INPLASY

The Effect of Combined Oral Contraceptive Pills on the Risk of Cardiovascular Diseases in Premenopausal Females with Endometriosis- Systematic Review & Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 January 2024 and was last updated on 08 January 2024.

INTRODUCTION

Review question / Objective What is the effect of combined oral contraceptive pills (COCP) on the risk of cardiovascular disease in premenopausal females with endometriosis?

Condition being studied Endometriosis is one of the most common enfeebling gynecologic diseases affecting women of reproductive age. An estimate of 10% of females worldwide are diagnosed with endometriosis. Endometriosis is linked to cardiovascular diseases as it promotes chronic systemic inflammation and proatherogenic lipid profile. COCP effect on cardiovascular disease has been studied extensively in both pre- and post-menopausal females. Endometriosis as the disease, and COCP as its preferred treatment, are both associated with an increased risk of CVD. This raises the question about the effect of COCP on the risk of cardiovascular disease in premenopausal females with endometriosis.

METHODS

Participant or population Premenopausal females diagnosed with endometriosis surgically or radiologically.

Intervention Combined oral contraceptive pills, taken as the only hormonal medication understudy, with different types and doses of estrogen and progestogen, of any generation, monophasic or multiphasic, cyclic or continuous. Medical treatment duration should be at least 3 months.

Comparator No COCP: Placebo or no treatment; Progestin only pills (POPs): any type of progestin used, daily PO intake.

Study designs to be included Randomized and non-randomized controlled clinical trials; Non-randomized studies of intervention/s (NRSI).

Eligibility criteria Exclusion Criteria: Case reports and cross-sectional studies; Studies using COCP as complementary therapy or those comparing COCP with medications other than progestin only pills.

Information sources Our search includes four electronic databases (Medline, Cochrane, Popline, Embase) using MeSH and Keywords. The search strategy was developed with the assistance of a medical librarian and content experts based on two concepts: Endometriosis and COCP. We developed the search strategy initially for Medline and adapted for the rest. The search was not limited to language or year of publication. Google Scholar, Clinical trial.gov, ICTRP, and references of included studies were searched as part of grey literature.

Main outcome(s) A. Clinical Outcomes (Cardiovascular disease):
Cardiovascular diseases include coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease (PAD).
– Acute coronary syndrome: angina, fatal myocardial infarction (MI), and nonfatal MI;
– Stroke: Transient Ischemic Attack, fatal stroke, and non-fatal stroke;
– Peripheral arterial diseases: Claudication, Acute Limb Ischemia, Critical Limb Ischemia, Ischemic Amputation, Revascularization
– Cardiovascular mortality
– All-cause mortality.
B. Surrogate Outcomes (Cardiovascular profile):
Cardiovascular profile is defined as lipid profile, inflammatory, and coagulation parameters.
– Lipid Profile: Castelli Index 1: (total cholesterol (TC)/ high-density lipoprotein (HDL)), low-density lipoprotein (LDL), Triglycerides (TG);
– Serum Inflammatory Markers: Interleukin 6 (IL-6), High sensitivity C-Reactive Protein (hs-CRP);
– Coagulation profile: Fibrinogen, homocysteine, Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), and Thrombin Time (TT);

The minimal follow up duration for surrogate and clinical outcomes is 3 months and 1 year, respectively.

Quality assessment / Risk of bias analysis We will assess the risk of bias of each outcome in duplicate and independently using Cochrane Risk of Bias Tool 2 (ROB2) for RCTs and the risk of bias (confounding, selection bias, reporting of selective outcomes, inadequate methods of ascertainment of exposure and outcomes) in comparative observational studies using the criteria recommended by GRADE. Using GRADE "Grades of Recommendations Assessment, Development and Evaluation", we will evaluate the quality of evidence by outcome.

Strategy of data synthesis We will use random-effects model to quantitatively synthesize study. We will perform the meta-analyses of RCTs separate from that of observational studies.
• Using Review Manager software (Revman), we will pool the means of each continuous outcome in RCTs separately from the adjusted means (when applicable) of cohorts and case-control studies. After the collection of number of events per each treatment arm for each categorical outcome in RCTs, we will pool the effect estimates to yield an overall Relative risk (in addition to absolute risk, when applicable) and will pool the adjusted effect estimates (when applicable) of observational studies to yield an overall Odds ratio (in addition to absolute risk, when applicable). We will compare in parallel the effect estimates of randomized vs comparative observed studies for each outcome.
• We will test for heterogeneity between studies: (I^2: 0-100). In case of high heterogeneity (I^2>=50 or P<0.1), we will attempt to provide an explanation by subgroup analysis.
In case quantitative synthesis is not appropriate, we will report a narrative summary of the findings.

Subgroup analysis Subgroup analysis, when applicable and data are available, will include the following, smoking status, age, COCP generations. In case data were not available other factors can be added to subgroup analysis, e.g.: BMI, treatment duration, time of assessment and cardiovascular risk.

Sensitivity analysis We will perform sensitivity analysis for studies of high risk of bias (omitting vs inclusion of those studies) and for studies with missing data (considering "data are not randomly missing" and replacing missing data using imputation methods).

Country(ies) involved Lebanon.

Keywords Endometriosis; cardiovascular risk; premenopausal women; combined oral contraceptives; progestin only pills; systematic review; meta-analysis.

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