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Does the use of oral contraceptives or hormone replacement therapy offer protection against the formation or rupture of intracranial aneurysms in women?: a systematic review and meta-analysis

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SUMMARY

OBJECTIVE: The aim of this study was to carry out a systematic review of the literature with meta-analysis to evaluate the effect of using oral contraceptive and hormone replacement therapy as a protective factor in the formation of intracranial aneurysms and subarachnoid hemorrhage.

METHODS: This is a systematic review of the literature with meta-analysis, using PubMed and Embase as databases and the PRISMA method. Case-control and cohort studies published until December 2022 were included in this review.

RESULTS: Four studies were included in this review; three of which were eligible for meta-analysis. Regarding the use of oral contraceptive and the development of subarachnoid hemorrhage, there was a lower risk of aneurysm rupture with an odds ratio 0.65 (confidence interval 0.5–0.85). In the analysis of patients using hormone replacement therapy and developing subarachnoid hemorrhage, there was also a lower risk of aneurysm rupture with an OR 0.54 (CI 0.39–0.74). Only one article analyzed the formation of intracranial aneurysm and the use of hormone replacement therapy and oral contraceptive, and there was a protective effect with the use of these medications. oral contraceptive: OR 2.1 (CI 1.2–3.8) and hormone replacement therapy: OR 3.1 (CI 1.5–6.2).

CONCLUSION: The use of hormone replacement therapy and oral contraceptive has a protective effect in intracranial aneurysm rupture and formation.

KEYWORDS: Subarachnoid hemorrhage. Combined oral contraceptive. Hormone replacement therapy. Intracranial aneurysm.

INTRODUCTION

Subarachnoid hemorrhage (SAH) due to the rupture of an intracranial aneurysm (IA) is an extremely serious situation whose mortality reaches approximately 50% of affected patients[1]. Approximately 65% of patients with IA are female[2]. There are several hypotheses that try to justify this higher incidence of IA in women, such as hormonal factors, endothelial factors, changes in the collagen content of the vessel wall, hemodynamic changes, genomic actions, endothelial factors, and the effects of environmental risk factors such as smoking, but the reason for this high prevalence is still unclear[3,4].

The use of oral contraceptives (OCs) has become common among women since the 1960s, initially with the aim of controlling menstrual symptoms and as birth control[5]. Also in the 1960s, hormone replacement therapy (HRT) began to be used to treat climacteric and menopausal symptoms[6]. Over the decades, dosages and types of hormonal combinations have been changing due to adverse effects. Increased risk of venous thromboembolism, thrombosis and thrombophilia, stroke, acute myocardial infarction, and breast cancer, among others, were being diagnosed more frequently in these populations. It was also evaluated that the use of these medications exerted some

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protective factors in some other diseases, such as endometrial and ovarian cancer, and, in some studies, there was also a reduction in the incidence of IA and a decrease in the risk of SAH, but the results of these protective factors related to the use of OC and HRT presented conflicting results in the literature[7].

The objective of this study was to answer the question of whether the use of OC and HRT has a protective effect against the formation of IA and the incidence of SAH.

METHODS

We used the PRISMA methodology to do this review[8]. The clinical question was: Do women who use HRT or OC have a lower incidence of IA or a lower risk of SAH when compared to women who do not use HRT or OC? The structured question in the PICO format was prepared as follows: population—women; intervention—use of OC or HRT; comparison—no use of OC or HRT; and outcome—incidence of IA or incidence of SAH secondary to ruptured IA.

Eligibility criteria

PICO components, cohort or case-control studies, no restrictions on time, just articles written in English, Portuguese, or Spanish with the full text or abstract containing the desired data. The results must be expressed in terms of relative risk with a confidence interval and the number of participants involved.

Exclusion criteria

Review articles, *in vitro* experimental articles or animal studies, case series or case reports, and observational or non-comparative studies.

Sources of information consulted and search strategies

Medline via PubMed, manual search; keywords used and search strategy: oral contraceptive AND brain aneurysm. Embase *via* Scopus, manual search; keywords used and search strategy: Intracranial AND aneurysm AND risk AND of AND rupture AND follow AND up AND oral AND contraceptive AND (LIMIT-TO (DOCTYPE, "air")) AND (LIMIT-TO (LANGUAGE, "English") OR (LIMIT-TO (LANGUAGE, "Portuguese ")) OR (LIMIT-TO (LANGUAGE, "Spanish")) AND (LIMIT-TO (EXACTKEYWORD, "Human")). Manual search in the references of selected articles.

The studies were selected according to the inclusion and exclusion criteria after reading the title and abstract. If there was any doubt regarding the inclusion or not of the article, we proceeded with the reading of the complete article, and if there were not the necessary data for the elaboration of this review, they would be discarded from the analysis. The reading and selection of articles were carried out solely by the main author. After choosing the articles, the extracted data were registered, and duplicates were excluded.

Risk of bias and quality of evidence

For this review, only the articles whose results presented the relative risks and confidence intervals of the questions that were formulated were selected. To define the cases, it was necessary to prove it with an imaging exam identifying an IA (digital angiography of intracranial vessels, angio-tomography, or angio-resonance) and/or SAH (computed tomography scan). Historical controls were accepted in this analysis as long as relative risk data and confidence intervals were also available. To collect data on the use of HRT or OC, an interview with the patient or a trusted close person was necessary, either by telephone or in person.

Extracted data

Author, year of publication, type of study, number of cases, number of controls, relative risk and confidence interval in the intervention group, relative risk and confidence interval in the comparison group, article quality, summary of findings, and textual result of findings (positive, negative, or inconclusive association).

If there was the possibility of comparing any of the data presented, these would be submitted to a meta-analysis using the *RevMan software* version 5.4.1 (*Cochrane*).

RESULTS

After the textual search using the Embase database, according to the criteria established in the methodology, 42 results were obtained; of which 6 were selected for abstract analysis, and of these, 1 article was selected for this review based on the exclusion and inclusion criteria. With the PubMed database search, 34 results were obtained, 10 of which were selected for abstract analysis. In the end, 2 of these articles were included for analysis. After reviewing the bibliography of the articles included in this study, one relevant article was also added (Figure 1). The risk of bias and the quality of the evidence are shown in Table 1.

The meta-analysis included 4 articles where the following aspects were analyzed: findings of IA in patients taking OC versus those who were not taking OC; the presence of IA in patients taking HRT versus those who were not taking HRT; findings of SAH among patients taking OC versus those who were not taking these drugs; and SAH findings among patients who take HRT versus those who did not take HRT.

CHARACTERISTICS OF THE INCLUDED PAPERS

Chen 2011[9]

A case-control study that interviewed in person or by telephone a group of cases (women with a finding of ruptured or unruptured IA) and a group of controls matched by age and demographic data without a history of treatment or diagnosis of IA. In this interview, they were asked about OC and HRT use and calculated the *Odds ratio* (OR) of HSAe and IA in those two groups. As a result, an OR 2.1 (CI 1.2–3.8; p=0.01) was obtained in the IA group in patients using OC and an OR 3.1 (CI 1.5–6.2; p<0.05) in the IA group in patients using HRT. There was no statistical difference regarding the risk of SAH in patients using OC and HRT compared to those who did not. As a summary of this article, a protective effect can be inferred regarding the formation of IA in patients who used HRT or OC. As for rupture, there was no statistical difference between the groups.

Longstreth 1994[10]

A case-control study that interviewed patients with a history of SAH in *King County, Washington*, whose controls were matched by sex and age, with a sample of 2 controls for each case, randomly chosen through the telephone number. The interviews took place in the patient's homes, directly with them or with close family members, lasting about 1 h, with questions about OC and HRT use and other risk factors for SAH too. As a result, an OR of 0.52 (CI 0.25–1.10; p<0.002) was obtained for patients using OC and at risk of SAH and an OR of 0.47 (0.26–0.86; p<0.002) for patients using HRT and risk of SAH. Both drug groups had a protective effect regarding the risk of SAH.

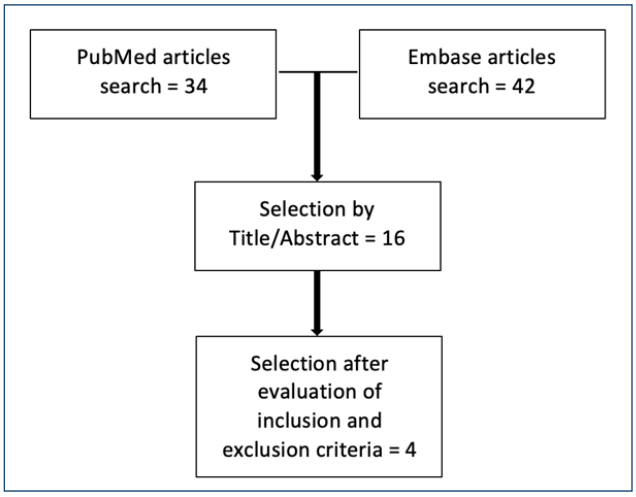


Figure 1. Flowchart of selected papers.

Qureshi 2016[11]

A cohort study was conducted to follow-up women between 50 and 79 years old who participated in the *Women's Health Initiative* (WHI) study for 12 years to analyze the risk of SAH during follow-up and to analyze which patients used and did not use HRT. A total of 93,676 patients were followed up in this study, and of these, 114 developed SAH during the follow-up. The relative risk (RR) of developing SAH (after adjusting for other confounding risk factors) in patients using HRT was 1.5 (CI 1.0–2.2). The article suggests that postmenopausal women diagnosed with IA, with a family history of aneurysm, and with cardiovascular risk factors should be advised not to use HRT. If it is necessary, preference should be given to combined drugs (estrogens associated with progestins).

Murchu 2001[12]

A multicentric case-control study that evaluated 268 women with a history of SAH and conducted personal interviews with patients or close family members defined 286 controls matched by sex, age, and city of residence randomly selected through electoral rolls and conducted interviews with the controls in the same way as cases. In the interview, the use of HRT and ACO was asked, as well as other risk factors related to SAH. The RR for SAH was 0.97 (CI 0.58–1.60) in patients using OC, without statistical significance, and 0.75 (CI 0.47–1.18) in patients using HRT, demonstrating a protective effect of HRT on the development of SAH.

Table 1. Risk of bias and quality of evidence.

Author/year	RR or OR and CI	Image exam to define the case	Personal interview or by telephone
Chen, 2011			
Longstreth, 1994			
Qureshi, 2016			
Mhurchu, 2001			

RR: relative risk; OR: odds ratio; CI: confidence interval. Green chart: the absence of bias.

META-ANALYSIS

Hormone replacement therapy and subarachnoid hemorrhage risk

According to Graph 1, three articles were included in this analysis, with the result showing the benefit of the intervention group.

Oral contraceptive and subarachnoid hemorrhage risk

According to Graph 2, three articles were included in this analysis, with the result showing the benefit of the intervention group.

Oral contraceptive and hormone replacement therapy and intracranial aneurysm formation

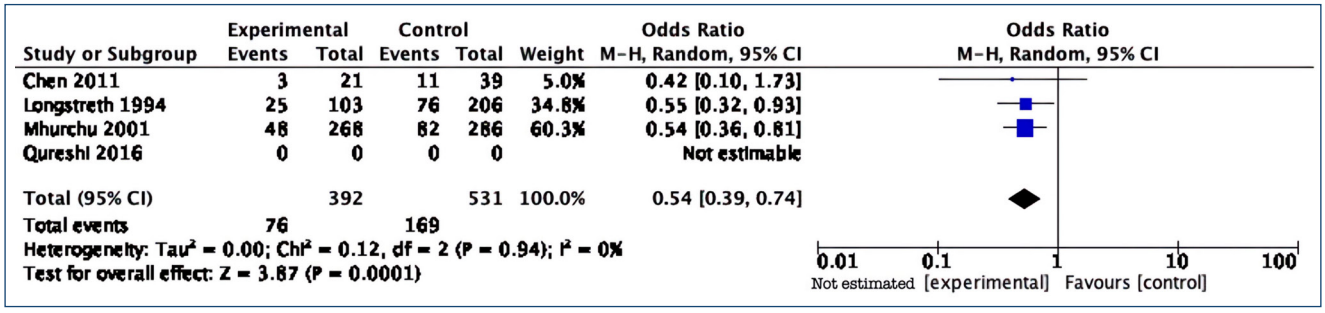
Only one article analyzed the formation of IAs and the use of HRT and OC, and there was a protective effect with the use of these medications. OC: OR 2.1 (CI 1.2–3.8) and HRT: OR 3.1 (CI 1.5–6.2). In this case, the meta-analysis was not performed[9].

DISCUSSION

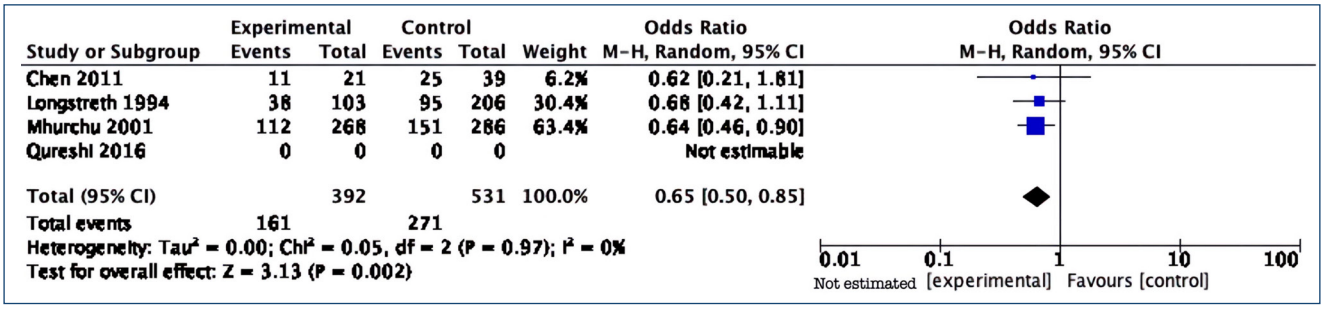
The use of HRT and OC has always been a very controversial topic in the medical literature due to the various associations of the use of these medications with increased cardiovascular risk, the development of malignant neoplasms, the association with thrombotic and thromboembolic events, and several other pathologies[13]. These associations have changed a lot over the decades, mainly due to changes in medications, dosages, and associations in the formulations studied, and we currently see a trend toward the use of lower doses of hormones and different combinations of estrogen and progestins or isolated progestins (as a contraceptive method) or isolated estrogen (as a treatment for menopausal symptoms in hysterectomized women), increasingly with fewer side effects and risks of developing diseases. The therapies have been individualized according to the characteristics of the patients, associated morbidities, and idealized goals with the treatments[14].

The diagnosis of IA is extremely challenging, mainly due to the risks of SAH, as this is an event of great morbidity and mortality[15]. Over the decades, discovering factors associated with a decrease in the risk of bleeding in these patients has always been a very important objective, especially in women, most affected by this disease[16,17]. Studies that demonstrate a lower risk of developing IA and SAH in women who use HRT and OC can bring much hope to the treatment of these diseases.

Some articles were excluded from this analysis mainly because they were experimental studies, case studies, and/or



Graph 1. The forest plot of the comparison analyzes the risk of subarachnoid hemorrhage in the group that used hormone replacement therapy versus the group that did not use hormone replacement therapy.



Graph 2. Forest plot of the comparison analyzing the risk of subarachnoid hemorrhage in the group that used oral contraceptive versus the group that did not use oral contraceptive.

review articles, for which it would not be possible to draw a statistical inference about the use of these medications as a protective factor. Something to consider in all the studies carried out was the fact that the controls did not undergo any type of imaging exam that would prove the non-existence of IA. This is a possible bias in these studies.

Other articles were not based on personal interviews with the patients involved; they only inferred the probable use of OC if the woman was married, divorced, or single, which is something subject to much criticism and currently inconceivable.

This review has some limitations, mainly due to variations in the baseline characteristics of the patients evaluated, variations in the medications used and their dosages, and a lack of control over the use of other medications. There are no controlled studies for this type of evaluation since it is unethical to use a placebo group in studies of contraceptive drugs in women of childbearing age, and, in addition, it is known that IAs and SAH are rare events in the general population.

CONCLUSION AND SUMMARY OF EVIDENCE

From the results of this meta-analysis, it is possible to infer that the use of OC and HRT has a protective effect in relation to the risk of SAH in women. There is limited data in the literature so far to infer that the use of ACO and TRH has a protective effect on the formation of IAs.

AUTHORS' CONTRIBUTIONS

DLPS: Formal Analysis, Writing – original draft, Writing – review & editing. **MBG:** Writing – review & editing. **VMHZ:** Writing – review & editing. **EGF:** Supervision, Writing – review & editing.

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