INPLASY

Efficacy and Safety of the Levonorgestrel-Releasing Intrauterine System Compared With Oral Progestogens for Endometrial Hyperplasia: A Systematic Review and Meta-analysis of Randomized Controlled Trials

INPLASY202690020

doi: 10.37766/inplasy2026.9.0020

Received: 4 September 2026

Published: 4 September 2026

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ADMINISTRATIVE INFORMATION

Support - This study did not receive any funding in any form.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202690020

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 September 2026 and was last updated on 4 September 2026.

INTRODUCTION

Review question / Objective To compare the efficacy and safety of the levonorgestrel-releasing intrauterine system (LNG-IUS) with oral progestogens for histologic regression of endometrial hyperplasia using randomized controlled trial data.

Condition being studied Endometrial hyperplasia comprises non-atypical hyperplasia and atypical endometrial hyperplasia/endometrial intraepithelial neoplasia (EIN), with markedly different malignant potential.Progestogen therapy is the principal conservative treatment. Oral agents such as medroxyprogesterone acetate, megestrol acetate, norethisterone, and dydrogesterone are familiar and readily discontinued but require sustained adherence and can produce systemic adverse effects. LNG-IUS delivers high local levonorgestrel exposure to the endometrium with lower systemic exposure and no daily dosing requirement.

METHODS

Participant or population Adult women with histologically diagnosed endometrial hyperplasia, atypical endometrial hyperplasia, or endometrial intraepithelial neoplasia.

Intervention Direct comparison between LNG-IUS and at least one oral progestogen.

Comparator Studies were excluded if they enrolled only endometrial carcinoma without separable hyperplasia data, used LNG-IUS only as part of a combination regimen without a comparable oral-only arm, lacked extractable regression data, were non-randomized or non-comparative studies, were duplicate secondary analyses without new outcome data, or were abstracts without usable numerical information.

Study designs to be included PubMed, Embase, Web of Science, Cochrane CENTRAL, and ClinicalTrials.gov were searched from database

inception through June 9, 2026. Searches combined terms for endometrial hyperplasia, atypical endometrial hyperplasia, endometrial intraepithelial neoplasia, LNG-IUS, levonorgestrel-releasing intrauterine device, oral progestogens, medroxyprogesterone acetate, megestrol acetate, norethisterone, dydrogesterone, and randomized trials. Reference lists of relevant reviews and included reports were screened to capture trials not indexed consistently across the primary sources.

Eligibility criteria Studies were eligible when they met all of the following criteria: (1) randomized controlled allocation; (2) adult women with histologically diagnosed endometrial hyperplasia, atypical endometrial hyperplasia, or endometrial intraepithelial neoplasia; (3) direct comparison between LNG-IUS and at least one oral progestogen; (4) reporting of histologic regression, complete response, or sufficient arm-specific data to calculate event counts; and (5) follow-up based on repeat endometrial sampling. Studies were excluded if they enrolled only endometrial carcinoma without separable hyperplasia data, used LNG-IUS only as part of a combination regimen without a comparable oral-only arm, lacked extractable regression data, were non-randomized or non-comparative studies, were duplicate secondary analyses without new outcome data, or were abstracts without usable numerical information.

Information sources PubMed, Embase, Web of Science, Cochrane CENTRAL, and ClinicalTrials.gov were searched from database inception through June 9, 2026. Searches combined terms for endometrial hyperplasia, atypical endometrial hyperplasia, endometrial intraepithelial neoplasia, LNG-IUS, levonorgestrel-releasing intrauterine device, oral progestogens, medroxyprogesterone acetate, megestrol acetate, norethisterone, dydrogesterone, and randomized trials. Reference lists of relevant reviews and included reports were screened to capture trials not indexed consistently across the primary sources.

Main outcome(s) The primary outcome was histologic regression of endometrial hyperplasia, defined according to each trial as complete histologic response, regression to normal endometrium, or absence of hyperplasia on follow-up endometrial sampling. Secondary outcomes of clinical interest were recurrence after regression, progression to carcinoma, hysterectomy, fertility and pregnancy outcomes including live birth, and adverse events or tolerability outcomes such as abnormal or irregular bleeding, amenorrhea, weight change, systemic progestogen-related adverse effects, and discontinuation. Because definitions, denominators, and assessment timing for these secondary outcomes were inconsistent across trials, they were summarized narratively rather than pooled quantitatively.

Quality assessment / Risk of bias analysis Risk of bias for the primary histologic-regression outcome was assessed using the formal Cochrane Risk of Bias 2 (RoB 2) tool across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. RoB 2 signaling questions and domain algorithms informed judgements of low risk, some concerns, or high risk, and the overall judgement followed the RoB 2 decision rules. The assessment was independently verified by a second reviewer, with disagreements resolved by consensus. Risk-of-bias judgements were displayed using traffic-light and summary plots.

Strategy of data synthesis For dichotomous histologic regression, trial-specific risk ratios (RRs) were analyzed on the log scale with 95% confidence intervals (CIs). Pooled effects were estimated with inverse-variance random-effects models. Between-study variance (τ^2) was estimated by restricted maximum likelihood (REML), and Hartung-Knapp adjustment was used for random-effects 95% CIs. Heterogeneity was summarized using Cochran Q, τ^2, and I^2. A 95% prediction interval was calculated for the overall pooled effect to describe the range expected for a future comparable study. Prespecified subgroup analyses were conducted by hyperplasia subtype (non-atypical versus mixed or atypical populations) and follow-up duration (six months or less versus more than six months). Exploratory mixed-effects meta-regression evaluated follow-up duration as a continuous moderator in months and oral progestogen type as a categorical moderator. For the oral-comparator model, medroxyprogesterone acetate and combined medroxyprogesterone/norethisterone regimens were grouped as the MPA-containing reference category, with norethisterone, dydrogesterone, and megestrol acetate as separate levels; moderator inference used Knapp-Hartung adjustment and an omnibus F test. Funnel-plot inspection and Egger-type regression were treated as exploratory because only 12 trials were available.

Subgroup analysis For dichotomous histologic regression, trial-specific risk ratios (RRs) were

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Sensitivity analysis Sensitivity analyses included leave-one-out analysis, Baujat diagnostics, and influence diagnostics. Analyses were conducted in R using the meta and metafor packages.

Country(ies) involved Egypt, Iran, Turkey, Norway, Pakistan, and Singapore.

Keywords Endometrial Hyperplasia; Levonorgestrel; Intrauterine Devices; Medicated; Progestins.

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