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Investigating the risks of cardiovascular disease among premenopausal women using oral contraceptive: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction The use of oral contraceptives (OCs) is linked to an increased risk of cardiovascular diseases (CVDs) in women of reproductive age. CVD remain one of the top causes of death worldwide, with at least three-quarters of deaths occurring in low-income and middle-income nations. The impact of various types of combined oral contraceptive (COC) on several modifiable risk factors associated with CVDs in premenopausal women is inconsistent regardless of genetic mutations. The aim of this systematic review will be to provide a comprehensive synthesis of the available evidence on the impact of COC usage on modifiable risk factors associated with CVDs and assess ethnic and geographic disparities in the reported prevalence of CVD.

Methods and analysis This systematic review protocol was prepared in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols 2015 statement. An extensive search on the Embase, MEDLINE and Cochrane Library will be conducted from inception until. Two reviewers will independently screen for eligible studies using a predefined criterion. The risk of bias and quality of included studies will be assessed using the modified Downs and Black's checklist. Whereas the overall quality of included studies will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation assessment tool.

Ethics and dissemination This is a review of existing studies and will not require ethical approval. The findings will be disseminated through peer-reviewed publication. The use of OC and the risk of CVDs including arterial and venous thrombosis remain a major concern among women of reproductive age. Thus, given the impact of COCs on the risk variables linked with CVDs, this review may provide an insight and assistance during COC use.

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INTRODUCTION

Women are exposed to estrogen fluctuations throughout their life which can either endogenous or exogenous in nature.[1] The use of exogenous combined oral contraceptives (COCs) remains one of the most commonly used modern methods of birth control due to their high efficacy and safety profile in

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will be a comprehensive synthesis of available evidence on the link between oral contraceptive (OC) usage and the risk of cardiovascular diseases (CVDs).
⇒ A comprehensive search strategy will be used to identify and retrieve articles relevant to our research question.
⇒ This will be the first systematic review and meta-analysis to assess the geographic disparities in the prevalence of CVD linked to OC usage.
⇒ The main limitation will be the heterogeneity of the studies available in terms of clinical, methodological, type of study and reported outcomes.

premenopausal women.[2] The prevalence of COC use in women of reproductive age is around 16% representing around 151 million women worldwide, and in developed countries this accounts for over 30%[3 4], despite certain risk identified to be associated with the usage.[2 5]

The use of oral contraceptives (OCs) is associated with an increased risk of cardiovascular events[6 7] such as coronary heart disease, arterial and venous thrombosis, ischaemic or haemorrhagic stroke, and myocardial infarction among others.[8] Although, these cardiovascular events appear to differ by geographic region, age and gender.[9 10] The risk for CVD increases when other modifiable cardiovascular factors, such as smoking, obesity, dyslipidaemia, diabetes mellitus, haemostatic disorders and hypertension, are considered.[11]

Notably, available data regarding the impact of COC on modifiable risk factors associated with cardiovascular diseases (CVDs) in women of reproductive age in different population settings are inconsistent.[12–14] For instance, findings from an epidemiological study reported changes in levels of systolic blood pressure and diastolic blood pressure

following the administration of OCs.[13] In contrast, the study by Kharbanda *et al*, observing the cardiovascular effects of COCs in adolescents, reported no changes in blood pressure.[12]

Furthermore, findings from previous studies investigating the impact of COC on haemostatic parameters are also inconsistent.[5 15] Nevertheless, the impact of COC on the modifiable risk factors associated with CVDs is usually attributed to the direct influence of the oestrogen component, which is known to impact the vascular wall and stimulate endothelial dysfunction, as well as altering the coagulation system.[2 16] The impact of the oestrogen appears to be countered by the progesterone component, which may be dependent on the dose and duration of use.[2 17] Prior studies have also revealed the effect of COCs on metabolic parameters, such as changes in lipid profiles,[14 18] and insulin sensitivity, all of which play a role in the development of a prothrombotic condition.[19 20]

In spite of high efficacy and safety profile attributed to OCs, data available regarding the impact on the occurrence of atherosclerosis, thrombosis, vasomotion and arrhythmogenesis among others are conflicting and insufficient.[21] More so, evidence are currently limited as regard the role of geographical areas and ethnicity on the association between the use of OC and risk of CVDs,[22] although emerging evidence suggest that ethnic differences can influence CVD risk even at a young age, with pronounced differences in some modifiable risk factors.[9] The justification for exploring the effect of OCs on cardiovascular events is simply due to the fact that the prolong use of COC and risk of CVD in women of reproductive age still remain an important issue despite premenopausal women having low risk.[2 23] Thus, determining the impact of COC usage on certain modifiable risk factors associated with CVDs, will help to provide insight and guidance in making an informed decision at each contraceptive consultation (initial and follow-up) in different population settings. Therefore, the aim of this systematic review and meta-analysis will be to provide a comprehensive synthesis of the available evidence on the impact of OC usage on modifiable risk factors associated with the occurrence of CVDs and to further assess the role of ethnic and geographic disparities in the reported prevalence of CVD in women on OCs.

Objectives
The objectives of this study are as follows:
1. To determine the prevalence of CVDs in premenopausal women using OC.
2. To determine the effect of OC on vascular and cellular markers of coagulation in association with immune cell activation in premenopausal women on OC.

METHODS
The systemic review protocol was prepared according to the Preferred Reporting Items for Systemic review and Meta-Analysis Protocol.

Patient and public involvement
There will be no patient and public involvement in the design, interpretation or dissemination of the findings.

Participants
The participants of the systematic review will mainly include healthy adolescent and adult premenopausal women between the age of 18 and 45 years who are not obese and non-smokers.

Exposure
This systematic review will include studies that report on the use of second-generation, third-generation and fourth-generation type of COC.

Comparators
The comparator will include healthy adolescent and adult women who not OCs.

Inclusion and exclusion criteria
This systematic review and meta-analysis will include cross-sectional, cohort, case–control studies and randomised control trials. Studies reporting on the effect of COC usage as form of hormonal therapy or as a method of contraception on the risk factors associated with CVD in healthy premenopausal women who are non-obese, and non-smokers will be included. There will be no language restriction. Reviews, books, letters to editors and studies will be excluded.

Outcomes
The study outcomes will include the following.

Primary outcome
Prevalence or incidence of cardiovascular events.

Surrogate outcome
1. Vascular and cellular markers of coagulation and endothelia dysfunction (endothelin 1, D-dimer, NO, fibrinogen and proinflammatory cytokines (TNF-α, IL-6, C-reactive protein).
2. Traditional cardiovascular risk variables (BMI, systolic and diastolic blood pressure, lipid profile, glucose intolerance and hyperinsulinaemia).

Information sources
A search strategy will be developed using medical subject headings (MeSH) words for MEDLINE, EMBASE and Google Scholar database. The electronic database search will be augmented by searching the Cochrane Central Register of Clinical trials. Papers published in both commercial and in non-commercially operated databases (grey literature) will also be considered. In addition, the reference list of the selected studies will be scanned to identify relevant literature.

Search strategy
The search strategy will be developed using MeSH terms and keywords related to OCs, CVD and premenopausal (online supplemental file). The keywords and

MeSH terms will include OC pills, birth control pills or OCs or contraceptives, premenopausal women, CVD, hypertension, or coronary heart disease.

Study selection

The screening of studies will be conducted by two independent authors (OAF and SRN) to avoid inconsistency in terms of eligibility of studies to enhance objectivity and prevent mistakes. At the initial stage, studies will be screened by the titles, abstracts, keywords and synonyms, then followed by the identification of the full-text articles. Should discrepancies arise (PD) will screen such studies, and consensus will be reached through discussion.

Data management

The Mendeley desktop reference manager (V.1.19.4) will be used to manage retrieved studies, archiving of relevant and excluded studies with reasons. Importantly, reference lists of included studies will be screened to confirm that no relevant studies are left out. Eligible will then be subjected to data collection, critical appraisal, risk and quality evaluation.

Data items and collection process

Relevant data items will be extracted using a structured form depending on the type of study design. To avoid errors during data entry from selected studies, two authors (OAF and SRN) will independently perform this process. Should discrepancies arise, the third and fourth authors (PVD) will be invited for arbitration. The author and year of publication, the country, population (sample size), study design, types, dosage and duration of contraceptive usage, plasma levels of cellular and vascular markers of coagulation, endothelia dysfunction and inflammation or immune activation, lipid profiles, glucose profiles, body mass index (BMI) and haemodynamic indices of hormonal contraceptive users and non-users will be extracted. In case of insufficient data, the main authors of studies will be contacted to obtain enough information.

Risk of bias in individual studies

The risk of bias and quality of included studies will be assessed using the modified Downs and Black's checklist.[24] Two reviewers (OAF and BBN) will make independent judgements based on the domains of the tool: reporting bias (10 items), external validity (3 items), internal validity (6 items) and selection bias (7 items). The scores will be rated as excellent (25–26), good (20–24), moderate (14–19), poor (11–13) and very poor (<10). In case of disagreements, PVD will be consulted to arbitrate.

Data synthesis

Review Manager (RevMan) V.5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) will be used for statistical analysis. Clinical and methodological heterogeneity assessment will be conducted

first which will then be followed by an assessment of statistical heterogeneity. The χ^2 and I^2 statistic tests will be used to determine the level of heterogeneity across the included studies. An I^2 value of >25 will be considered as moderate or substantial heterogeneity.[25] If studies are similar with regard to (participants, intervention, comparisons and outcomes), and more so, information extracted from this sufficient number of studies included are homogeneous, we will conduct a fixed-effect meta-analysis using R statistical Software (The R foundation for statistical computing, Vienna, Austria). A random-effects model will be employed where studies show a substantial level of heterogeneity. Furthermore, a subgroup analysis base on the reported outcome and meta-regression will be conducted to assess the role of geographical areas and ethnicity in association with the use of COC and risk of CVD. The levels of inter-rater agreement will be assessed using Cohen's kappa[26] and the funnel plots will be used to assess publication bias.

Quality cumulative evidence

The quality of evidence for primary outcomes will also be evaluated using the grading of recommendations assessment, development and evaluation tool.[27] The findings will be summarised and presented in the summary of findings table.

Sensitivity analysis

The sources of statistical heterogeneity will be assessed by performing a sensitivity analysis and excluding studies with high risk of bias based on the risk of bias assessment.

Ethics and dissemination

This is a review of existing studies and will not require ethical approval. The findings will be disseminated through peer-reviewed publication. The use of OC and the risk of CVDs including arterial and venous thrombosis remain a significant concern among premenopausal women. Thus, given the impact of COCs on the risk variables associated with CVDs, this review may provide an insight and assistance during COC use.

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