. Overall, 35/49 (71%) of pregnancies resulted in live births.

Intrauterine Progestin: Analysis of the two studies involving IUD progestin treatment involved 22 patients with grade 1 Stage I EC; overall, 15/22 (68%, 95% CI 45-86%) achieved pathological complete response with levonorgestrel or progesterone IUD treatment for six months or longer. Response rates were similar across both studies: 7/11 (64%) in the Montz study and 8/11 (73%) in the QCGC series. No relapses or progressions were reported after 6-71 months of follow-up. Fertility outcomes were not reported.

Sensitivity analyses

When selection criteria were extended to include studies involving three or more eligible patients in either treatment arm requiring at least three or more months of treatment, the resulting meta-analysis involved 34 studies and 17 patients from the QCGC case series (470 patients, 239 with CAH, 231with grade 1 Stage I EC) [15, 27-42, 46, 48-63]. Among patients treated with oral progestins, 118/194 (61%, 95% CI 54 – 68%) patients with CAH and 128/194 (66%, 95% CI 59–73%) patients with EC achieved pathological complete response. Among patients treated with intrauterine progestins, 38/45 (84%, 95% CI 71–94%) patients with CAH and 17/37 (46%, 95% CI 29–63%) patients with EC achieved pathological complete response. Table 2 summarises the results of both analyses.

Risk of publication bias

The funnel plot to assess publication bias showed reasonable symmetry around the overall estimated response rate, as did the funnel plot from the sensitivity analysis involving broadened selection criteria (not shown). This suggests that the risk of publication bias is low. A formal test for publication bias based on p-values could not be performed, due to lack of comparative arm in individual studies from which to obtain p-values [64].

DISCUSSION

In the absence of data from randomised controlled trials, this meta-analysis provides evidence to counsel patients about likely benefit, as well as risk, of non-response and relapse. The estimated pathological complete response rate is 74% for CAH and 72% for grade 1 Stage I EC following six months or longer of oral progestin treatment, and 68% following progesterone IUD treatment. More recent studies tended to show higher response rates, possibly reflecting improving standards of treatment over time.

Previous reviews on the subject included studies with very low numbers of patients. Some reviews did not control for study quality by failing to pose restrictions on treatment duration [43-45, 65], by not requiring radiological staging for EC [44, 45], or not limiting outcome to pathological complete response [43-45]. Our analysis addressed these concerns by limiting inclusion to studies involving at least ten patients in either treatment arm and requiring a period of treatment of at least six months, allowing reasonable time for complete response. We predefined diagnosis and outcome criteria in an effort to minimise heterogeneity between studies. However, the sensitivity analysis allowed assessment of the impact of these somewhat arbitrary decisions.

Oral progestin treatment was effective in achieving pathological complete response in at least two in three patients across all included studies, and for patients with EC intrauterine progestin appeared similarly effective. However, of patients that responded, one in five subsequently relapsed at a mean follow-up of two years following the end of progestin treatment. A small proportion of patients worsened from CAH to Stage I EC on oral progestins. When analysis was extended to include studies with smaller numbers of eligible patients or shorter treatment period, the estimates obtained for response to both oral (CAH and EC patients) and intrauterine progestins (EC patients) were lower, due to low response rates observed in several of the smaller studies. The transparency of study procedures in several of these smaller studies was less well developed compared to the larger studies included in our main analyses, indicating possible methodological problems. This supports our approach in limiting analysis to larger, higher-quality studies.

Results from the extended analysis suggest that up to 84% of patients with CAH may achieve a pathological complete response with intrauterine progestin treatment, a higher response rate than that obtained with oral progestin treatment (61%). This finding is comparable to a 90% regression rate to intrauterine progestin in CAH patients reported by Gallos and colleagues, a review that included both partial and complete response as the outcome variable [43]. Intrauterine progestin may be a more effective option for conservative treatment of patients with CAH, and may avoid the systemic side-effects commonly reported under oral progestin treatment such as weight gain; however, further studies are required to compare the effectiveness and adverse effect profiles of these two routes of progestin administration. Among patients with CAH treated with oral progestin, the estimated pathological complete response rate from our main analysis is better than the regression rate (including both complete and partial response) reported in the systematic review by Gallos and colleagues (74% vs. 69%). This may be due to the fact that our analysis includes only CAH patients

288 treated for six months or longer, whereas Gallos et al. did not pose any treatment duration
289 criteria in their analysis. Our findings suggest that treatment duration of at least six months
290 for CAH patients should be recommended to obtain optimal response rates.

291 Among patients with grade 1 Stage 1 EC, we obtained an estimated pathological complete
292 response rate to oral progestin slightly lower than that reported in a previous review of nine
293 small retrospective case series (72% vs. 79%) [44] and a recent review of eleven small
294 studies (72% vs 81%) [66]. Neither of these reviews, however, limited the outcome variable
295 to complete response, nor excluded patients that had additional treatment apart from systemic
296 progestin, which may explain the higher response rate reported in these reviews.While the
297 majority of patients in our analysis achieved a pathological complete response to oral
298 progestin treatment, relapses and disease progression were observed. Overall, 6/219 (2.7%)
299 patients progressed from CAH to EC, and 32/159 (20%) of patients who initially achieved a
300 pathological complete response subsequently relapsed at a mean of two years following the
301 end of treatment. Some case reports not included in this analysis due to small sample size
302 even document a patient progressing from Stage I to Stage IV EC under progestin treatment
303 [67], and development of EC one and four years after patients were treated with IUD-
304 delivered progestin for non-malignant causes [68, 69]. The data on risk of persistent or
305 progressive disease or relapse needs to be discussed with patients considering progestin
306 treatment.

307 Insufficient reported information was available from included studies about clinical
308 characteristics or treatment details of those patients who relapsed to allow analysis of factors
309 associated with relapse. Smaller doses of oral progestin treatment [32, 37], obesity [70], and a
310 history of anovulation or sporadic ovulation [32, 37] have been suggested by some authors as
311 factors to consider. A study by Penner and colleagues did not find a difference in response

rate depending on patients age (<35 years or 35-48 years); however, there was a trend for patients with BMI <35 to have higher response rates ($p<0.10$) [71]. There is insufficient reported data from studies included in our analysis to assess trends with increasing age. Of patients included in our analysis who relapsed, three of six received a second course of oral progestins and achieved another pathological complete response. Thus, further conservative treatment may still be used for patients who relapse.

Limitations

The present analysis is limited by the observational study design and small sample sizes of included studies, which used different drugs, dosages, regimens, and follow-up durations. There is also limited information on patients clinical and demographic characteristics, thus prohibiting assessment of factors associated with response or relapse. No randomised controlled trials were available. Given the complex results reported in this meta-analysis and the lack of evidence for factors associated with response to oral or intrauterine progestin treatment, further prospective studies are needed, which should collect detailed demographic and clinical data. Two non-randomised open label Phase II clinical trials are currently underway to examine the efficacy of levonorgestrel-releasing (LNG) IUD in patients with endometrial hyperplasia (including hyperplasia with atypia) or grade 1 endometrioid endometrial cancer (ClinicalTrials.gov Identifier: NCT01234818, NCT00788671) [72]. A difficulty with conducting randomised trials directly comparing conservative treatment with the standard of definitive surgery, is the ethical dilemma posed by allocating patients to a treatment associated with a significant risk of nonresponse. A select group of patients who are unsuitable for a hysterectomy (patients who still desire fertility, patients unfit for major surgery for medical reasons) are suitable candidates for conservative treatment. Randomised

trials on the efficacy of oral and IUD-delivered treatment are urgently warranted and will require close supervision of experienced gynaecological oncologists.

Conflict of Interest

All authors have declared no conflicts of interest.

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Figure 1: Study selection and exclusion process

†Complex atypical endometrial hyperplasia ‡Grade 1 Stage I Endometrial adenocarcinoma

552 Table 1: Characteristics of studies included in the systematic review and meta-analysis

Oral progestin treatment							
Reference	Design	No. of patients†	CAH	EC	Treatment(n), duration	Outcome	Follow-up
Ferenczy 1989	Prospective cohort	20	20	-	Daily oral MPA 20mg(20), 6 months	Histological response, recurrence of disease	Mean 84 months, range 48-144 months
Randall 1997	Retrospective case series	10	10	-	Daily oral MPA 10-30mg(4) or daily oral Megace 80-160mg(5) or daily oral Megace 40mg for 4 months then daily oral MPA for 12 months(1), 6-12 months	Histological response, pregnancy and hysterectomy rates	Mean 48.8 months, range 27-79 months
Jobo 2001	Retrospective comparative study	20	20	-	Daily oral MPA 400mg(8) or cyclic MPA 10mg daily/14 days(12), 6 months	Histological response, pregnancy rates, recurrence of disease	Mean 66 months, range 8-281 months
Kaku 2001	Retrospective case series	10	10	-	Daily oral MPA 400-600mg(10), 6-23 months	Histological response, pregnancy rates, recurrence of disease	Mean 43.2 months, range 17-96 months
Ota 2005	Retrospective case series	10	-	10	Daily oral MPA 600mg(10), 6-12 months	Histological response, pregnancy and hysterectomy rates, recurrence of disease	Mean 48.6 months, range 13-127 months
Minaguchi 2007	Retrospective case series	25	11	14	Daily oral MPA 2.5 - 600mg(25), 6-18 months	Histological and immunohistochemical response, pregnancy and hysterectomy rates, recurrence of disease	Mean 44.9 months, range 12-102 months
Ushijima 2007	Multicentre prospective case series	39	17	22	Daily oral MPA 600mg(39), 6-12 months	Histological response, toxicity, pregnancy rate, progression-free interval	36 months
Wheeler 2007	Retrospective cohort study	12	12	-	Oral progestin(12), dose/regimen not reported, 6-24 months	Histological response	Mean 11.6 months, median 11 months, range 6-24 months
Eftekhar 2009	Prospective case series	21	-	21	Daily oral Megace 160-320mg(21), 6-12 months (mean 8.85)	Histological response, pregnancy and hysterectomy rate, recurrence of disease	Mean 48 months, median 42 months, range 18-84 months
Hahn 2009	Retrospective case series	35	-	35	Daily oral MPA 250-1500mg (20) or daily oral Megace 160mg(8) or both(7), 6-12 months	Histological and immunohistochemical response, recurrence	Median 39 months, range 6-108 months

Oral progestin treatment

Reference	Design	No. of patients†	CAH	EC	Treatment(n), duration	Outcome	Follow-up
Yu 2009	Retrospective case series	17	17	-	Daily oral MPA 100-500mg(17), 6 months or more	Histological and immunohistochemical response, pregnancy rates, recurrence of disease	Mean 34.6 months, range 7-114 months (for complete responders)

Intrauterine progestin treatment

Reference	Design	No. of patients	CAH	EC	Treatment(n), duration	Outcome	Follow-up
Montz 2002	Prospective pilot cohort study with historical control cohort	11	-	11	Progesterone-releasing IUD 65mcg/day(11), 6-12 months	Histological response, postoperative complications avoided, recurrence rates	Mean 19.4 months, range 6-36 months
QCGC series 2011	Unpublished retrospective case series	11	-	11	Levonorgestrel-releasing IUD (11), 20mcg/day, 6 months or more	Histological response	Mean 24.7 months, range 7-71 months

Abbreviations CAH: complex atypical endometrial hyperplasia EC: endometrial adenocarcinoma

MPA: medroxyprogesterone acetate Megace: megestrol acetate

†Represents the number of women that were extracted from each study, fulfilling selection criteria for this meta-analysis

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555 Table 2: Summary proportion of patients with pathological complete response

	Response rate (95% CI)				
	Primary analysis			Extended analysis	
	Oral	IUD		Oral	IUD
CAH	74% (65 - 81%)	-	-	61% (54 - 68%)	84% (71 - 94%)
EC	72% (62 - 80%)	68% (45 - 86%)	-	66% (59 - 73%)	46% (29 - 63%)

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557 Abbreviations CAH:complex atypical endometrial hyperplasia; EC: endometrial adenocarcinoma;

558 IUD: intrauterine device

559 Figure 2: Pathological complete response to oral and intra-uterine device delivered progestin
560 treatment (Weighted mean and exact binomial 95% confidence interval)

561 Abbreviations CAH: complex atypical endometrial hyperplasia; EC: endometrioid
562 adenocarcinoma; IUD: intra-uterine device