

INPLASY PROTOCOL

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Effect of phytoestrogens on endometrial thickness: a systematic review

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Review question: What are the effects of phytoestrogen administration on endometrial changes?

Information sources: The research will be conducted by exhaustively searching the Medical Literature Analysis and Retrieval System Online (MEDLINE) databases via PubMed, Latin American and Caribbean Health Sciences Literature (LILACS), and Excerpta Medical Database (Embase) and Cochrane Library. The databases will be searched using the following terms: "Phytoestrogens", "Endometrium", "endometrial hyperplasia", "clinical trials" and their synonyms. Research will be limited to humans, regardless of the language of the studies analyzed. The reference lists of all selected studies will be checked as well as the gray literature. In addition, references to meta-analysis-relevant assessments, guidelines and comments identified in PubMed, LILACS, Cochrane Library will be found.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 March 2020 and was last updated on 15 March 2020 (registration number INPLASY202030001).

INTRODUCTION

Objectives / Review question: What are the effects of phytoestrogen administration on endometrial changes?

Condition being studied: Spontaneous or natural menopause, recognized after 12 months of amenorrhea, can occur between 40 and 58 years, with an average of 52 years. Menopausal estrogen deficiency leads to adverse symptoms, which vary in

duration and severity. In the United States, between 50% and 82% of women with natural menopause report vasomotor symptoms. In addition, urogenital symptoms such as vaginal dryness, pruritus, dyspareunia, and sexual dysfunction are noted by up to 40% of US women. Symptoms such as fatigue, lethargy, sleep disorders, palpitations, headaches and others related to depression and anxiety disorders are reported (THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, 2014; SUWANVESH et al., 2017). Current hormone therapy (HT) is mainly based on the use of estrogen and progesterone in women with uterus and has been questioned due to its side effects and efficacy in replacing a functional ovary (JAMESON et al., 2013). Phytoestrogens are a broad group of compounds consisting of isoflavones, lignans and coumestanes. Among these, isoflavones are heterocyclic phenols, the main constituents of genistein, daidzein and glycitein. They have a structure similar to 17-beta-estradiol, and a biological activity similar to the effects of estrogen has been shown, both in vitro and in vivo (SATHYAPALAN et al., 2016).

METHODS

Participant or population: Randomized controlled trials evaluating endometrial thickness after use of phytoestrogens in postmenopausal women, compared with a control group or on hormone replacement therapy.

Intervention: Use of phytoestrogens in postmenopausal women compared to a control group or on hormone replacement.

Comparator: Placebo.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Randomized controlled trials evaluating endometrial thickness after use of phytoestrogens in postmenopausal women, compared with a

control group or on hormone replacement therapy.

Information sources: The research will be conducted by exhaustively searching the Medical Literature Analysis and Retrieval System Online (MEDLINE) databases via PubMed, Latin American and Caribbean Health Sciences Literature (LILACS), and Excerpta Medical Database (Embase) and Cochrane Library. The databases will be searched using the following terms: "Phytoestrogens", "Endometrium", "endometrial hyperplasia", "clinical trials" and their synonyms. Research will be limited to humans, regardless of the language of the studies analyzed. The reference lists of all selected studies will be checked as well as the gray literature. In addition, references to meta-analysis-relevant assessments, guidelines and comments identified in PubMed, LILACS, Cochrane Library will be found.

Main outcome(s): Endometrial thickness after use of phytoestrogens.

Additional outcome(s): Effects of phytoestrogens on: estradiol levels, testosterone levels, total cholesterol change, cholesterol LDL change, and mammography failure and vaginal maturation.

Quality assessment / Risk of bias analysis: All included studies will be assessed for their methodological quality. The Cochrane Collaboration's risk of bias tool will be used (RevMan 5.3). The criteria consist of 7 items: random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.

Strategy of data synthesis: The extraction of data will be performed by a standard form with: age, number of individuals in the population exposed and control, dose, the administered supplement, and time. The studies that meet the inclusion criteria will have their data extracted by two reviewers, TC and AJG. Any disagreement will be

resolved, if necessary by a third author MIR. The data will be analyzed by mean and standard deviations to derive a standard mean difference (SMD) with 95% confidence intervals using RevMan 5.3 software. Pooled-effect estimates using a random-effects model with Mantel-Haenszel statistics. Study heterogeneity was determined using the I^2 statistic (in which numbers greater than 75% suggest considerable heterogeneity) (DerSimonian & Laird 1986).

Subgroup analysis: None.

Sensibility analysis: If necessary, sensitivity analysis using standards will be performed.

Countries involved: Brazil.

Keywords: Phytoestrogens, endometrium, menopause, endometrial, endometria, hyperplasia, systematic review.

Contributions of each author:

- 1 - Selection of studies and data extraction, writing of the project.
- 2 - Selection of studies and data extraction, writing of the project.
- 3 - Project writing, search strategy, selection of studies, analysis of results.
- 4 - Project writing, search strategy, selection of studies, analysis of results.
- 5 - Analysis of results.