

INPLASY PROTOCOL

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Effect of intravaginal administration of estriol on the serum levels of different estrogens, gonadotropins, and other hormones in postmenopausal women: A Systematic Review

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Review question / Objective: Are the serum levels of estrogens (estrone, estradiol, estriol), gonadotropins (FSH, LH), or other hormones altered after intravaginal application of estriol for the treatment of genitourinary syndrome of menopause?

Condition being studied: The aim of this review is to study whether the vaginal application of estriol has any effects on the serum levels of different sex hormones, mainly estriol, estradiol, and FSH, as those have been previously used as proxies for the safety of similar estrogenic products.

Study designs to be included: Included: RCTs, controlled studies, head-to-head comparisons, systematic reviews, meta-analyses, quasi-experimental studies (intervention/no control).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 February 2023 and was last updated on 06 February 2023 (registration number INPLASY202320023).

INTRODUCTION

Review question / Objective: Are the serum levels of estrogens (estrone, estradiol, estriol), gonadotropins (FSH, LH), or other hormones altered after intravaginal application of estriol for the treatment of genitourinary syndrome of menopause?

Condition being studied: The aim of this review is to study whether the vaginal

application of estriol has any effects on the serum levels of different sex hormones, mainly estriol, estradiol, and FSH, as those have been previously used as proxies for the safety of similar estrogenic products.

METHODS

Search strategy: Complex literature searches were designed on the topic and were run in the following databases:

- MEDLINE (Ovid) (incl. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE Versions (1946 – January 26, 2023))
- CINAHL (1937 – January 26, 2023)
- Embase (Ovid) (1974 – January 26, 2023)
- Cochrane Library (Wiley) (1996 – January 26, 2023)
- Web of Science (Clarivate) (1900 – January 26, 2023)
- ClinicalTrials.gov (NLM)
- No language restrictions
- Re-run prior to final analysis depending on the time
- No search for unpublished studies.

Participant or population: Inclusion: postmenopausal women (natural, treatment-induced, or surgical menopause). Exclusion: route of application other than intravaginal, study types: other than the ones mentioned below.

Intervention: Inclusion: intravaginal administration of estriol. Exclusion: other routes of estriol administration.

Comparator: Inclusion: intravaginal administration of estriol of different dosage, intravaginal administration of estradiol, intravaginal administration of lubricant (placebo), no intravaginal administration of any product.

Study designs to be included: Included: RCTs, controlled studies, head-to-head comparisons, systematic reviews, meta-analyses, quasi-experimental studies (intervention/no control).

Eligibility criteria: N/A.

Information sources: • MEDLINE (Ovid) (incl. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE Versions (1946 – January 26, 2023))

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- Web of Science (Clarivate) (1900 – January 26, 2023)
- ClinicalTrials.gov (NLM).

Main outcome(s): Serum level changes of estrogens (estrone, estradiol, estriol), follicle-stimulating hormone, luteinizing hormone.

Additional outcome(s): Serum level changes of other hormones measured by the included studies, including but not limited to prolactin, and sex hormone-binding globulin.

Quality assessment / Risk of bias analysis: Randomization, blinding, inclusion and exclusion criteria, reporting of dropouts and explanation, intention to treat vs per protocol.

Strategy of data synthesis: Descriptive analysis.

Subgroup analysis: No subgroup analysis intended.

Sensitivity analysis: No sensitivity analysis is planned.

Language restriction: None.

Country(ies) involved: Switzerland.

Other relevant information: The protocol was initially prospectively submitted to PROSPERO on April 6th, 2022, yet due to the focus on studies on COVID-19, it was automatically deemed out of scope. Therefore a retrospective registration with INPLASY was decided, with the exact same information as the initial protocol (documentation available upon request).

Keywords: menopause; GSM; vaginal estriol; serum levels; estradiol; FSH.

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