Fertility-preserving treatment for stage IA endometrial cancer: a systematic review and meta-analysis

Yukio Suzuki, MD, PhD; Jennifer S. Ferris, PhD; Ling Chen, MD, MPH; Shayan Dioun, MD; John Usseglio, MPH; Koji Matsuo, MD, PhD; Xiao Xu, PhD; Dawn L. Hershman, MD; Jason D. Wright, MD

OBJECTIVE: The increasing use of fertility-preserving treatments in reproductive-aged patients with early-stage endometrial cancer necessitates robust evidence on the effectiveness of oral progestins and levonorgestrel-releasing intrauterine device. We conducted a systematic review and meta-analysis to examine the outcomes following these 2 primary progestin-based therapies in reproductive-aged patients with early-stage endometrial cancer.

DATA SOURCES: We conducted a systematic review of observational studies and randomized controlled trials following the Cochrane Handbook guidance. We conducted a literature search of 5 databases and 1 trial registry from inception of the study to April 16, 2024.

STUDY ELIGIBILITY CRITERIA: Studies reporting complete response within 1 year in reproductive-aged patients with clinical stage IA endometrioid cancer undergoing progestin therapy treatment were included. We used data from both observational and randomized controlled studies.

STUDY APPRAISAL AND SYNTHESIS METHODS: The primary exposure assessed was the type of progestational treatment (oral progestins or LNG-IUD). The primary outcome was the pooled proportion of the best complete response (CR) within 1 year of primary progestational treatment. We performed a proportional meta-analysis to estimate the treatment response. Sensitivity analyses were performed by removing studies with extreme effect sizes or removing grade 2 tumors. The risk of bias was assessed in each study using the Joanna Briggs Institute critical appraisal checklist.

RESULTS: Our analysis involved 754 reproductive-aged patients diagnosed with endometrial cancer, with 490 receiving oral progestin and 264 receiving levonorgestrel-releasing intrauterine device as their primary progestational treatment. The pooled proportion of the best complete response within 12 months of oral progestin and levonorgestrel-releasing intrauterine device treatment were 66% (95% CI, 55—76) and 86% (95% CI, 69—95), respectively. After removing outlier studies, the pooled proportion was 66% (95% CI, 57—73) for the oral progestin group and 89% (95% CI, 75—96) for the levonorgestrel-releasing intrauterine device group, showing reduced heterogeneity. Specifically, among studies including grade 1 tumors, the pooled proportions were 66% (95% CI, 54—77) for the oral progestin group and 83% (95% CI, 50—96) for the levonorgestrel-releasing intrauterine device group. The pooled pregnancy rate was 58% (95% CI, 37—76) after oral progestin treatment and 44% (95% CI, 6—90) after levonorgestrel-releasing intrauterine device treatment.

CONCLUSION: This meta-analysis provides valuable insights into the effectiveness of oral progestins and levonorgestrel-releasing intrauterine device treatment within a 12-month timeframe for patients with early-stage endometrial cancer who desire to preserve fertility. These findings have the potential to assist in personalized treatment decision-making for patients.

Key words: endometrial cancer, fertility-preserving treatment, hormonal therapy, levonorgestrel-releasing intrauterine device, progestin

From the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY (Suzuki, Ferris, Chen, Dioun, Xu, Hershman, and Wright); Department of Gynecology, Kanagawa Cancer Center, Yokohama, Kanagawa, Japan (Suzuki); Joseph L. Mailman School of Public Health, Columbia University, New York, NY (Ferris, Xu, and Hershman); Herbert Irving Comprehensive Cancer Center, New York, NY (Dioun, Hershman, and Wright); Department of Obstetrics and Gynecology, New York Presbyterian Hospital, New York, NY (Dioun, Hershman, and Wright); Augustus C. Long Health Sciences Library, Columbia University Irving Medical Center, New York, NY (Usseglio); and University of Southern California, Los Angeles, CA (Matsuo).

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Corresponding author: Jason D. Wright, MD. jw2459@columbia.edu

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AJOG at a Glance

What was this study conducted?

We conducted a systematic review and meta-analysis to examine outcomes following these 2 primary progestin-based therapies in reproductive-aged patients with early-stage endometrial cancer.

Key findings

Our analysis included 754 patients of reproductive age diagnosed with endometrial cancer, 490 of whom received oral progestin and 264 received LNG-IUD as their primary progestational therapy. The pooled proportion of the best CR within 12 months with oral progestin and LNG-IUD treatment were 66% (95% CI, 55−76) and 86% (95% CI, 69−95), respectively.

What does this add to what is known?

This meta-analysis exclusively concentrated on reproductive-aged patients pathologically assessed within 12 months of treatment initiation, providing relevant evidence for individuals with early-stage endometrial cancer who wish to preserve fertility. Moreover, our data provide the individual effectiveness of the 2 primary types of conservative treatment.

Introduction

The incidence of endometrial cancer is rising, particularly among younger patients. In the United States, approximately 12% of newly diagnosed endometrial cancers occur in women under the age of 50,[1] and the increasing incidence of endometrial cancer is particularly occurring among women in their 30s of age in the past decades.[2] The rising rate of endometrial cancer in young women is likely influenced by a number of factors including the increased prevalence of obesity and trends toward delayed childbearing.[3]

While the standard of care for endometrial cancer is total hysterectomy, the procedure results in loss of fertility. For young women who have not completed childbearing, hormonal therapy is an alternative treatment option.[4] Hormonal therapy with progestins is most frequently utilized in patients with low-grade endometrioid tumors with minimal myometrial invasion.[5−7]

Prior studies have suggested that complete response (CR) rates to hormonal treatment range from 50% to 80%, among patients with early-stage tumors.[5,8−10] Patients treated with progestins are typically monitored with endometrial sampling every 3 months.[4] While data are limited, hysterectomy is typically recommended for patients with persistence or progression of disease after 6 to 12 months of treatment.[4,5]

Oral progestins and the levonorgestrel-releasing intrauterine device (LNG-IUD) have both been considered for hormonal therapy for endometrial cancer.[4,5] Guidelines from National Comprehensive Cancer Network (NCCN) state that LNG-IUD is the preferred regimen,[4] while other progestational agents, including megestrol acetate and medroxyprogesterone acetate, are listed as other recommended regimens. However, there is a lack of high-quality evidence describing the efficacy of the different progestin-based therapies and no randomized controlled trials (RCTs) to compare outcomes of the 2 regimens.[5]

Objective

Given the limited comparative data on the currently available progestin therapies, we performed a systematic review and meta-analysis to describe the efficacy of oral progestins and the LNG-IUD in reproductive-aged patients with early-stage endometrial cancer.

Methods

This systematic review was conducted in accord with the Cochrane Handbook.[11] This systematic review and meta-analysis of observational studies and randomized controlled trials followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting guidelines.[12] This study protocol was registered in the International Prospective Register of Systematic Reviews under the registration number, CRD42023480405.

Search strategy

A systematic literature search for the meta-analysis was conducted by a Columbia University Health Sciences Library informationist (J.U.) using 5 major databases, including PubMed, Embase, Cochrane Library, Scopus, and Web of Science from inception of the study to April 16, 2024. The strategy comprised a combination of search strings related to intrauterine devices/progestin and endometrial hyperplasia/endometrial cancer. No filters were applied to the search results. In addition to the databases, ClinicalTrials.gov was also searched to identify published data, unpublished data, and ongoing or recently completed clinical trials. We also performed an additional reference search in each initially identified studies. The search strategies appear in Appendix 1.

All studies identified through the search were exported to the citation management software, EndNote (version X9). We conducted a deduplication process within the EndNote library to eliminate any duplicate entries. Subsequently, we imported the deduplicated library into Covidence (Covidence, Melbourne, Australia)[13] for screening, assessment, and data extraction procedures for the meta-analysis.

Eligibility criteria

We included (1) clinical stage IA endometrioid cancer patients <50 years of age per the World Health Organization's age cutoff for reproductive age, (2) studies examining patients with endometrial cancer undergoing conservative, nonsurgical progestin therapy treatment, (3) studies with at least 10 cases of endometrial cancer in a treatment group, (4) studies that included the CR proportion within 1 year among patients treated with oral progestins or LNG-IUD, and (5) full text papers in English.

We incorporated data from both nonrandomized studies and randomized studies. In this study, we defined data from nonrandomized study as a cohort study.

Exposure and outcome measures

The primary exposure was the type of fertility-preserving treatment (oral progestins or LNG-IUD). The primary outcome was the pooled proportion of the best CR within 12 months of primary fertility-preserving treatment. This time point was selected as the majority of CR event occurring in this timeframe. Secondary outcomes included CR at 6 months from the primary hormonal treatment, number of pregnancies and live births, number of hysterectomies, the number of recurrences among patients who achieved an initial complete response, and venous thromboembolism (VTE), a serious adverse event associated with progestational agents. For obstetric outcomes, the numerator is the number of subjects that each paper provided as pregnancy or live births. The denominator is the number that attempted to pregnancy. We did not consider specific assessment timeframes for the secondary outcomes, except for CR at 6 months. Complete response was defined as cases with pathological assessment of the complete response.

Study selection and data extraction

The title and abstract screening, full-text screening, data extraction, and quality assessment were independently performed by 2 reviewers (Y.S. and J.S.F.). Discrepancies were resolved through discussion between the 2 reviewers, and a third reviewer (J.D.W.) was consulted when necessary. The extracted data included the first author's name, year of publication, country of the study, tumor grade, type of progestin therapy, hormonal regimen, and the use of adjunct therapies such as metformin, gonadotropin-releasing hormone (GnRH) agonist, or transcervical resection (TCR). All outcome measures were also extracted.

Quality assessment

The risk of bias was assessed in each study using the Joanna Briggs Institute (JBI) critical appraisal checklist.[14] The JBI critical appraisal checklist for cohort studies comprises 11 items, with a maximum overall score of 11, aimed at evaluating the methodological quality of a study and its ability to address potential biases in its design. Similarly, the JBI critical appraisal checklist for RCTs consists of 13 items, with a maximum overall score of 13 (Supplemental Tables 1 and 2). Higher scores on these checklists indicate a higher level of study quality.

Data synthesis and statistical analysis

Given the limited number of studies directly comparing oral progestins to LNG-IUD, we performed a proportional meta-analysis to estimate the treatment response associated with each modality. We calculated outcome proportions by dividing the number of patients who experienced the outcome of interest following treatment by the total number of patients who received the treatment. We computed 95% confidence intervals (CIs) using the Clopper-Pearson exact method,[15] which is well-suited for handling small samples and extreme proportions, such as those close to 0% or 100%.

Before conducting the meta-analysis, we applied logit transformation to the proportions. Subsequently, we developed generalized logistic mixed-effect models to estimate the pooled effect,[15] using the metaprop function in R for effect size estimation. Anticipating substantial heterogeneity among the included studies, we employed Hartung-Knapp adjustments for the random-effects model to yield more conservative estimates of the 95% CIs around the pooled proportions.[15–17] We also used I-square statistics to assess inter-study heterogeneity.

As an additional outcome, we calculated the pooled odds ratio (OR) by comparing the best CR within 12 months following LNG-IUD treatment compared with oral progestin treatment, including the 2 studies that had both treatment arms within the same study. We employed the Mantel-Haensel method for pooling and applied Hartung-Knapp adjustments for the random-effects model to calculate the 95% CI around the pooled effect, using the metabin function in R.[15]

Sensitivity analyses were conducted to examine the influence of outlier studies. These analyses focused on the CR proportion within 12 months and secondary outcomes (CR rate at 6 months and the pregnancy rate) and involved the removal of outlier studies that could potentially bias the results. Outlier studies were identified using the leave-one-out method and alternatively by employing a Baujat plot,[15] targeting those contributing the most to the heterogeneity in the meta-analysis results. Additionally, given the potential difference in treatment response by tumor grade, we conducted another sensitivity analysis excluding studies that included grade 2 endometrioid cancer in their cohorts.

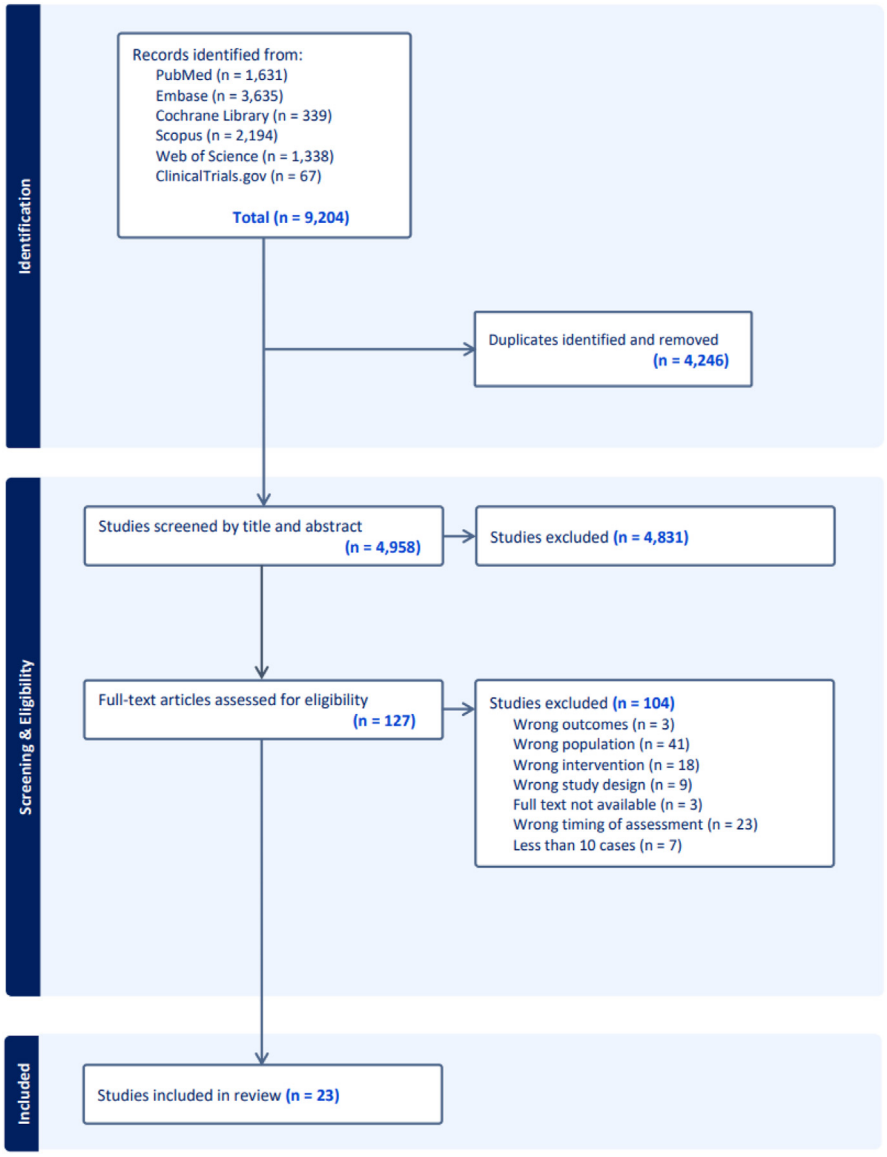
To assess publication bias, we employed a funnel plot and the Egger's test.[15,18] For the LNG-IUD group, where the number of studies was limited, we applied Peter's test to detect bias.[15,19] A 2-sided *P*-value of less than .05 was considered statistically significant. All statistical analyses were performed using R software, version 4.2.2 (R Core Team, Vienna, Austria).

Results

Study selection and characteristics

A total of 9204 records were identified through searches in the 5 databases and ClinicalTrials.gov. After removing 4246 duplicates, we screened the remaining 4958 unique records for inclusion in the meta-analysis. Following a review of titles and abstracts and a subsequent full-text evaluation, 23 studies were eventually extracted (Figure 1, Supplemental Table 3). Among those, 21 studies were categorized as cohort studies,[20–40] while 2 study was an RCT[41] (Table 1). Among the cohort studies, 15 were single-exposure cohort studies.[42] The studies originated from 8 countries, including 3 from Europe (Germany, Italy, and Russia) and 5 from Asia (China, Iran, Japan, Korea, and Taiwan). The dataset encompassed 18 oral progestin treatment arms and 7 LNG-IUD arms across all included studies. Details of the

FIGURE 1
PRISMA flow diagram



adjunctive therapy used are provided in Table 1. Our analysis ultimately involved 754 reproductive-aged patients diagnosed with endometrial cancer, of which 490 received oral progestin and 264 received LNG-IUD as their primary progestational treatment.

Primary outcome

The pooled proportion of the best CR within 12 months of oral progestin treatment was 66% (95% CI, 55–76) (Figure 2). However, a statistically significant between-study heterogeneity was observed (I^2=69%, P<.01). For LNG-IUD treatment, the pooled proportion of the best CR within 12 months was 86% (95% CI, 69–95), and again, a statistically significant between-study heterogeneity was present (I^2=76%, P<.01) (Figure 2).

Secondary outcomes

The pooled proportion of CR at 6 months after oral progestin treatment was 52% (95% CI, 36–67), while for LNG-IUD treatment, it was 75% (95% CI, 43–92) (Figure 3). Following oral progestin treatment, the pooled pregnancy proportion was 58% (95% CI, 37–76), whereas for LNG-IUD treatment, it was 44% (95% CI, 6–90) (Figure 4, A). The pooled live birth proportion after oral progestin treatment was 39% (95% CI, 23–57), whereas for LNG-IUD treatment, it was 24% (95% CI, 2–84) (Figure 4, B).

The pooled proportion for hysterectomy and recurrence after CR following oral progestin treatment were 33% (95% CI, 22–46) and 31% (95% CI, 22–41), respectively (Figure 4, C and D). However, only 1 study addressed the hysterectomy rate with LNG-IUD treatment (Figure 4, C), which did not enable us to calculate the pooled estimate. The pooled proportion of recurrence after CR following LNG-IUD was 14% (95% CI, 5–31). No cases of VTE were reported in the included studies (Figure 4, E).

For the 2 studies that examined both LNG-IUD and oral progestin, we estimated a pooled OR of the best response within 12 months of treatment. Our analysis did not find a statistically significant association between the type of treatment (LNG-IUD vs oral progestin) and achieving CR within 12 months of hormonal treatment (OR 3.54; 95% CI, 0.02–425.28), however, the confidence intervals were wide (Supplemental Figure 1).

Sensitivity and additional analyses

We conducted sensitivity analyses using various methods to remove outliers. The pooled estimate of the best CR within 12 months of oral progestin treatment was 63% (95% CI, 54–72) with the lowest level of heterogeneity observed when applying the leave-one-out method (Table 2). The outcomes for leave-one-out analyses are presented in Supplemental Figure 2, A. Two outliers were identified through the Baujat plot (Supplemental Figure 3, A) and were subsequently removed, resulting in a pooled proportion of 66% (95% CI, 57–73) with an I^2 value of 58% (95% CI, 27–76) (Table 2, Supplemental Figure 4). For LNG-IUD treatment, the pooled estimate of the best CR within

TABLE 1
Characteristics of studies included in final meta-analysis

Study	Year	Country	Tumor grade	Progestin therapy group	Regimen	Adjunct therapy (Met/GnRH/TCR)	Outcomes, number of patients (%)						
							Best complete regression within 12 mo	Complete regression at 6 mo	Pregnancy[a]	Live birth	Hysterectomy	Recurrence after CR	VTE
Cohort studies (n=21)													
Chen	2022	China	G1	Oral	MA, 160 mg/d or MPA, 500 mg/d	None	15/22 (68.1)	NR	3/7 (42.8)	1/7 (14.3)	NR	5/15 (33.3)	0/22 (0.0)
			G1	IUD	IUD	GnRH agonist	37/40 (92.5)	NR	7/27 (25.9)	2/27 (7.4)	NR	5/37 (13.5)	0/40 (0.0)
Jing[e]	2022	China	G1	Oral	MA, 160 mg/d	Met	41/48 (85.4)	39/48 (81.3)	NR	15/48 (31.3)	NR	15/45 (33.3)	0/48 (0.0)
Akhavan[e]	2021	Iran	G1	Oral	Megestrol, 160 mg	None	2/14 (14.3)	2/18 (11.1)	1/5 (20.0)	1/5 (20.0)	9/22 (40.9)	2/7 (28.5)	NR
Andress	2021	Germany	G1	Oral	MA, 160–320 mg/d or MPA, 500 mg/d	None	5/10 (50.0)	5/10 (50.0)	NR	NR	NR	4/5 (80.0)	NR
Fang	2021	China	NR	IUD	IUD	None	15/25 (60.0)	15/25 (60.0)	7/15 (46.7)	3/15 (20.0)	NR	NR	NR
Kuang	2021	China	G1	Oral	MA, 160 mg/d	TCR	29/65 (44.6)	29/65 (44.6)	57/65 (87.7)	53/65 (81.5)	NR	NR	0/65 (0.0)
Novikova	2021	Russia	G1 or G2	IUD	IUD	GnRH agonist	128/139 (92.1)	NR	NR	NR	NR	NR	NR
			G1 or G2	Oral	MPA, 500 mg/d		22/27 (81.5)	NR	NR	NR	NR	NR	NR
Ou[e]	2021	Taiwan	G1	Oral	MA, 160 mg/d or MPA, 500 mg/d	None	31/45 (68.9)	22/45 (48.9)	9/23 (39.1)	9/23 (39.1)	19/45 (42.2)	11/41 (26.8)	NR
Roh	2021	Korea	G1 or G2	Oral	MA, 40–320 mg/d or MPA, 10–400 mg/d	None	8/18 (44.4)	NR	NR	NR	NR	NR	0/18 (0.0)
Casadio[e]	2020	Italy	G1	Oral	MA, 160 mg/d	TCR	34/36 (94.4)	NR	21/34 (61.8)	14/34 (41.1)	NR	4/34 (11.8)	NR
Giampaolino[e]	2019	Italy	G1	IUD	IUD	TCR	11/13 (84.6)	11/13 (84.6)	NR	NR	3/14 (21.4)	2/14 (14.3)	NR
Falcone[e]	2017	Korea	G1 or G2	IUD	IUD	TCR	20/22 (90.9)	20/22 (90.9)	11/12 (91.7)	10/12 (83.3)	NR	2/22 (9.1)	NR
Chen[e]	2016	China	G1	Oral	MA, 160–480 mg/d or MPA, 250–500 mg/d	GnRH agonist (depends on the response)	17/37 (45.9)	17/37 (45.9)	8/33 (24.2)	5/33 (15.2)	10/37 (27.0)	8/37 (21.6)	NR
Mitsuhashi[e]	2016	Japan	G1	Oral	MPA, 400 mg/d	Met	13/19 (68.4)	NR	NR	NR	NR	NR	0/19 (0.0)
Ohyagi-Hara[e]	2015	Japan	G1	Oral	MPA, 400–600 mg/d	None	11/16 (68.8)	NR	1/NA (NA)[b]	1/NA (NA)[b]	NR	NR	NR
Park[e]	2012	Korea	G1	Oral	MA, 160–240 mg/d or MPA, 30–500 mg/d	None	11/12 (91.7)	9/12 (75.0)	3/6 (50.0)	3/6 (50.0)	2/12 (16.7)	3/12 (25.0)	0/12 (0.0)
Pashov[e]	2012	Russia	G1	IUD	IUD	GnRH agonist	11/11 (100.0)[c]	NR	NR	NR	NR	NR	NR

(continued)

TABLE 1
Characteristics of studies included in final meta-analysis *(continued)*

Study	Year	Country	Tumor grade	Progestin therapy group	Regimen	Adjunct therapy (Met/GnRH/TCR)	Outcomes, number of patients (%)					
							Best complete regression within 12 mo	Complete regression at 6 mo	Pregnancy[a]	Live birth	Hysterectomy	Recurrence after CR	VTE
Minig[e]	2011	Italy	G1	IUD	IUD	GnRH agonist	8/14 (57.1)	8/14 (57.1)	1/8 (12.5)	1/8 (12.5)	NR	2/8 (25.0)	0/14 (0.0)
Hahn[e]	2009	Korea	G1	Oral	MA, 160 mg/d or MPA, 250–1500 mg/d	None	22/35 (62.9)	NR	10/12 (83.3)	8/12 (66.7)	17/35 (48.6)	9/22 (40.9)	0/35 (0.0)
Ushijima[e]	2007	Japan	G1	Oral	MPA, 600 mg/d	None	14/22 (63.6)	12/22 (54.5)	4/NA (NA)[b]	3/NA (NA)[b]	3/22 (13.6)	8/14 (57.1)	0/22 (0.0)
Kaku[e]	2001	Japan	G1 or G2	Oral	MPA, 100–800 mg/d	None	8/12 (66.7)	6/12 (50.0)	2/2 (100.0)	1/2 (50.0)	4/12 (33.3)	2/8 (25.0)	0/12 (0.0)
Randomized controlled trials (n=2)													
Xu[d]	2023	China	G1	Oral	MA, 160 mg/d	None	16/28 (57.1)	NR	13/21 (61.9)	5/21 (23.8)	NR	NR	0/31 (0.0)
Yang	2020	China	G1	Oral	MA, 160 mg/d	Met	12/15 (80.0)	NR	NR	NR	NR	NR	NR
			G1	Oral	MA, 160 mg/d	None	6/9 (66.7)	NR	NR	NR	NR	NR	NR

CA, chlormadinone acetate; *CR*, complete regression; *GnRH*, gonadotropin-releasing hormone; *IUD*, levonorgestrel intrauterine device; *MA*, megestrol acetate; *Met*, metformin; *MPA*, medroxyprogesterone acetate; *NA*, not applicable; *NoA*, nomegestrol acetate; *NR*, not reported; *Oral*, oral progestin; *TCR*, transcervical resection; *VTE*, venous thromboembolism.

[a] The denominator is the total number of patients who attempted to conceive; [b] There is no information on the number of patients who attempted to conceive; [c] In this study, the assessment was performed at 12 to 14 months; [d] Another arm with oral progestin and IUD was excluded; [e] A single exposure cohort study.

12 months was 89% (95% CI, 75–96) with the lowest level of heterogeneity using the leave-one-out method (Table 2, Supplemental Figure 2, B). No outliers were identified using the Baujat plot (Table 2, Supplemental Figure 3, B).

When we limited the analysis to the 15 studies exclusively involving grade 1 endometrioid cancer patients treated with oral progestin, the pooled estimate for the best CR within 12 months of treatment was 66% (95% CI, 54–77) (Table 2, Supplemental Figure 5). Among studies involving only grade 1 patients treated with LNG-IUD, the pooled estimate of the best CR within 12 months was 83% (95% CI, 50–96). Sensitivity analyses for the pooled CR proportion at 6 months and pregnancy proportion are also detailed in Table 2.

Publication bias and risk of bias

Funnel plots for the studies included in the analysis of the primary outcome are provided in Supplemental Figure 6. We did not observe publication bias among studies investigating oral progestin (Egger's test, $P=.13$), and similarly, there was no indication of publication bias among studies exploring LNG-IUD (Egger's test, $P=.93$, Peter's test, $P=.12$).

The risk of bias assessment is summarized in Supplemental Tables 1 and 2. The overall score was also described to facilitate the comparison of study quality. Scores ranged from 5 to 9 out of 11. The primary factors that contributed to lower scores included item 1 ("Were the 2 groups similar and recruited from the same population?"), item 2 ("Were the exposures measured similarly to assign people to both exposed and unexposed groups?"), item 5 ("Were strategies to deal with confounding factors stated?"), and item 10 ("Were strategies to address incomplete follow up utilized?") (Supplemental Table 1).

Comment

Principal findings

In our systematic review and meta-analysis, we investigated the effectiveness of 2 primary progestational therapies, oral progestin and LNG-IUD, in treating early-stage endometrial cancer among young patients. Analyzing data from 21

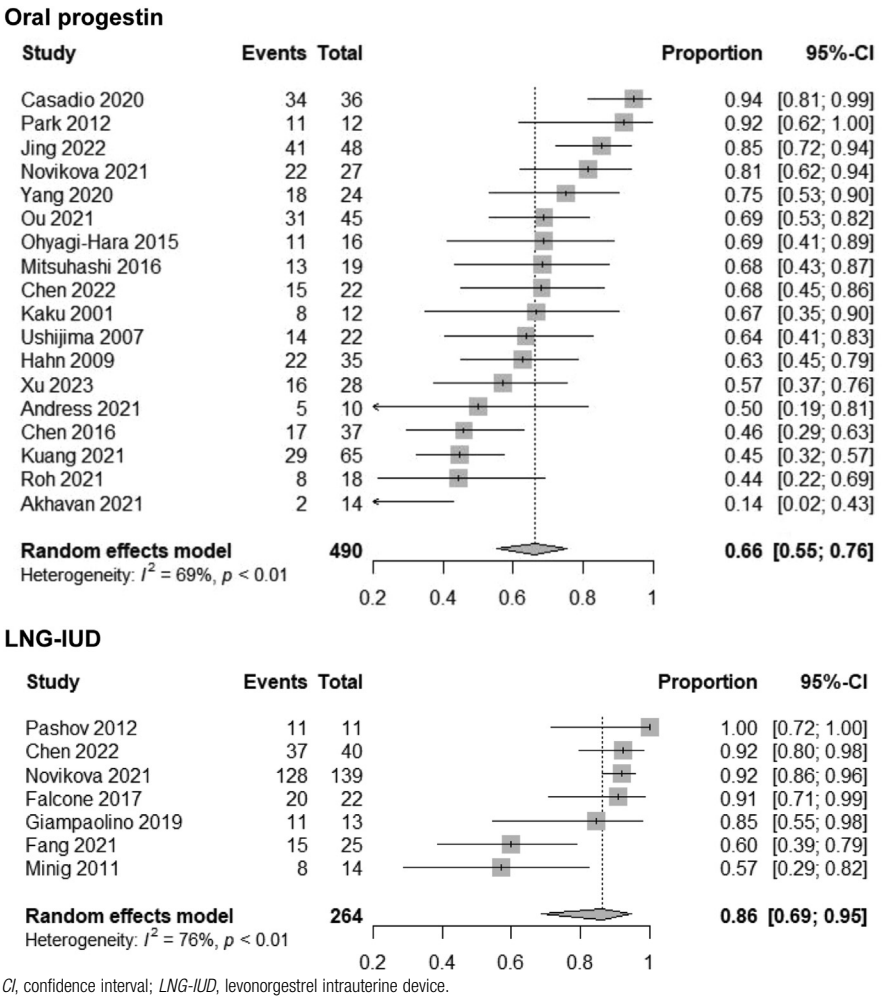
observational studies and 2 small RCT, we observed that the best CR proportion within 12 months of treatment initiation was 66% for oral progestins and 85% for LNG-IUD. Sensitivity analyses reinforced these findings, indicating consistent effect sizes with reduced heterogeneity. These results suggest that a substantial proportion of young patients with low-grade early-stage endometrial cancer can achieve a CR within the first 12 months, irrespective of the primary treatment regimen.

Comparison with existing literature and strengths

Currently, the standard of care for early-stage endometrial cancer involves complete surgical resection, even for those with low-grade tumors and without myometrial invasion. However, this surgical option might not be readily accepted by young patients seeking to preserve fertility. Recognizing this need, guidelines offer alternative options for those wishing to preserve fertility.[4,5,7,43] While no RCT has directly compared these 2 different types of hormonal treatment, both are included as alternatives to surgical intervention in guidelines across various regions, including the US, Europe, the UK, and many Asian countries.[4,5,7,43] The recent update in the NCCN guidelines (version 1.2024) has elevated the level of recommendation for LNG-IUD as a preferred regimen, while conventional oral progestational agents are categorized as other recommended regimens.[4] However, this recommendation does not necessarily account for the emergence of updated high-quality evidence. Notably, intensive surveillance, involving assessments every 3 to 6 months pathologically by either endometrial biopsy, dilation and curettage, or hysteroscopic biopsy,[4,5,7] is imperative to identify resistant or refractory cases to conservative therapy. Also, repeat pelvic magnetic resonance imaging is preferred for patients exhibiting persistent disease after 6 to 9 months of primary progestational therapy.[4]

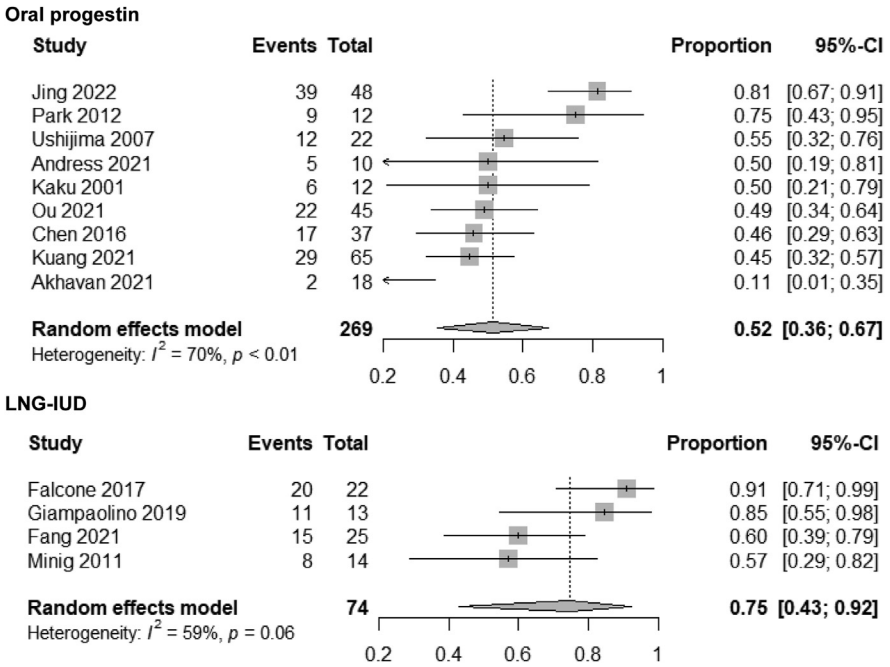
Prior studies examining the efficacy of progestational treatments for early-stage endometrial cancer have reported varying response rates. For instance, Cappelletti's study encompassed 831 patients treated with progestin-based therapies among 42 studies, indicating the pooled CR proportion of 79.9%.[10] However, this study lacked a specific assessment timepoint and did not differentiate the effectiveness based on the type of progestins used. Similarly, Wei *et al* reported in 2017 the pooled CR rate of 71% among 1083 patients undergoing hormone therapy across 28 studies; however, their study included patients both younger and older than 50 years of age, combined patients with cancer and atypical hyperplasia, and lacked a specific assessment timepoint.[44] Another recent meta-analysis examined conservative treatment including systemic or intrauterine progestational therapy and hysteroscopic resection with hormonal therapy. Pooling data from 35 observation studies, the pooled CR rate among 624 patients was 77%. This analysis included patients who were assessed after 12 months of the conservative treatment initiation.[45] A 2021 U.S. prospective trial reported a 54% CR rate among patients treated with LNG-IUD at 12 months of treatment initiation; however, this cohort included postmenopausal patients and had a limited sample size of 15 evaluable cases.[46] As such, while these studies offer insights into progestational treatment outcomes, their inclusion criteria and assessment parameters differ from the specific focus

FIGURE 2
Forest plots showing the best complete response proportion within 12 months-LNG-IUD



CI, confidence interval; *LNG-IUD*, levonorgestrel intrauterine device.

FIGURE 3
Forest plots showing the best complete response proportion at 6 months

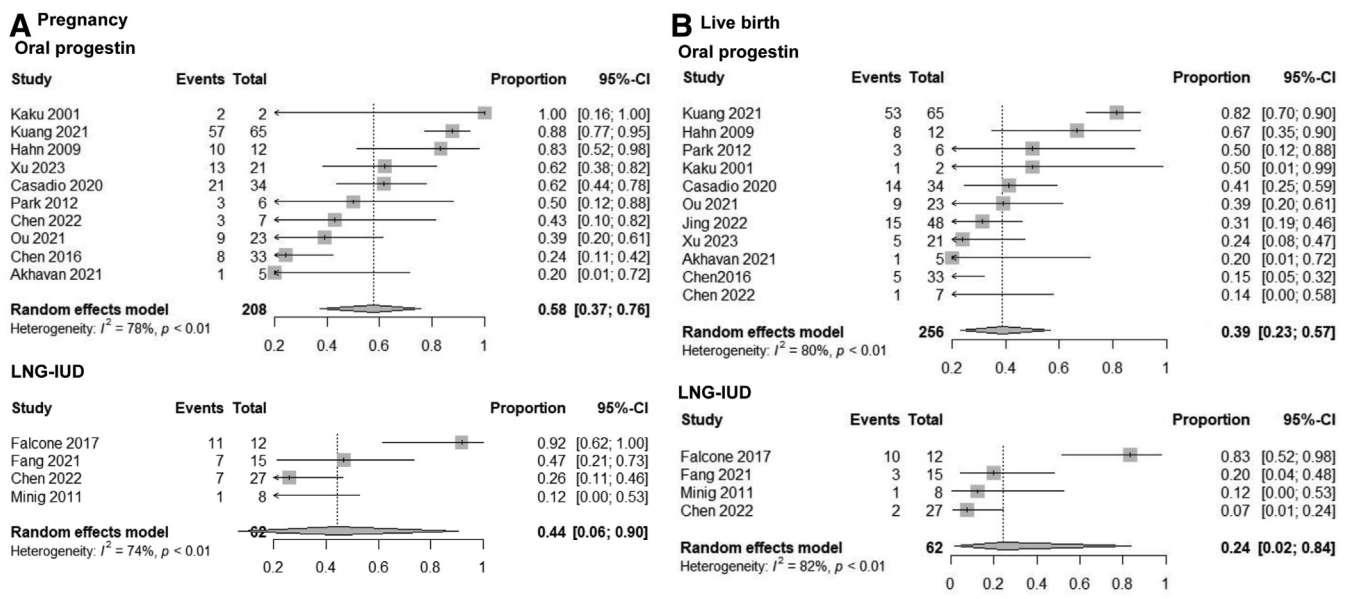


CI, confidence interval; *LNG-IUD*, levonorgestrel intrauterine device.

of our analysis. Our investigation exclusively concentrated on reproductive-aged patients pathologically assessed within 12 months of treatment initiation, providing relevant evidence for individuals with early-stage endometrial cancer who wish to preserve fertility. Moreover, our data provide the individual effectiveness of the 2 primary types of conservative treatment.

There are few comparative meta-analyses looking at the effectiveness of LNG-IUD vs oral progestins among reproductive-aged patients with endometrial cancer. Elassall *et al* reported in 2022 a higher resolution rate in the LNG-IUD group compared with the oral progestin group (OR 2.91, 95% CI, 0.75−11.24) based on 2 studies.[47] However, these 2 studies included pre- and post-menopausal patients.[48,49] Wei et al[44] reported no significant difference in CR rates between patients treated with oral progestin and LNG-IUD, drawing from only 2 studies. However, one of these studies included postmenopausal patients,[49] and the other was limited by a small sample size comprising only 14 cases.[50] Additionally, their comparative meta-analysis included patients with cancer or hyperplasia.[44] In our study, there were few studies directly comparing the effectiveness of oral progestins and LNG-IUD, thus we could not perform a comparative meta-analysis as a primary outcome. While further study

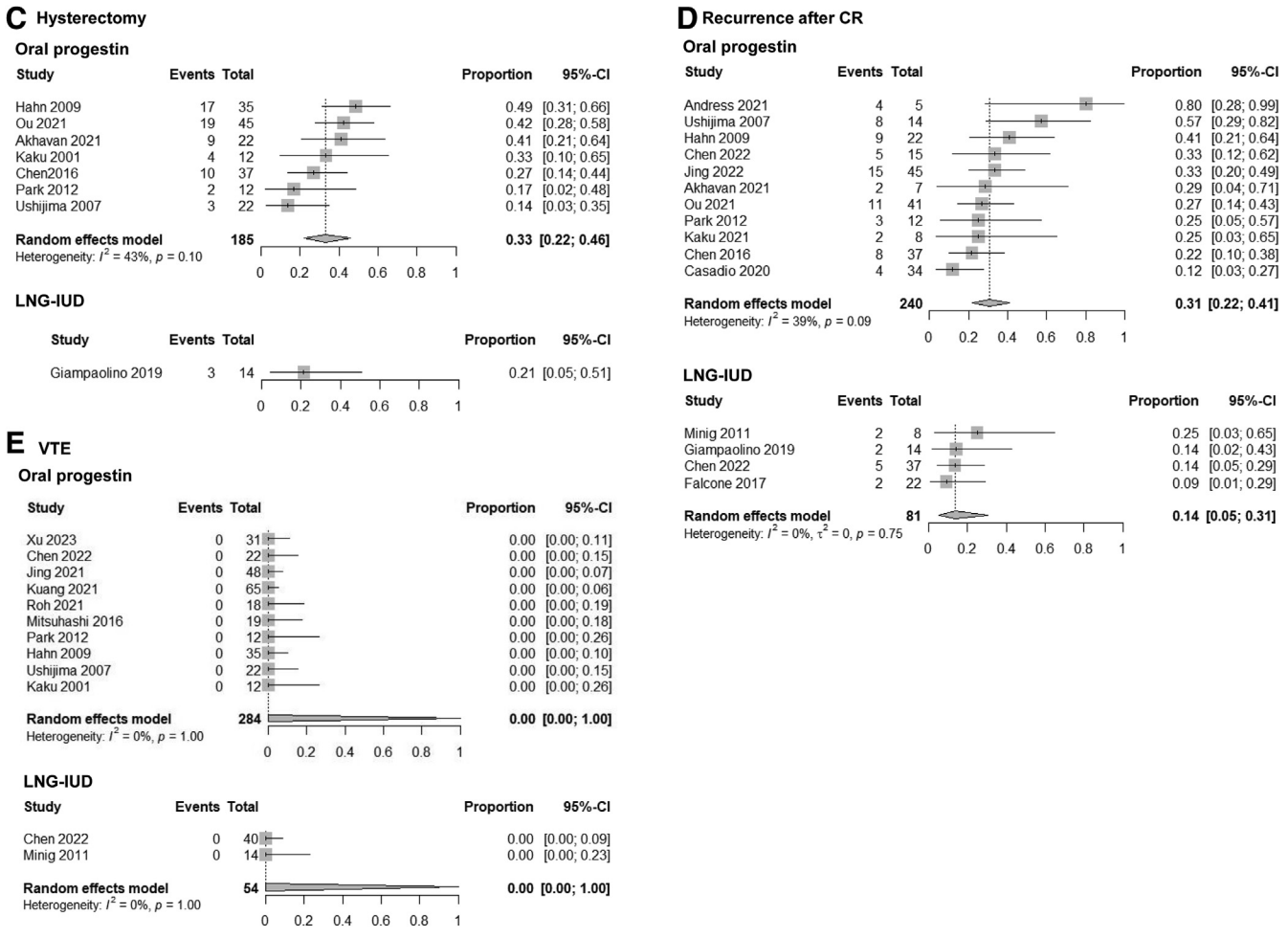
FIGURE 4
Forest plot showing secondary outcomes



A, Pregnancy. **B,** Live birth. **C,** Hysterectomy. **D,** Recurrence after CR. **E,** VTE.

CI, confidence interval; *CR*, complete response; *LNG-IUD*, levonorgestrel intrauterine device; *VTE*, venous thromboembolism.

FIGURE 4
Continued



is clearly needed, based on review of ClinicalTrials.gov, we were unable to identify any ongoing randomized controlled trials comparing the effectiveness of oral progestin and LNG-IUD for premenopausal patients with early-stage endometrial cancer.

A comprehensive meta-analysis involving 826 patients who underwent conservative management for early-stage endometrial cancer reported a 26.7% pregnancy rate and a 20.5% live birth rate among those treated with progestin-based therapy.[10] However, this study did not differentiate outcomes by the type of progestin used, and the data included cases that did not have specific assessment timepoint within 12 months of treatment initiation. In a study by De Rocco *et al*, they reported a pregnancy rate of 56.3% for women treated with oral progestins and 63.1% for women treated with LNG-IUD. Notably, these data included patients with endometrial cancer or hyperplasia.[51] This limited pregnancy rate is also reported in a real-world data in U.S.[52] In our study, we observed comparative pregnancy rates for both primary progestational therapies. However, the limited number of studies including pregnancy outcomes that met our inclusion criteria, particularly for the LNG-IUD group, constrained our ability to robustly analyze pregnancy outcomes.

Several adjunctive agents aimed at enhancing the effectiveness of primary progestational treatment have been reported in the literature. Metformin, known for its antiproliferative effects on endometrial cells, has been considered a promising adjunctive agent with progestin-based therapy for endometrial cancer.[53,54] In our meta-analysis, we did not perform subgroup analysis by metformin use because only 2 studies in the oral progestin group included metformin. Operative hysteroscopy with resection has shown promise as a preferred endometrial sampling method, with high remission rates reported in a 2019 meta-analysis of 65 studies, although these data included case with hyperplasia or endometrial cancer.[55] Our meta-analysis only included 2 studies in each progestational treatment group using operative

TABLE 2
Sensitivity analysis for the pooled CR rate and the pregnancy rate

	Oral progestin				LNG-IUD			
Outcomes	**n**	**Proportion [95% CI]**	**I^2 [95% CI]**	***P***	**n**	**Proportion [95% CI]**	**I^2 [95% CI]**	***P***
Primary outcome (the best CR proportion within 12 mo)								
Overall estimated pooled CR	18	0.66 [0.55; 0.76]	69 [50, 81]	<.01	7	0.86 [0.69; 0.95]	76 [50, 89]	<.01
Leave-one-out[a]	17	0.63 [0.54; 0.72]	64 [40, 79]	<.01	6	0.89 [0.75; 0.96]	62 [8, 84]	.02
Removal of outliers	16	0.66 [0.57; 0.73]	58 [27, 76]	<.01	NA	NA	NA	NA
Removal of studies including Grade 2	15	0.66 [0.54; 0.77]	71 [52, 83]	<.01	5	0.83 [0.50; 0.96]	64 [4, 86]	.03
Secondary outcome (CR proportion at 6 mo)								
Overall estimated pooled CR	9	0.57 [0.34; 0.78]	81 [64, 90]	<.01	4	0.75 [0.43; 0.92]	59 [0, 86]	.06
Leave-one-out[a]	8	0.46 [0.36; 0.57]	36 [0, 72]	.14	3	0.65 [0.35; 0.87]	24 [0, 92]	.27
Removal of outliers	7	0.49 [0.41; 0.58]	0 [0, 71]	.70	NA	NA	NA	NA
Secondary outcome (Pregnancy)								
Overall estimated pooled rate	10	0.58 [0.37; 0.76]	78 [60, 88]	<.01	4	0.44 [0.06; 0.90]	74 [28, 91]	<.01
Leave-one-out[a]	9	0.51 [0.34; 0.68]	55 [5, 79]	.02	3	0.30 [0.10; 0.62]	36 [0, 80]	.21
Removal of outliers	NA	NA	NA	NA	NA	NA	NA	NA

The pregnancy rate was defined as the number of patients who were able to conceive divided by the number of patients who attempted to become pregnant.

P-value was tested by the wald test.

CI, confidence interval; *CR*, complete response; *LNG-IUD*, levonorgestrel intrauterine device; *NA*, not applicable.

[a] All outcomes by the leave-one-out are shown in Supplemental Figures. The pattern of the least I-square was selected in this table.

hysteroscopy, which precluded us from conducting subgroup analyses. Additionally, the efficacy of GnRH agonists as adjunctive treatment has been documented in several studies.[56] An investigation examining the synergistic effects of GnRH agonists with LNG-IUD or aromatase inhibitors reported a remarkable CR rate of 93.3% among patients with endometrial cancer, although they included the case that assessed after 12 months.[56] However, our study did not allow for a subgroup analysis among the LNG-IUD group based on GnRH agonists' use due to an insufficient number of studies available for assessment. Adjunctive weight loss measure is an emerging area of interest, warranting further investigation.[57]

Limitations

This meta-analysis is subject to several limitations that merit acknowledgment. First, our stringent inclusion criteria to identify studies examining the effectiveness of 2 primary progestin-based therapies among reproductive-aged patients with early-stage endometrial cancer led to the exclusion of many studies including patients aged 50 or older and/or hyperplasia cases. Additionally, studies lacking specific outcome reporting by treatment type or clearly defined assessment timepoints were excluded, further reducing the pool of eligible studies. Consequently, our analysis is based on a limited number of studies focusing on fertility preservation among patients with early-stage endometrial cancer. Second, there were few studies directly comparing the effectiveness of oral progestins and LNG-IUD, thus we analyzed the proportional meta-analysis for each primary treatment group. Third, our detailed inclusion criteria unintentionally favored studies from certain countries; thus, our findings may not be generalizable to patients from different countries. Fourth, we acknowledge that the majority of studies assessed received lower scores on the JBI critical appraisal tool due to the inapplicability of several items for single exposure cohort studies. Fifth, regional areas of publication are somehow limited to Asia and Europe in this study, and generalizability of the results in the other region such as Northern America is unknown. Sixth, the capabilities of our research team limited us only to consider English language publications, which may have resulted in the undercapture of a small number of studies. Lastly, while every effort was made to provide an inclusive search, we cannot exclude the possibility that a small number of relevant studies were not included.

Conclusions and implications

This meta-analysis provides valuable insights into the effectiveness of oral progestins and LNG-IUD treatment within a 12-month timeframe for patients with early-stage endometrial cancer who desire to preserve fertility. These data may aid in guiding personalized treatment decision for patients. However, comparative studies directly assessing the different types of progestin treatments are necessary to reinforce clinical guidelines. Further study is warranted to consider difference of the oncologic and obstetric outcomes by molecular profiles in each case.

Data availability

The datasets were derived from public sources. The data underlying this study can be shared based on the request to the corresponding author. ■

GLOSSARY

CI Confidence interval
CR Complete response
GnRH Gonadotropin-releasing hormone
LNG-IUD Levonorgestrel-releasing intrauterine device
NCCN National Comprehensive Cancer Network
RCT Randomized controlled trial
TCR Transcervical resection
VTE Venous thromboembolism

REFERENCES

1. SEER*Explorer: an interactive website for SEER cancer statistics [internet]. Surveillance Research Program NCIAcAAfh. 2024. Available at: https://seer.cancer.gov/statistics-network/explorer/. Accessed April 16, 2024.
2. Matsuo K, Mandelbaum RS, Matsuzaki S, et al. Ovarian conservation for young women with early-stage, low-grade endometrial cancer: a 2-step schema. Am J Obstet Gynecol 2021;224:574–84.
3. Suzuki Y, Chen L, Hou JY, et al. Systemic progestins and progestin-releasing intrauterine device therapy for premenopausal patients with endometrial intraepithelial neoplasia. Obstet Gynecol 2023;141:979–87.
4. Network NCC. NCCN clinical practice guidelines version 1.2024 uterine neoplasms. Plymouth Meeting, PA. 2024.
5. Rodolakis A, Scambia G, Planchamp F, et al. ESGO/ESHRE/ESGE guidelines for the fertility-sparing treatment of patients with endometrial carcinoma. Int J Gynecol Cancer 2023;33:208–22.
6. Practice Bulletin No. 149: endometrial cancer. Obstet Gynecol 2015;125:1006–26.
7. Morrison J, Balega J, Buckley L, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol 2022;270:50–89.
8. Gunderson CC, Fader AN, Carson KA, et al. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 2012;125:477–82.
9. Qin Y, Yu Z, Yang J, et al. Oral progestin treatment for early-stage endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer 2016;26:1081–91.
10. Herrera Cappelletti E, Humann J, Torrejón R, et al. Chances of pregnancy and live birth among women undergoing conservative management of early-stage endometrial cancer: a systematic review and meta-analysis. Hum Reprod Update 2022;28:282–95.
11. Higgins JPT, Thomas J, Chandler J, et al, eds. Cochrane handbook for systematic reviews of interventions version 6.4 (updated August 2023). Cochrane. 2023. Available at: www.training.cochrane.org/handbook. Accessed April 16, 2024.
12. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.
13. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at: www.covidence.org. Accessed April 16, 2024.
14. Aromataris E, Munn Z. JBI manual for evidence synthesis. Melbourne, Australia: JBI; 2020.
15. Harrer M, Cuijpers P, Furukawa TA, et al. Doing meta-analysis with R: a hands-on guide, 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021.
16. Borenstein M, Hedges LV, Higgins JPT, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.
17. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003;22:2693–710.
18. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
19. Peters JL. Comparison of two methods to detect publication bias in meta-analysis. JAMA 2006;295:676.
20. Chen J, Cao D, Yang J, et al. Fertility-sparing treatment for endometrial cancer or atypical endometrial hyperplasia patients with obesity. Front Oncol 2022;12:812346.
21. Jing CY, Li SN, Shan BE, et al. Hysteroscopic curettage followed by megestrol acetate plus metformin as a fertility-sparing treatment for women with atypical endometrial hyperplasia or well-differentiated endometrioid endometrial carcinoma. Clin Med Insights Oncol 2022;16:11795549221110522.
22. Akhavan S, Sabet F, Mousavi A-S, et al. Effectiveness of megestrol for the treatment of patients with atypical endometrial hyperplasia or endometrial endometrioid adenocarcinoma (stage IA, well differentiated). J Res Pharm Pract 2021;10:138–43.
23. Andress J, Pasternak J, Walter C, et al. Fertility preserving management of early endometrial cancer in a patient cohort at the Department of Women's Health at the University of Tuebingen. Arch Gynecol Obstet 2021;304:215–21.
24. Fang F, Xu H, Wu L, et al. LNG-IUS combined with progesterone ameliorates endometrial thickness and pregnancy outcomes of patients with early-stage endometrial cancer or atypical hyperplasia. Am J Transl Res 2021;13:5412–9.
25. Kuang J, Sun S, Xu H, et al. Curative effects of hysteroscopic resection combined with progesterone on early-stage endometrial cancer and its prognosis. J BUON 2021;26:1320–6.
26. Novikova OV, Nosov VB, Panov VA, et al. Live births and maintenance with levonorgestrel IUD improve disease-free survival after fertility-sparing treatment of atypical hyperplasia and early endometrial cancer. Gynecol Oncol 2021;161:152–9.
27. Ou YC, Fu HC, Lan J, et al. The role of prolonged progestin treatment and factors predicting successful fertility-sparing treatment for early endometrial endometrioid adenocarcinoma. Eur J Obstet Gynecol Reprod Biol 2021;267:99–104.
28. Roh H, Yoon H, Jeong D, et al. Prognostic factors of oncologic outcomes after fertility-preservative management with progestin in early-stage of endometrial cancer. J Res Med Sci 2021;26:48.
29. Casadio P, La Rosa M, Alletto A, et al. Fertility sparing treatment of endometrial cancer with and without initial infiltration of myometrium: a single center experience. Cancers (Basel) 2020;12:3571.
30. Giampaolino P, Di Spiezio Sardo A, Mollo A, et al. Hysteroscopic endometrial focal resection followed by levonorgestrel intrauterine device insertion as a fertility-sparing treatment of atypical endometrial hyperplasia and early endometrial cancer: a retrospective study. J Minim Invasive Gynecol 2019;26:648–56.
31. Falcone F, Laurelli G, Losito S, et al. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. J Gynecol Oncol 2017;28:e2.
32. Chen M, Jin Y, Li Y, et al. Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. Int J Gynecol Obstet 2016;132:34–8.
33. Mitsuhashi A, Sato Y, Kiyokawa T, et al. Phase II study of medroxyprogesterone acetate plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer. Ann Oncol 2016;27:262–6.
34. Ohyagi-Hara C, Sawada K, Aki I, et al. Efficacies and pregnant outcomes of fertility-sparing treatment with medroxyprogesterone acetate for endometrioid adenocarcinoma and complex atypical hyperplasia: our experience and a review of the literature. Arch Gynecol Obstet 2015;291:151–7.
35. Park H, Seok JM, Yoon BS, et al. Effectiveness of high-dose progestin and long-term outcomes in young women with early-stage, well-differentiated endometrioid

adenocarcinoma of uterine endometrium. Arch Gynecol Obstet 2012;285:473–8.
36. Pashov AI, Tskhay VB, Ionouchene SV. The combined GnRH-agonist and intrauterine levonorgestrel-releasing system treatment of complicated atypical hyperplasia and endometrial cancer: a pilot study. Gynecol Endocrinol 2012;28:559–61.
37. Minig L, Franchi D, Boveri S, et al. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol 2011;22:643–9.
38. Hahn HS, Yoon SG, Hong JS, et al. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. Int J Gynecol Cancer 2009;19:1068–73.
39. Ushijima K, Yahata H, Yoshikawa H, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 2007;25:2798–803.
40. Kaku T, Yoshikawa H, Tsuda H, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett 2001;167:39–48.
41. Yang BY, Gulinazi Y, Du Y, et al. Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial. BJOG 2020;127:848–57.
42. Mathes T, Pieper D. Clarifying the distinction between case series and cohort studies in systematic reviews of comparative studies: potential impact on body of evidence and workload. BMC Med Res Methodol 2017;17:107.
43. Koppikar S, Oaknin A, Babu KG, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with endometrial cancer. ESMO Open 2023;8:100774.
44. Wei J, Zhang W, Feng L, et al. Comparison of fertility-sparing treatments in patients with early endometrial cancer and atypical complex hyperplasia: a meta-analysis and systematic review. Medicine (Baltimore) 2017;96:e8034.
45. Ogunbiyi MO, Oxley S, Graham R, et al. The oncological and reproductive outcomes of fertility-preserving treatments for stage 1 grade 1 endometrial carcinoma: a systematic review and meta-analysis. J Obstet Gynaecol 2024;44:2294329.
46. Westin SN, Fellman B, Sun CC, et al. Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer. Am J Obstet Gynecol 2021;224:191.e1–15.
47. Elassall GM, Sayed EG, Abdallah NA, et al. Levonorgestrel-releasing intrauterine system versus systemic progestins in management of endometrial hyperplasia: a systemic review and meta-analysis. J Gynecol Obstet Hum Reprod 2022;51:102432.
48. Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. Am J Surg Pathol 2007;31:988–98.
49. Hubbs JL, Saig RM, Abaid LN, et al. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol 2013;121:1172–80.
50. Laurelli G, Di Vagno G, Scaffa C, et al. Conservative treatment of early endometrial cancer: preliminary results of a pilot study. Gynecol Oncol 2011;120:43–6.
51. De Rocco S, Buca D, Oronzii L, et al. Reproductive and pregnancy outcomes of fertility-sparing treatments for early-stage endometrial cancer or atypical hyperplasia: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2022;273:90–7.
52. Harrison RF, He W, Fu S, et al. National patterns of care and fertility outcomes for reproductive-aged women with endometrial cancer or atypical hyperplasia. Am J Obstet Gynecol 2019;221:474.e1–11.
53. Chae-Kim J, Garg G, Gavrilova-Jordan L, et al. Outcomes of women treated with progestin and metformin for atypical endometrial hyperplasia and early endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer 2021;31:1499–505.
54. Meireles CG, Pereira SA, Valadares LP, et al. Effects of metformin on endometrial cancer: systematic review and meta-analysis. Gynecol Oncol 2017;147:167–80.
55. Guillon S, Popescu N, Phelippeau J, et al. A systematic review and meta-analysis of prognostic factors for remission in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma. Int J Gynecol Obstet 2019;146:277–88.
56. Chen J, Cao D, Yang J, et al. Oncological and reproductive outcomes for gonadotropin-releasing hormone agonist combined with aromatase inhibitors or levonorgestrel-releasing intra-uterine system in women with endometrial cancer or atypical endometrial hyperplasia. Int J Gynecol Cancer 2022;32:1561–7.
57. Violette CJ, Agarwal R, Mandelbaum RS, et al. The potential role of GLP-1 receptor agonist targeting in fertility-sparing treatment in obese patients with endometrial malignant pathology: a call for research. Expet Rev Anticancer Ther 2023;23:385–95.

Appendix 1. Search strategy

Database	Date searched	Number of results
PubMed (pubmed.gov)	4/16/2024	1631
Embase (ELSEVIER)	4/16/2024	3635
Cochrane Library (cochranelibrary.com)	4/16/2024	339
Scopus (ELSEVIER)	4/16/2024	2194
Web of Science (Core Collection)	4/16/2024	1338
		9137
Grey literature source	**Date searched**	**Number of results**
ClinicalTrials.gov (clinicaltrials.gov)	4/16/2024	67
		67

Database: PubMed (pubmed.gov)
Date Searched: 4/16/2024
Number of Results: 1631
Search strategy:

("Intrauterine Devices"[Mesh] OR "Progestins"[Mesh] OR "Progesterone"[Mesh] OR "Intrauterine device*"[tiab] OR "Intrauterine contracept*"[tiab] OR "Intra-uterine device*"[tiab] OR "Intra-uterine contracept*"[tiab] OR "Intrauterine system*"[tiab] OR "Intra-uterine system*"[tiab] OR "IUD"[tiab] OR "IUDs"[tiab] OR "IUS"[tiab] OR "IUSs"[tiab] OR FibroPlant[tiab] OR Kyleena[tiab] OR Jaydess[tiab] OR Liletta[tiab] OR Levosert[tiab] OR Mirena[tiab] OR Skyla[tiab] OR Progestin*[tiab] OR Progestagen*[tiab] OR Progestational*[tiab] OR Progestogen[tiab] OR Gestagen*[tiab] OR Progesterone*[tiab] OR "Megestrol acetate*"[tiab] OR "Medroxyprogesterone acetate*"[tiab]) AND ("Endometrial Hyperplasia"[Mesh] OR "Endometrial hyperplasia*"[tiab] OR "Endometrial intraepithelial neoplasia*"[tiab] OR "Early endometrial cancer*"[tiab] OR "Early endometrial neoplasia"[tiab] OR "Early stage endometrial cancer*"[tiab] OR "Endometrial histopatholog*"[tiab])

Database: Embase (ELSEVIER — embase.com)
Date Searched: 4/16/2024
Number of Results: 3635
Search strategy:

('intrauterine contraceptive device'/exp OR 'gestagen'/exp OR 'progesterone'/exp OR 'Intrauterine device*':ti,ab OR 'Intrauterine contracept*':ti,ab OR 'Intra-uterine device*':ti,ab OR 'Intra-uterine contracept*':ti,ab OR 'Intra-uterine system*':ti,ab OR 'Intra-uterine system*':ti,ab OR 'IUD':ti,ab OR 'IUDs':ti,ab OR 'IUS':ti,ab OR 'IUSs':ti,ab OR FibroPlant:ti,ab OR Kyleena:ti,ab OR Jaydess:ti,ab OR Liletta:ti,ab OR Levosert:ti,ab OR Mirena:ti,ab OR Skyla:ti,ab OR Progestin*:ti,ab OR Progestagen*:ti,ab OR Progestational*:ti,ab OR Progestogen:ti,ab OR Gestagen*:ti,ab OR Progesterone*:ti,ab OR 'Megestrol acetate*':ti,ab OR 'Medroxyprogesterone acetate*':ti,ab) AND ('endometrium hyperplasia'/exp OR 'Endometrial hyperplasia*':ti,ab OR 'Endometrial intraepithelial neoplasia*':ti,ab OR 'Early endometrial cancer*':ti,ab OR 'Early endometrial neoplasia':ti,ab OR 'Early stage endometrial cancer*':ti,ab OR 'Endometrial histopatholog*':ti,ab)

Database: Cochrane Library (cochranelibrary.com)
Date Searched: 4/16/2024
Number of Results: 339 (Cochrane Reviews, Cochrane Protocols, & Trials)
*Note: 1 of the 340 was a Clinical Answer, which was not a relevant publication type for the meta-analysis, and so it was not included in the search results
Search strategy:

ID	Search	Hits
#1	MeSH descriptor: [Intrauterine Devices] explode all trees	1012
#2	MeSH descriptor: [Progestins] explode all trees	773
#3	MeSH descriptor: [Progesterone] explode all trees	4025
#4	((Intrauterine NEXT device*) OR (Intrauterine NEXT contracept*) OR (Intra-uterine NEXT device*) OR (Intra-uterine NEXT contracept*) OR (Intrauterine NEXT system*) OR (Intra-uterine NEXT system*) OR "IUD" OR "IUDs" OR "IUS" OR "IUSs" OR FibroPlant OR Kyleena OR Jaydess OR Liletta OR Levosert OR Mirena OR Skyla OR Progestin* OR Progestagen* OR Progestational* OR Progestogen OR Gestagen* OR Progesterone* OR (Megestrol NEXT acetate*) OR (Medroxyprogesterone NEXT acetate*)):ti,ab,kw (Word variations have been searched)	17,924
#5	#1 OR #2 OR #3 OR #4	18,102
#6	MeSH descriptor: [Endometrial Hyperplasia] explode all trees	217
#7	((Endometrial NEXT hyperplasia*) OR (Endometrial intraepithelial NEXT neoplasia*) OR (Early endometrial NEXT cancer*) OR (Early endometrial NEXT neoplasia*) OR (Early stage endometrial NEXT cancer*) OR (Endometrial NEXT histopatholog*)):ti,ab,kw (Word variations have been searched)	983
#8	#6 OR #7	983
#9	#5 AND #8	340

Database: Scopus (ELSEVIER — scopus.com)
Date Searched: 4/16/2024
Number of Results: 2194
Search strategy:

TITLE-ABS-KEY(("Intrauterine device*" OR "Intrauterine contracept*" OR "Intra-uterine device*" OR "Intra-uterine contracept*" OR "Intrauterine system*" OR "Intra-uterine system*" OR "IUD" OR "IUDs" OR "IUS" OR "IUSs" OR FibroPlant OR Kyleena OR Jaydess OR Liletta OR Levosert OR Mirena OR Skyla OR Progestin* OR

Progestagen* OR Progestational* OR Progestogen OR Gestagen* OR Progesterone* OR "Megestrol acetate*" OR "Medroxyprogesterone acetate*") AND ("Endometrial hyperplasia*" OR "Endometrial intraepithelial neoplasia*" OR "Early endometrial cancer*" OR "Early endometrial neoplasia" OR "Early stage endometrial cancer*" OR "Endometrial histopatholog*"))

Database: Web of Science (Core Collection — webofscience.com)

Date Searched: 4/16/2024

Number of Results: 1338

Search strategy:

TS=(("Intrauterine device*" OR "Intrauterine contracept*" OR "Intra-uterine device*" OR "Intra-uterine contracept*" OR "Intrauterine system*" OR "Intra-uterine system*" OR "IUD" OR "IUDs" OR "IUS" OR "IUSs" OR FibroPlant OR Kyleena OR Jaydess OR Liletta OR Levosert OR Mirena OR Skyla OR Progestin* OR Progestagen* OR Progestational* OR Progestogen OR Gestagen* OR Progesterone* OR "Megestrol acetate*" OR "Medroxyprogesterone acetate*") AND ("Endometrial hyperplasia*" OR "Endometrial intraepithelial neoplasia*" OR "Early endometrial cancer*" OR "Early endometrial neoplasia" OR "Early stage endometrial cancer*" OR "Endometrial histopatholog*"))

Database: ClinicalTrials.gov (clinicaltrials.gov)

Date Searched: 4/16/2024

Number of Results: 67

Search strategy:

Condition or disease: Endometrial hyperplasia OR Endometrial intraepithelial neoplasia OR Early endometrial cancer OR Early endometrial neoplasia OR Early stage endometrial cancer OR Endometrial histopathology

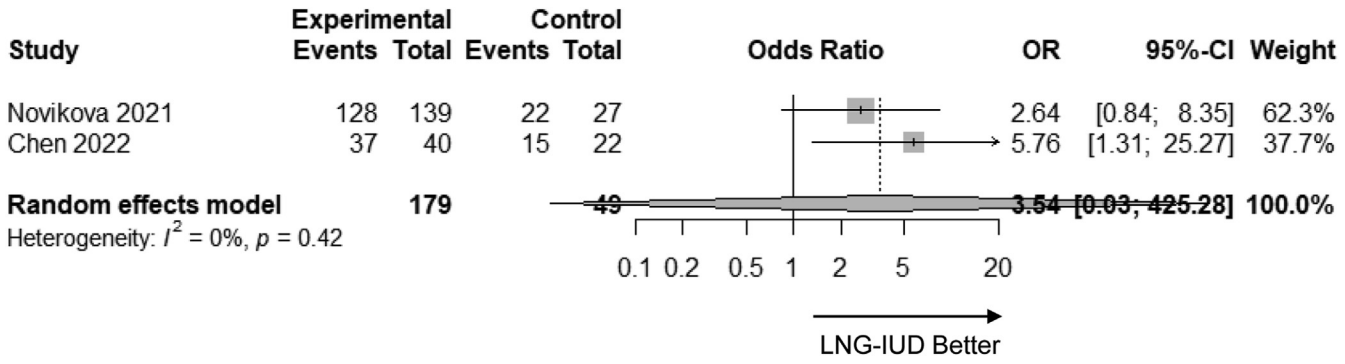
Other terms: Intrauterine device OR Intrauterine contracept OR Intra-uterine device OR Intra-uterine contracept OR Intrauterine system OR Intra-uterine system OR IUD OR IUDs OR IUS OR IUSs OR FibroPlant OR Kyleena OR Jaydess OR Liletta OR Levosert OR Mirena OR Skyla OR Progestin OR Progestagen OR Progestational OR Progestogen OR Gestagen OR Progesterone OR Megestrol acetate OR Medroxyprogesterone acetate

Study type: All studies

Study results: All studies

SUPPLEMENTAL FIGURE 1

Forest plots showing the odds ratio (OR) of the best response rate within 12 months (LNG-IUD vs Oral P)



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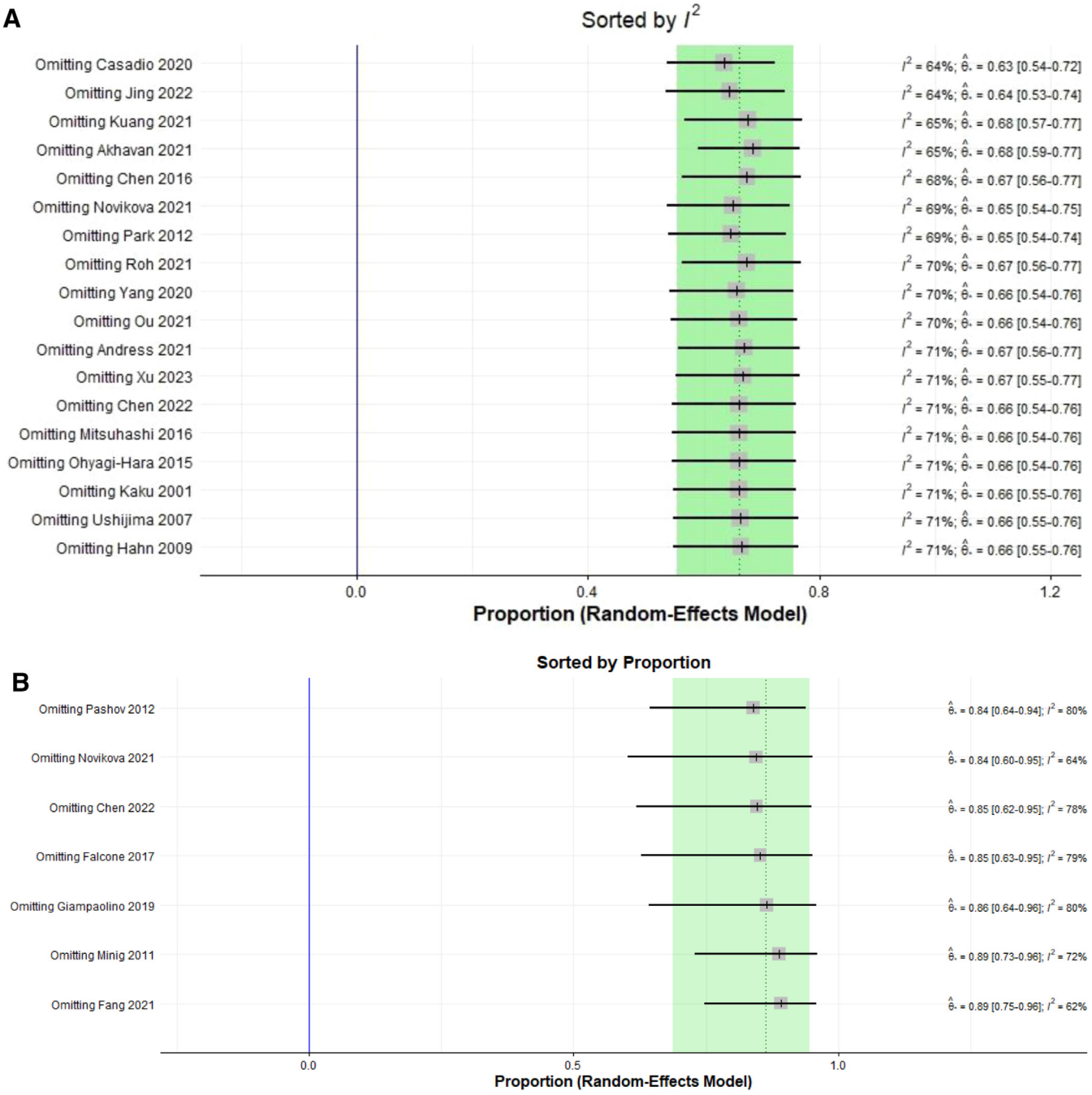
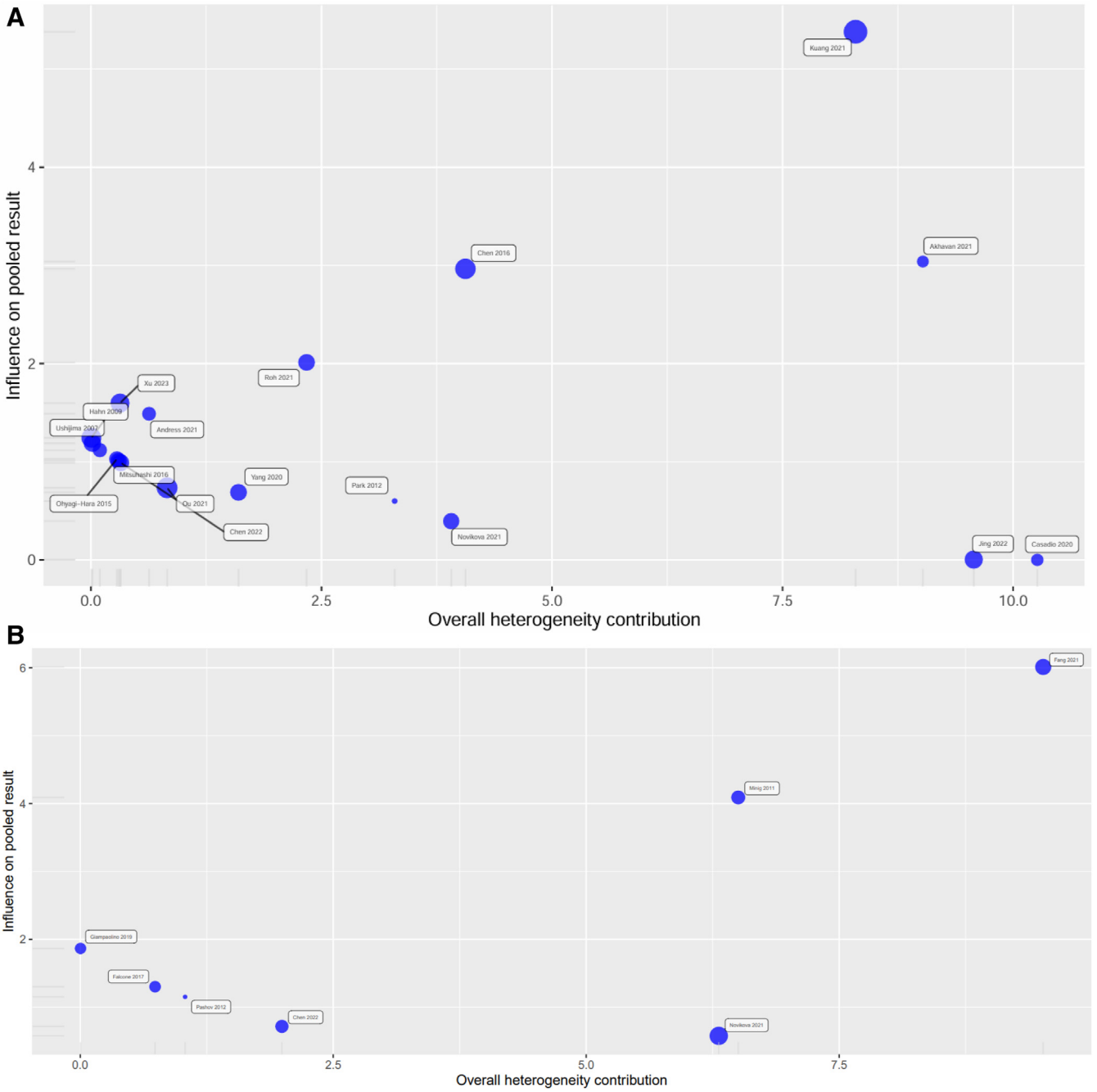
SUPPLEMENTAL FIGURE 2
Sensitivity analyses



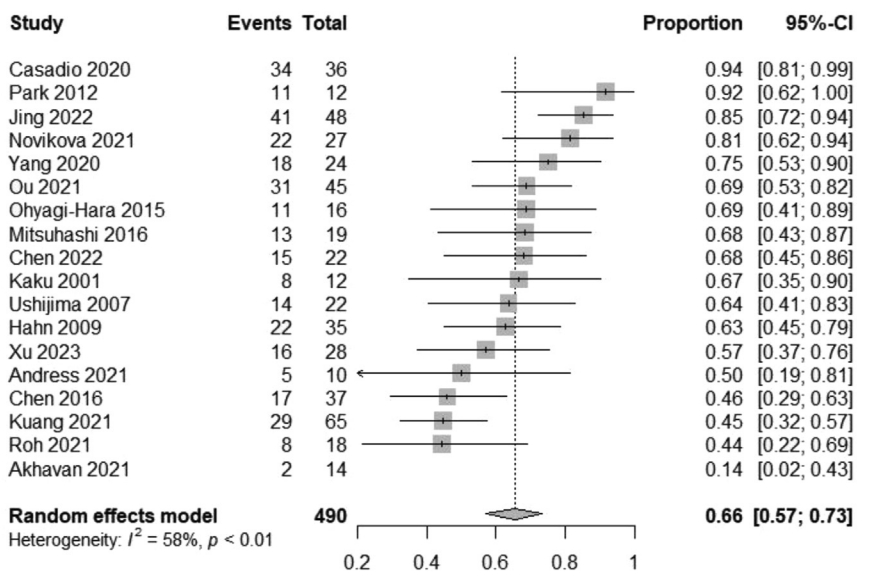
A, Overall effect and I^2 heterogeneity of all meta-analyses among oral progesterone group by leave-one-out method (Sensitivity analysis). **B,** Overall effect and I^2 heterogeneity of all meta-analyses among LNG-IUD group by leave-one-out method (Sensitivity analysis).

SUPPLEMENTAL FIGURE 3
Baujat plots



A, Diagnostic plots to detect studies which overly contribute to heterogeneity among oral progesterone group by a Baujat plot. **B,** Diagnostic plots to detect studies which overly contribute to heterogeneity among LNG-IUD group by a Baujat plot.

SUPPLEMENTAL FIGURE 4
Sensitivity analysis

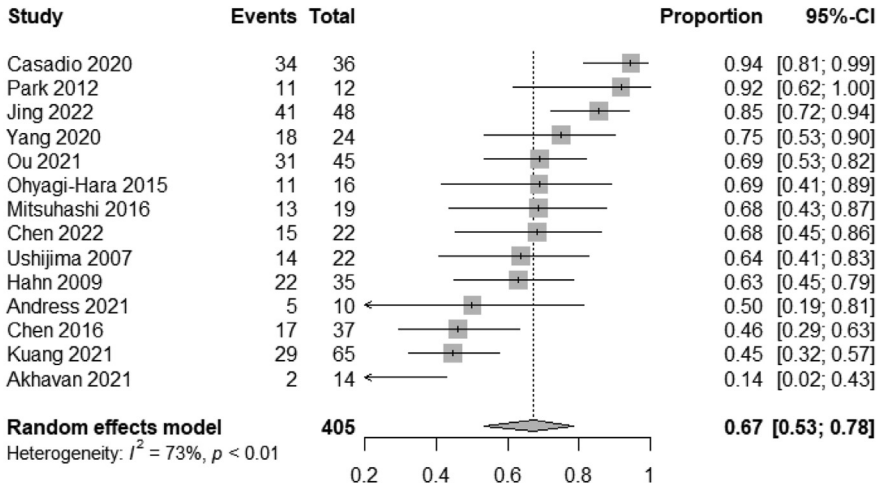


Forest plot after removing outliers among oral progesterone group showing the best complete response rate within 12 months (Sensitivity analysis). Outlying by "find.outliers function". This function can search for all studies with the upper bound of the 95% CI is lower than the lower bound of the pooled effect CI or with the lower bound of the 95% CI is higher than the upper bound of the pooled effect CI.

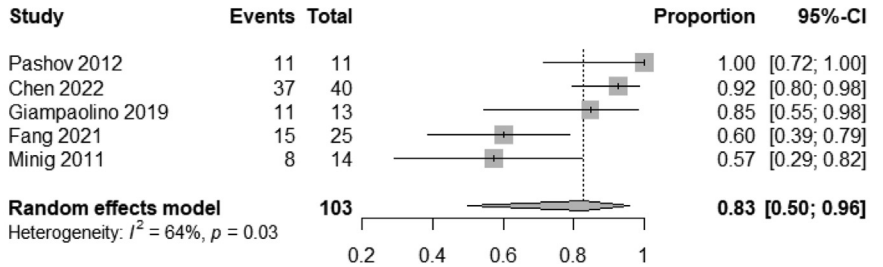
SUPPLEMENTAL FIGURE 5

The best CR proportion within 12 months among studies only including grade 1 endometrioid carcinoma

Oral progestin

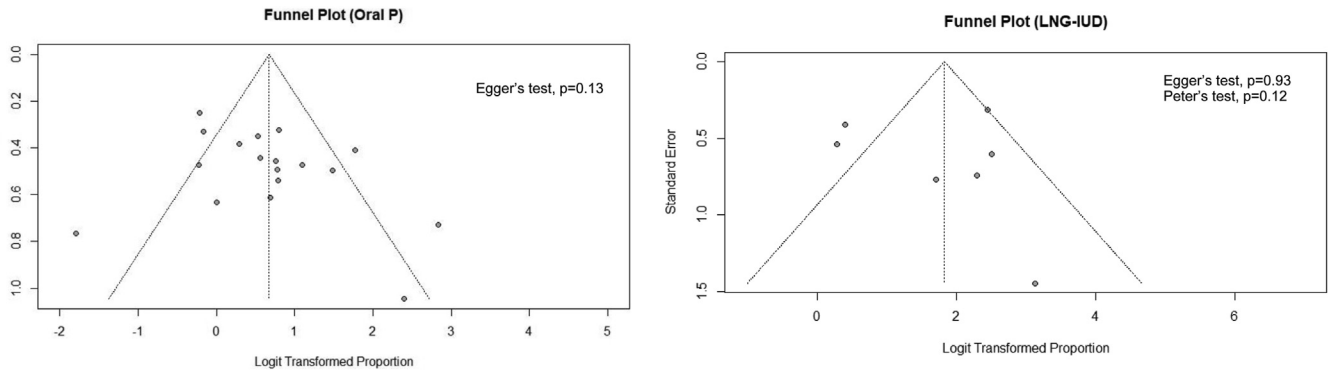


LNG-IUD



SUPPLEMENTAL FIGURE 6

Publication bias funnel plot. For the LNG-IUD group, given that the number of studies was small, Peter's test to detect bias was applied



A 2-sided *P*-value <.05 was considered statistically significant.

SUPPLEMENTAL TABLE 1

Joanna Briggs Institute (JBI) critical appraisal checklist for cohort studies

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Overall
Chen 2022	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	9
Jing 2022	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Akhavan 2021	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Unclear	NA	Yes	6
Andress 2021	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Fang 2021	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	NA	Yes	8
Kuang 2021	NA	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	8
Novikova 2021	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	9
Ou 2021	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Casadio 2020	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Giampaolino 2019	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	No	No	Yes	6
Kim 2019	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Falcone 2017	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Chen 2016	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Mitsuhashi 2016	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Ohyagi-Hara 2015	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Kim 2013	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Park 2012	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Pashov 2012	NA	NA	Yes	No	NA	Yes	Yes	Yes	Yes	NA	Yes	6
Minig 2011	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Hahn 2009	NA	NA	Yes	No	NA	Yes	Yes	Yes	No	NA	Yes	5
Ushijima 2007	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7
Kaku 2001	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	7

Item 1: Were the 2 groups similar and recruited from the same population?

Item 2: Were the exposures measured similarly to assign people to both exposed and unexposed groups?

Item 3: Was the exposure measured in a valid and reliable way?

Item 4: Were confounding factors identified?

Item 5: Were strategies to deal with confounding factors stated?

Item 6: Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?

Item 7: Were the outcomes measured in a valid and reliable way?

Item 8: Was the follow up time reported and sufficient to be long enough for outcomes to occur?

Item 9: Was follow up complete, and if not, were the reasons to loss to follow up described and explored?

Item 10: Were strategies to address incomplete follow up utilized?

Item 11: Was appropriate statistical analysis used?

Overall score is the total number of "Yes" out of 11 items.

SUPPLEMENTAL TABLE 2

Joanna Briggs Institute (JBI) critical appraisal tool for the assessment of risk of bias for randomized controlled trials

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Overall
Xu 2023	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	10
Yang 2020	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	9

Item 1: Was true randomization used for assignment of participants to treatment groups?

Item 2: Was allocation to treatment groups concealed?

Item 3: Were treatment groups similar at the baseline?

Item 4: Were participants blind to treatment assignment?

Item 5: Were those delivering the treatment blind to treatment assignment?

Item 6: Were treatment groups treated identically other than the intervention of interest?

Item 7: Were outcome assessors blind to treatment assignment?

Item 8: Were outcomes measured in the same way for treatment groups?

Item 9: Were outcomes measured in a reliable way?

Item 10: Was follow up complete, and if not, were differences between groups in terms of their follow up adequately described and analyzed?

Item 11: Were participants analyzed in the groups to which they were randomized?

Item 12: Was appropriate statistical analysis used?

Item 13: Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Overall score is the total number of "Yes" out of 13 items.

SUPPLEMENTAL TABLE 3

A list of articles excluded at the full-text screening

Title	Study	Exclusion reason
HE4 is a novel tissue marker for therapy response and progestin resistance in medium- and low-risk endometrial hyperplasia	òrbo 2016	Wrong population
Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility?	Yamagami 2018	Wrong timing of assessment
Adjuvant endocrine treatment with medroxyprogesterone acetate or tamoxifen in stage I and II endometrial cancer—a multicentre, open, controlled, prospectively randomised trial	Von Minckwitz 2002	Wrong population
Metformin in Combination with Progesterone Improves the Pregnancy Rate for Patients with Early Endometrial Cancer	Yuan 2022	Wrong timing of assessment
Significance of progesterone receptors (PR-A and PR-B) expression as predictors for relapse after successful therapy of endometrial hyperplasia: a retrospective cohort study	Sletten 2019	Wrong population
Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: results of a randomized clinical trial	Janda 2021	Wrong study design
Oncological and reproductive outcomes for gonadotropin-releasing hormone agonist combined with aromatase inhibitors or levonorgestrel-releasing intra-uterine system in women with endometrial cancer or atypical endometrial hyperplasia	Chen 2022	Wrong intervention
Clinical implications of morular metaplasia in fertility-preserving treatment for atypical endometrial hyperplasia and early endometrial carcinoma patients	Wu 2022	Wrong population
Clinical Usefulness of Endometrial Cytology in Determining the Therapeutic Effect of Fertility Preserving Therapy	Yoshimura 2022	Wrong population
Efficacy of Levonorgestrel-intrauterine Releasing System Combined with Goserelin in Treatment of Atypical Endometrial Hyperplasia	Liu 2022	Full text not available
Efficacy and pregnancy outcomes of hysteroscopic surgery combined with progestin as fertility-sparing therapy in patients with early stage endometrial cancer and atypical hyperplasia	Xi 2022	Wrong timing of assessment
Maintenance Therapy Can Improve the Oncologic Prognosis and Obstetrical Outcome of Patients With Atypical Endometrial Hyperplasia and Endometrial Cancer After Fertility-Preserving Treatment: A Multicenter Retrospective Study	He 2021	Wrong population
Significance of serum and pathological biomarkers in fertility-sparing treatment for endometrial cancer or atypical hyperplasia: a retrospective cohort study	Wang 2021	Wrong intervention
Insulin Resistance and Metabolic Syndrome Increase the Risk of Relapse For Fertility Preserving Treatment in Atypical Endometrial Hyperplasia and Early Endometrial Cancer Patients	Li 2021	Wrong population
Effect and Management of Excess Weight in the Context of Fertility-Sparing Treatments in Patients With Atypical Endometrial Hyperplasia and Endometrial Cancer: 8-Year Experience of 227 Cases	Shan 2021	Wrong study design
Fertility-preserving treatment outcome in endometrial cancer or atypical hyperplasia patients with polycystic ovary syndrome	Wang 2021	Wrong outcomes
The results of different fertility-sparing treatment modalities and obstetric outcomes in patients with early endometrial cancer and atypical endometrial hyperplasia: Case series of 30 patients and systematic review	Piatek 2021	Wrong population
Fibroblast growth factor receptor 2 isoforms detected via novel rna ish as predictive biomarkers for progestin therapy in atypical hyperplasia and low-grade endometrial cancer	Sengal 2021	Wrong timing of assessment
Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer	Westin 2021	Wrong population
Outcomes of the conservative management of the patients with endometrial intraepithelial neoplasia/endometrial cancer: Wait or treat!	Bostanci 2021	Wrong population

(continued)

SUPPLEMENTAL TABLE 3
A list of articles excluded at the full-text screening *(continued)*

Title	Study	Exclusion reason
Route-specific association of progestin therapy and concurrent metformin use in obese women with complex atypical hyperplasia	Matsuo 2020	Wrong population
Comparison of diagnostic accuracy between endometrial curettage and aspiration biopsy in patients treated with progestin for endometrial hyperplasia: A Korean gynecologic oncology group study	Kim 2020	Wrong population
Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing intrauterine device vs systemic therapy	Mandelbaum 2020	Wrong population
The addition of metformin to progestin therapy in the fertility-sparing treatment of women with atypical hyperplasia/endometrial intraepithelial neoplasia or endometrial cancer: Little impact on response and low live-birth rates	Acosta-Torres 2020	Wrong intervention
Fertility preservation in early-stage endometrial cancer and endometrial intraepithelial neoplasia: A single-center experience	Ayhan 2020	Wrong timing of assessment
Baseline serum HE4 but not tissue HE4 expression predicts response to the levonorgestrel-releasing intrauterine system in atypical hyperplasia and early stage endometrial cancer	Behrouzi 2020	Wrong population
Fertility-sparing treatment in young women with atypical endometrial hyperplasia and low-grade endometrial cancer: A tertiary center experience	Shikeli 2020	Wrong intervention
Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients	Mitsuhashi 2019	Wrong population
Efficacy and fertility outcomes of levonorgestrel-releasing intra-uterine system treatment for patients with atypical complex hyperplasia or endometrial cancer: A retrospective study	Maggiore 2019	Wrong timing of assessment
Impact of treatment duration in fertility-preserving management of endometrial cancer or atypical endometrial hyperplasia	Wang 2019	Wrong intervention
Treatment efficiency of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young women with endometrial atypical hyperplasia and endometrial cancer	Yang 2019	Wrong intervention
Mutations in the PI3K-AKT/MAPK signaling pathway and upregulation of CYP17A1 are associated with progesterone therapy resistance in low grade endometrial neoplasia	Djordjevic 2019	Full text not available
Insulin resistance and overweight prolonged fertility-sparing treatment duration in endometrial atypical hyperplasia patients	Yang 2018	Wrong timing of assessment
Fertility-Sparing Management Using Progestin for Young Women with Endometrial Cancer From a Population-Based Study	Kim 2018	Wrong intervention
Treatment of low-risk endometrial cancer and complex atypical hyperplasia with the levonorgestrel-releasing intrauterine device	Pal 2018	Wrong population
Fertility preserved hysteroscopic approach for the treatment of stage Ia endometrioid carcinoma	Wang 2017	Wrong intervention
Significance of body weight change during fertility-sparing progestin therapy in young women with early endometrial cancer	Park 2017	Wrong timing of assessment
Gonadotropin-releasing hormone agonist combined with a levonorgestrel-releasing intrauterine system or letrozole for fertility-preserving treatment of endometrial carcinoma and complex atypical hyperplasia in young women	Zhou 2017	Wrong intervention
Long-Term Oncologic and Reproductive Outcomes in Young Women with Early Endometrial Cancer Conservatively Treated: A Prospective Study and Literature Update	Laurelli 2016	Wrong study design
Management of endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: A Korean gynecologic-oncology group study	Kim 2016	Wrong population

(continued)

SUPPLEMENTAL TABLE 3

A list of articles excluded at the full-text screening *(continued)*

Title	Study	Exclusion reason
Prognostic factors of oncological and reproductive outcomes in fertility-sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin in Chinese patients	Zhou 2015	Wrong timing of assessment
Prognostic factors of regression and relapse of complex atypical hyperplasia and well-differentiated endometrioid carcinoma with conservative treatment	Yang 2015	Wrong intervention
Dual-specificity phosphatase 6 predicts the sensitivity of progestin therapy for atypical endometrial hyperplasia	Zhang 2015	Wrong population
Fertility-sparing treatment of early endometrial cancer and complex atypical hyperplasia in young women of childbearing potential	Pronin 2015	Wrong population
Hysteroscopic resection in fertility-sparing surgery for atypical hyperplasia and endometrial cancer: Safety and efficacy	DeMarzi 2015	Wrong study design
Impact of obesity on the results of fertility-sparing management for atypical hyperplasia and grade 1 endometrial cancer	Gonthier 2014	Wrong intervention
Pathologic features associated with resolution of complex atypical hyperplasia and grade 1 endometrial adenocarcinoma after progestin therapy	Gunderson 2014	Wrong population
Fertility sparing treatment of complex atypical hyperplasia and low grade endometrial cancer using oral progestin	Simpson 2014	Wrong population
Long-term outcomes after progestogen treatment for early endometrial cancer	Cade 2013	Wrong study design
Predictive diagnosis of endometrial hyperplasia and personalized therapeutic strategy in women of fertile age	Goncharenko 2013	Wrong outcomes
Comparison of dilatation & curettage and endometrial aspiration biopsy accuracy in patients treated with high-dose oral progestin plus levonorgestrel intrauterine system for early-stage endometrial cancer	Kim 2013	Wrong timing of assessment
Predictive ability of estrogen receptor (ER), progesterone receptor (PR), COX-2, Mlh1, and Bcl-2 expressions for regression and relapse of endometrial hyperplasia treated with LNG-IUS: A prospective cohort study	Gallos 2013	Wrong population
LNG-IUS vs oral progestogen treatment for endometrial hyperplasia: A long-term comparative cohort study	Gallos 2013	Wrong population
Fertility-sparing treatment of endometrial cancer precursors among young women: A reproductive point of view	Ricciardi 2012	Wrong timing of assessment
Conservative management of atypical hyperplasia and grade i endometrial carcinoma: Review of the literature and presentation of a series	Bakkum-Gamez 2012	Wrong timing of assessment
Biomarkers of progestin therapy resistance and endometrial hyperplasia progression	Upson 2012	Wrong population
A Turkish Gynecologic Oncology Group study of fertility-sparing treatment for early-stage endometrial cancer	Dursun 2012	Wrong timing of assessment
Prolonged conservative treatment of endometrial cancer patients: More than 1 pregnancy can be achieved	Perri 2011	Wrong timing of assessment
Levonorgestrel intra-uterine system as a treatment option for complex endometrial hyperplasia	Haoula 2011	Wrong population
Down-regulated progesterone receptor A and B coinciding with successful treatment of endometrial hyperplasia by the levonorgestrel impregnated intrauterine system	òrbo 2010	Wrong population
Progestogen treatment options for early endometrial cancer	Cade 2010	Wrong timing of assessment
Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins	Wheeler 2007	Wrong population
Bcl-2, BAX, and apoptosis in endometrial hyperplasia after high dose gestagen therapy: A comparison of responses in patients treated with intrauterine levonorgestrel and systemic medroxyprogesterone	Vereide 2005	Wrong population
Intrauterine progesterone treatment of early endometrial cancer	Montz 2002	Wrong population

(continued)

SUPPLEMENTAL TABLE 3
A list of articles excluded at the full-text screening *(continued)*

Title	Study	Exclusion reason
Treatment for complex atypical hyperplasia of the endometrium	Jobo 2001	Wrong population
EFFECT OF A PROGESTATIONAL AGENT ON ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CANCER.	Wentz 1964	Wrong population
Fertility sparing treatment in patients with endometrial cancer (FERT-ENC): a multicentric retrospective study from the Spanish Investigational Network Gynecologic Oncology Group (SPAIN-GOG)	Lago 2022	Wrong intervention
Mismatch repair status influences response to fertility-sparing treatment of endometrial cancer	Chung 2021	Wrong timing of assessment
Effectiveness of progestin-based therapy for morbidly obese women with complex atypical hyperplasia	Ciccone 2019	Wrong timing of assessment
Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40	Randall 1997	Wrong timing of assessment
Reproductive and oncologic outcomes after progestin therapy forendometrial complex atypical hyperplasia or carcinoma	Kudesia 2013	Wrong intervention
Does hormonal therapy for fertility preservation affect the survival ofyoung women with early-stage endometrial cancer?	Greenwald 2016	Wrong study design
Clinical outcomes of levonorgestrel-releasing intrauterine device present during controlled ovarian stimulation in patients with early stage endometrioid adenocarcinoma and atypical endometrial hyperplasia after fertility-sparing treatments: 10-year experience in 1 tertiary hospital in China	Yin 2022	Wrong study design
Effect of levonorgestrel IUD and oral medroxyprogesterone acetate on glandular and stromal progesterone receptors (PRA and PRB), and estrogen receptors (ER-alpha and ER-beta) in human endometrial hyperplasia	Vereide 2006	Wrong population
Oral Progestogens vs Levonorgestrel-Releasing Intrauterine System for Treatment of Endometrial Intraepithelial Neoplasia<sup/>	Marnach 2017	Wrong population
Impacts of ovarian reserve on conservative treatment for endometrial cancer and atypical hyperplasia	Wu 2023	Wrong population
Obstetric outcomes after medroxyprogesterone acetate treatment for early stage endometrial cancer or atypical endometrial hyperplasia: a single hospital-based study	Oishi 2023	Wrong study design
Molecular subtyping in endometrial cancer: A promising strategy to guide fertility preservation	Dagher 2023	Less than 10 cases
Fertility-sparing hormonal treatment in patients with stage I endometrial cancer of grade 2 without myometrial invasion and grade 1,Äi2 with superficial myometrial invasion: Gynecologic Oncology Research Investigators coLLaborAtion study (GORILLA-2001)	Lee 2023	Wrong study design
Serum HE4 predicts progestin treatment response in endometrial cancer and atypical hyperplasia: A prognostic study	Barr 2023	Wrong outcomes
Comparison of Mirena and Liletta levonorgestrel intrauterine devices for the treatment of endometrial intraepithelial neoplasia and grade 1 endometrioid endometrial cancer	Chaudhari 2023	Wrong population
PTEN mutation predicts unfavorable fertility preserving treatment outcome in the young patients with endometrioid endometrial cancer and atypical hyperplasia	Xue 2023	Wrong intervention
Efficacy and pregnancy outcomes of hysteroscopic surgery combined with progestin as fertility-sparing therapy in patients with early stage endometrial cancer and atypical hyperplasia	Xi 2023	Wrong intervention
Characteristics of molecular classification in 52 endometrial cancer and atypical hyperplasia patients receiving fertility-sparing treatment	Wang 2023	Wrong population

(continued)

SUPPLEMENTAL TABLE 3

A list of articles excluded at the full-text screening *(continued)*

Title	Study	Exclusion reason
Oncologic, fertility, and obstetric outcomes with MPA therapy in women with endometrial cancer and atypical endometrial hyperplasia	Takeda 2024	Less than 10 cases
Prognosis of patients with endometrial cancer or atypical endometrial hyperplasia after complete remission with fertility-sparing therapy	Ga 2023	Wrong population
Application of molecular classification to guiding fertility-sparing therapy for patients with endometrial cancer or endometrial intraepithelial neoplasia	Zhang 2023	Wrong timing of assessment
Postoperative Adjuvant Treatment in Women with Stage i Endometrial Cancer: A Retrospective Study	Fu 2023	Wrong population
Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer	Chen 2016	Wrong intervention
Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma	Kudesia 2014	Less than 10 cases
The use of releasing systems and gonadotropin-releasing hormone agonists in the treatment of atypical hyperplasia and early-stage endometrial cancer	Pronin 2013	Full text not available
Oncologic and pregnancy outcomes with fertility-sparing management for early endometrial cancer in young women	Chung 2019	Wrong timing of assessment
The results of fertility-sparing treatment and obstetric outcomes in patients with atypical endometrial hyperplasia and early endometrial cancer: a case series from belarus	Milishkevich 2022	Wrong timing of assessment
Efficacy of fertility-sparing treatment with LNG-IUS is associated with different ProMisE subtypes of endometrial carcinoma or atypical endometrial hyperplasia	Lv 2023	Wrong population
Trends and characteristics of fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer in Japan: a survey by the Gynecologic Oncology Committee of the Japan Society of Obstetrics and Gynecology	Ushijima 2023	Wrong timing of assessment
DNA methylation profiling identifies subset of lowgrade endometrial neoplasms with poor response to progestin therapy	Lin 2024	Wrong population
Prolonged Conservative Treatment of Endometrial Cancer Patients *More Than 1 Pregnancy Can Be Achieved*	Perri 2011	Wrong timing of assessment
Combined medroxyprogesterone acetate/levonorgestrel-intrauterine system treatment in young women with early-stage endometrial cancer	Kim 2013	Wrong intervention
Progestin treatment of atypical hyperplasia and well-differentiated adenocarcinoma of the endometrium to preserve fertility	Koskas 2012	Less than 10 cases
Fertility-preserving treatment in young women with well-differentiated endometrial carcinoma and severe atypical hyperplasia of endometrium	Yu 2009	Less than 10 cases
Complex atypical hyperplasia of the Endometrium: Differences in outcome following conservative management of pre- and postmenopausal women	Brownfoot 2014	Wrong population
Clinical Predictive Factors of Response to Treatment in PatientsUndergoing Conservative Management of Atypical Endometrial Hyperplasia andEarly Endometrial Cancer	Raffone 2020	Less than 10 cases
Efficacy of medroxyprogesterone acetate treatment and retreatment foratypical endometrial hyperplasia and endometrial cancer	Tamauchi 2017	Less than 10 cases
Six months response rate of combined oral medroxyprogesterone/levonorgestrel-intrauterine system for early-stage endometrial cancer in young women: a Korean Gynecologic-Oncology Group Study	Kim 2019	Wrong intervention

PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2–3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P4–5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5–6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P5–6
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	P5–6, Supplementary material 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P6–7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P6–7
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P6–7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study, and whether they worked independently, and if applicable, details of automation tools used in the process.	P7
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	P7–8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P7–8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	P7–8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P7–8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P7–8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	P7–8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P8

(continued)

PRISMA 2020 checklist *(continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P9, Figure 1, Supplemental material 1
Study characteristics	17	Cite each included study and present its characteristics.	P9, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary table 1, 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Table 2, Figures, P9—10
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	P12 Supplementary table 1,2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P9—11, Table 2, Figures
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P9—11, Table 2, Figures, Supplemental figures
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P11, Table 2, Supplementary figures
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplementary Figure 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P9—11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P11
	23b	Discuss any limitations of the evidence included in the review.	P16
	23c	Discuss any limitations of the review processes used.	P16
	23d	Discuss implications of the results for practice, policy, and future research.	P12—16

(continued)

PRISMA 2020 checklist *(continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number or state that the review was not registered.	P5
	24b	Indicate where the review protocol can be accessed or state that a protocol was not prepared.	P5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	P5
Support	25	Describe sources of financial or nonfinancial support for the review and the role of the funders or sponsors in the review.	P17–18
Competing interests	26	Declare any competing interests of review authors.	P17–18
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P17

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