INPLASY PROTOCOL

To cite: Stute et al. Systematic review on the influence of progestogens on the endometrium. Inplasy protocol 202360028. doi: 10.37766/inplasy2023.6.0028

Received: 09 June 2023

Published: 09 June 2023

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Support: **No.**

Review Stage at time of this submission: **Risk of bias assessment.**

Conflicts of interest:
None declared.

Systematic review on the influence of progestogens on the endometrium

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Review question / Objective: **The objective of this systematic review is to summarize published data from randomized controlled trials regarding the influence of a combined menopausal hormone therapy on the endometrium with specific focus on endometrial hyperplasia and endometrial cancer incidence.**
Eligibility criteria: **The following progestagens will be investigated: Norethisterone (acetate) = NET(A), Dienogest = DNG, Dydrogesterone = DYD, Micronized Progesterone = MP, Drospirenone = DRSP, Levonorgestrel = LNG, Cyproterone acetate = CPA, Medroxyprogesterone acetate = MPA, Chlormadinone acetate = CMAExogenously administered on oral, transdermal or vaginal route; duration of study at least 3 months; in humans.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 June 2023 and was last updated on 09 June 2023 (registration number INPLASY202360028).

INTRODUCTION

Review question / Objective: **The objective of this systematic review is to summarize published data from randomized controlled trials regarding the influence of a combined menopausal hormone therapy on the endometrium with specific focus on endometrial hyperplasia and endometrial cancer incidence.**

Rationale: **The metabolically neutral progestagens DYD and MP are often accused of not being potent enough at the endometrium to counteract the proliferative influence of estrogens, thus**

increasing endometrial hyperplasia and endometrial carcinoma, respectively.

Condition being studied: Endometrial hyperplasia and endometrial carcinoma.

METHODS

Search strategy: Search Strategy / Identifying Relevant Studies: An initial search strategy was developed in MEDLINE by a medical information specialist and tested against a list of core references to see if they were included in the search result. After refinement and consultation with the researchers, complex search strategies were set up by the information specialist for each information source based on database-specific controlled vocabulary (thesaurus terms / subject headings) and textwords. Synonyms, acronyms and similar terms were included in the textword search. No database-provided limits have been applied in any of the sources considering study types, languages, publication years or any other formal criteria. All searches were run on 30th November 2022.
The following search concepts were applied: 1. "Endometrium", 2. "Menopause", 3. "Gestagens". Index terms, synonyms, acronyms, similar terms and drug names were used the search in MEDLINE, Embase, CINAHL and the Cochrane Library. The searches in the Web of Science Core Collection and the trial registers were performed using free text search terms and acronyms only. Studies concerning exclusively animals were excluded from the searches in MEDLINE, Embase and CINAHL by using double-negative search strategies based on the "Humans only" filters by Ovid and the CINAHL Plus RCT filter by Cochrane (https://training.cochrane.org/handbook/version-6/chapter-4-tech-suppl). No other filter strategies were applied. The detailed final search strategies are presented in the Appendix // searchRxiv.

Participant or population: All (post/perimenopausal) women (natural or surgical menopause) using systemic estrogen replacement therapy (estradiol or conjugated equine estrogen; estriol and estrogen were excluded).

Intervention: Combined menopausal hormone therapy.

Comparator: Placebo.

Study designs to be included: Randomized controlled trials and meta-analysis.

Eligibility criteria: The following progestagens will be investigated: Norethisterone (acetate) = NET(A), Dienogest = DNG, Dydrogesterone = DYD, Micronized Progesterone = MP, Drospirenone = DRSP, Levonorgestrel = LNG, Cyproterone acetate = CPA, Medroxyprogesterone acetate = MPA, Chlormadinone acetate = CMAExogenously administered on oral, transdermal or vaginal route; duration of study at least 3 months; in humans.

Information sources: • MEDLINE (Ovid) (Ovid MEDLINE(R) ALL (1946 — 29/11/2022)) • Embase (Ovid) (1974 — 29/11/2022) • Cochrane Library (Wiley) (CDSR, Protocols, CENTRAL (1996 — Present)) • CINAHL (EBSCO) (CINAHL with Full Text (1981 — Present)) • Web of Science Core Collection (Clarivate) (1900 — Present) • ClinicalTrials.gov (NLM) • ICTRP (WHO).

Main outcome(s): Influence of combined menopausal hormone therapy on the histology of the endometrium, assessed by endometrial histology or incidence of endometrial cancer.

Quality assessment / Risk of bias analysis: NIH Quality assessment tool https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Strategy of data synthesis: Two reviewers independently will select the studies to be considered in the review, and those selected articles will be retrieved for closer examination. Differences in data extraction will be resolved by referencing original articles and discussion to establish consensus. The process of extraction will

be conducted by four reviewers independently to minimize bias and error. Citations of each article, type of study, participants characteristics, analysis methods, type of interventions (including dosage forms, frequency), and outcomes measures will be extracted. All data and descriptives will be collected in an excel file.

Subgroup analysis: None.

Sensitivity analysis: This systematic review will not include a meta-analysis or run any quantitative analysis.

Country(ies) involved: Switzerland, Greece and Germany.

Keywords: endometrial hyperplasia, endometrial carcinoma, combined menopausal hormone therapy, endometrial cancer.

Contributions of each author:

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