Association between the use of oral contraceptives and the occurrence of systemic hypertension: A systematic review with statistical comparison between randomized clinical trial interventions

Ingrid Soares de Souza [a], Gabriel Zorello Laporta [a], Juliana Zangirolami-Raimundo [a,b], Isabel Cristina Esposito Sorpreso [b], Heloisa Carla Lopes Silva dos Santos [a], José Maria Soares Júnior [b], Rodrigo Daminello Raimundo [a,b,*]

[a] Laboratório de Delineamento de Estudos e Escrita Científica, Centro Universitário FMABC, Santo André, São Paulo, Brazil
[b] Laboratório de investigação médica em ginecologia estrutural e molecular, Disciplina de Ginecologia, Departamento de Obstetrícia e Ginecologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Sao Paulo, São Pauloṭ, Brazil

ABSTRACT

Introduction: In the WHO eligibility criteria, there is agreement that hypertensive women taking Oral Contraceptive Hormonal Combined (OCHC) may be at increased risk of cardiovascular disease. The risk-to-benefit ratio hinges on the severity of the condition. While a mild increase in blood pressure is a common occurrence in consumers of OCHC, the potential for developing high blood pressure exists during oral contraceptive use. Consequently, there is a possibility of increased cardiovascular risk, with limited available data on this issue.
Objective: To evaluate the potential effects of OCHC on blood pressure through a systematic review with statistical analysis of existing randomized controlled trials.
Method: This systematic review with statistical comparison adheres to the recommendations outlined in the PRISMA (Principal Reporting Items for Systematic Reviews and Meta-analyses) guidelines. The analysis strategy involves comparing the mean difference in blood pressure change according to the type of treatment, in addition to the calculation of clinically relevant outcomes (CRO).
Results: Our findings suggest a clinically relevant outcome related to the increase in blood pressure in users of ethinyl estradiol combined with gestodene in a cyclic regimen over 6 months. Conversely, a decrease in blood pressure was observed among users of ethinyl estradiol combined with chlormadinone over 24 months of usage.
Conclusion: While our study found minor variations in blood pressure across varying forms of oral contraceptives, these differences are not significant enough to warrant specific clinical recommendations. However, the results suggest that individuals with hypertension should exercise caution with ethinyl estradiol, particularly when administered cyclically alongside gestodene, due to the potential risk of increased blood pressure. Additionally, the use of oral contraceptives containing ethinyl estradiol paired with chlormadinone acetate or ethinyl estradiol combined with drospirenone may be more suitable for individuals at a high risk of developing hypertension.

1. Introduction

Oral Contraceptive Hormonal Combined (OCHC) refers to orally administered drugs designed to prevent conception by suppressing ovulation through various mechanisms. These include inhibiting the release the release of the gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland, modifying cervical mucus to impede sperm migration, and altering tubal ciliary cells to hinder ovum transport. The pills are classified as follows: a) combined, which contain both an estrogen and a synthetic progestogen; b) isolated progestogen [1].

OCHC stands as one of the most utilized contraceptive method worldwide, with an estimated 100 million women relying on them for birth control due to their effectiveness. When used correctly, the failure rate of OCHC is less than one per 100 women per year, though this figure increases to five per 100 women per year with improper use [2]. In

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Brazil, approximately 27 % of women of reproductive age reportedly use OCHC [1].

Advancements in technology and the development of new drugs have led to a significant reduction in the steroid content of OCHC pills. Additionally, there has been a proliferation of formulations aimed at minimizing the dosage of synthetic hormones, particularly estrogen. This is crucial as higher estrogen doses have been associated with increased risks of thromboembolism, hyperlipidemia and systemic hypertension [3–5].

Systemic hypertension is characterized as a chronic non-communicable disease with multifactorial causes, encompassing functional, structural, and metabolic alterations [6]. These changes significantly contribute to cardiovascular morbidity and mortality.

The use of ethinyl estradiol used in OCHC leads to an increase in hepatic proteins, such as albumin and sex hormone-binding globulin (SHBG). While this change does not result in clinically relevant effects, it does elevate the renin substrate, leading to angiotensin synthesis and stimulation of aldosterone production by the adrenal cortex. Consequently, vasoconstriction and sodium retention occur, followed by water retention [6].

Furthermore, ethinyl estradiol is implicated in the elevation of coagulation factors, particularly factors VII and XII, along with decreased levels of antithrombin III and increased plasminogen activator inhibitor (PAI-1), resulting in pro-thrombotic profile [1]. Elevated fibrinogen levels lead to increased deposition in injured vascular endothelium, potentially increasing the risk of thromboembolism and vascular stiffness, thereby contributing to elevated blood pressure [7].

Platelets, when activated, can rapidly adhere to various surfaces, containing vasoconstrictive agents such as serotonin, epinephrine, and synthesize thromboxane A2. This adherence may lead to intense vascular spasms, potentially damaging vessels, especially when activated near the endothelium. Hemodynamic changes described, including those in the renin-angiotensin-aldosterone system, insulin sensitivity, and erythrocyte-cation transport, have been documented in the literature, independent of the estrogenic and progestogenic components of OCHC, suggesting their possible contribution to these alterations [8].

While the majority of women receiving estrogen-containing OCHC remain normotensive, a small percentage may experience a rise in blood pressure. Epidemiological data also indicate a slight increase in hypertension incidence associated with OCHC use, affecting approximately 5 % of women using contraceptives for five years [4].

According to the World Health Organization eligibility criteria [9] for low-dose combined oral contraceptives (OCHC containing ≤ 35 mg ethinyl estradiol) in hypertensive individuals, current formulations with low estrogen doses pose minimal risk of hypertension development. However, prescribing OCHC should consider individual patient characteristics, particularly in those with a history of hypertension.

In summary, while there is agreement within WHO criteria that hypertensive women taking OCHC may face an elevated risk of cardiovascular disease, the risk-to-benefit ratio depends on the severity of the condition. While a slight increase in blood pressure is common among OCHC users [1], significant elevation during use may exacerbate existing conditions.

This variant poses a significant risk due to its typical complications, making it a major global public health concern. These complications include stroke, acute myocardial infarction (AMI), acute or chronic renal failure, retinopathy, and others. Given the widespread use of OCHC among women and lingering uncertainties regarding the association between hypertension and OCHC use, it is essential to evaluate clinical studies in the literature to assess the potential adverse effects of OCHC.

2. Methods

This study represents a systematic review with statistical comparison on interventions derived from Randomized Clinical Trials (RCTs). It adheres to the recommendations outlined in the PRISMA (Main Items to Report Systematic Reviews and Meta-Analyses) [10] guidelines. The study was instigated by a clinical question formulated using the PICO strategy, which stands for Patient, Intervention, Comparison and Outcomes. These recommendations are considered essential for the preparation of a consistent systematic review study of clinical trials.

2.1. Protocol and registration

As recommended in the literature, prior to the data extraction, the present study was registered with the PROSPERO Systematic Review protocol database (registration code: CRD42022379900) to ensure transparency and rigor in the research process. The objectives of this registration include preventing duplication of studies on the selected topic, offering full transparency regarding the methodology employed, and confirming or enhancing the methodological quality of the ongoing study.

2.2. Eligibility criteria

For the eligibility criteria of this study, we opted to include Randomized Clinical Trials directly related to the central theme, without language restrictions, published in the last 15 years, and presenting sufficient content to address the clinical question. The evaluation encompassed adult females, irrespective of body type or functional status, with or without comorbidities. Drawing from the state-of-the-art overview presented in the study's introduction, the following clinical question was formulated: "Do women who use oral contraceptives face an increased risk of developing hypertension?".

2.3. Information sources and search

Based on the clinical question, the following terms were extracted and identified as scientific descriptors with the DeCS Terms (http://decs.bvs.br/) and MeSH Terms (https://www.ncbi.nlm.nih.gov/mesh/) systems: "Contraceptives", "Contraceptive Agents", "Contraceptives, Oral", "Blood Pressure" and "Hypertension". On 7th May 2022, scientific documents were searched in PubMed (Medline) (https://www.ncbi.nlm.nih.gov/pubmed/), Scopus (http://www.scopus.com), EMBASE (https://www-embase.ez67.periodicos.capes.gov.br/) and Web Of Science (https://www.webofscience.com/wos/woscc/basic-search).

These descriptors were used interleaved with the Boolean operators 'AND' and 'OR', as follows: ("Contraceptives" OR "Contraceptive Agents" OR "Contraceptives, Oral") AND ("blood pressure" OR "hypertension"). Filters such as "last 10 years" and "randomized clinical trials" were used.

To gather a comprehensive array of evidence, a "snowball" search was performed from the references of included articles, in addition to the search in the references of the "Eligibility Criteria for Contraceptive Use" elaborated by the World Health Organization [9].

2.4. Study selection and data collection

All the documents found were gathered in the virtual environment of the Rayyan QCRI application - Qatar Computing Research Institute [11, 12], for the identification and elimination of all the duplicates existing among the documents related in the different databases.

Next, the 1st step of the eligibility evaluation for inclusion or exclusion of each of the related documents was performed in a paired manner between two reviewers who were members of the research team. In this step, after reading the article, each reviewer pointed in a spreadsheet one of the three options (included, maybe, or excluded), and these individual options were transferred to a general spreadsheet, followed by the definition of the eligibility of each study by absolute agreement between the options pointed out by each reviewer.

In cases where discrepancies arose between the reviewers' assessments or when uncertainty persisted ("maybe" designation), resolution

was reached by consulting a third researcher, in accordance with literature recommendations. Quantitative data pertaining to the document identification process across various databases up to the exclusion stage, as well as details regarding screening, eligibility assessment, and subsequent inclusion or exclusion of scientific documents for analysis, are shown in the flowchart (Fig. 1).

Data related to the primary or secondary variables, such as: methodological components, general characteristics of the participants, intervention and/or diagnostic procedures, assessed outcomes and assessment methods, and the results obtained, among others, were selected and extracted independently among the examiners, as described above. This process extended to resolving any discrepancies regarding specific data points.

2.5. Risk of bias and quality of evidence assessment

Considering the choice for studies of the type, randomized controlled trials, the included documents will be evaluated in a paired way between the evaluators, based on the instrument 'Risk of Bias in randomized trials - RoB2' proposed by the Cochrane Collaboration [12], in which the domains of selection, performance, detection, follow-up, reporting and others are evaluated with the objective of evaluating the risk of bias in randomized trials included, considering the variation of the classification of bias as: high, uncertain and low. The GRADE method was used to grade the quality of evidence and the strength of health recommendations of our findings [13].

2.6. Statistical analysis

The data analysis strategy involved comparing the mean difference in blood pressure changes as a function of treatment types. The control group consisted of individuals using non-hormonal contraceptive, while the intervention group included those using any contraceptive formulation containing hormones. The equations utilized to extract the mean difference and standard deviation of blood pressure were as follows:

$$Diff_{mean} = mean_{end} - mean_{initial}$$

$$Diff_{SD} = \sqrt[2]{SD_{initial}^2 + SD_{end}^2}$$

Mean and standard deviation differences were computed individually for both systolic and diastolic blood pressure.

The database used in the data analysis can be found in Supplementary Material Sheet S1. This database was imported into the program *R* v. 4.2.1 using the package *readxl* v. 1.4.1. Control and intervention values were generated using the *rnorm* function, utilizing the mean difference ($Diff_{mean}$), difference in standard deviation ($Diff_{SD}$) and the sample size of each group (refer to the database for details). A two-sample t-test was conducted 100 times between the simulated control and intervention values. The average p-value was computed from the results of these tests. Statistical significance was inferred if the mean p-value was less than 0.05; otherwise, no significant differences were assumed.

Charts displaying the values $Diff_{mean}$ e $Diff_{SD}$ for both systolic and diastolic pressures were generated. The R script detailing the step-by-step data analysis process is provided in Supplementary Material Text S1.

2.7. Clinically relevant outcomes

The clinically relevant outcome (CRO) was determined by calculating the percent change in blood pressure from baseline, with the following equation:

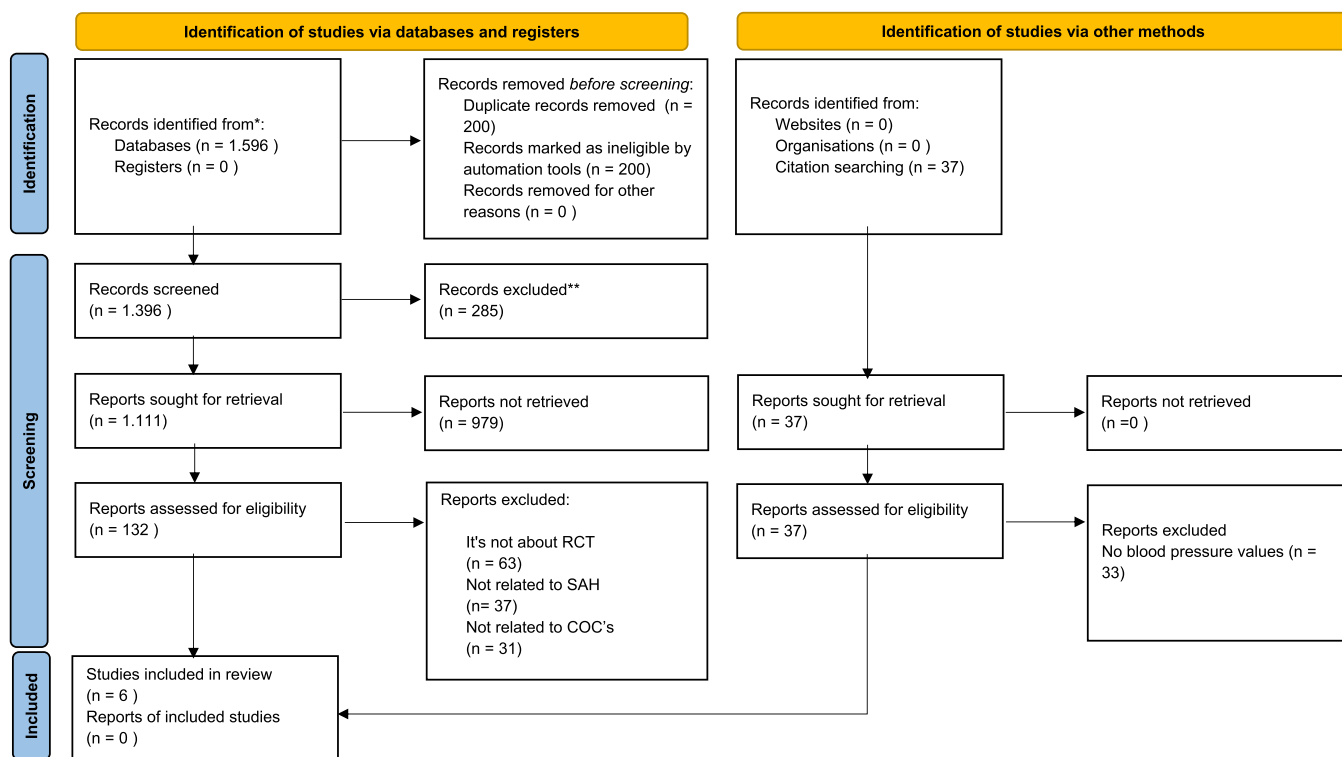$$CRO(\%) = \frac{|Diff_{mean}|}{Baseline_{mean}}$$

Fig. 1. BMJ 2021;372:n71. DOI: 10.1136/bmj.n71, PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.
Source: [10]Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.

The formula computes the relative frequency (expressed as a percentage) by comparing the modulus of the mean difference (final minus initial) to the mean initial (baseline) value. CRO values are categorized as follows: changes up to 5 % (i.e., 5 % points of relative blood pressure change) are considered not relevant, 5–10% are considered relevant, and changes exceeding 10% are regarded as highly clinically relevant.

These outcome criteria were established a priori to mitigate the risk of drawing erroneous conclusions by exhaustively testing multiple variables until statistical significance is achieved. The selection of a 5 % threshold to distinguish between normal and significant changes in blood pressure is based on the findings of Bobrow et al., 2014 [14]. These authors conducted a randomized controlled trial to test the effectiveness of a system designed to improve blood pressure control and adherence to treatment versus usual care in adults treated for hypertension in a single primary care center in Cape Town, South Africa. Their study posited that a decrease of 5 mmHg in systolic blood pressure correlates with a clinically meaningful reduction in the relative risk of stroke and coronary heart disease, as corroborated by Collins et al., 1990 [15].

Considering that normotensive women of reproductive age typically exhibit an average systolic blood pressure of 110 mmHg [16], a 5 mmHg change equates to a percentage change of 4.545 % (5/110 mm Hg) or 5 % for simplicity. In this study, we extend this 5 % threshold to signify clinically relevant results for both systolic and diastolic pressures, regardless of direction (increase or decrease), and across a biological gradient (0–5 %, no clinical relevance; 5–10%; clinically relevant; and >10 %, highly clinically relevant).

2.8. Ethical aspects

Although ethical approval is not required in this type of study, the ethical character of the present study will be assured by the strict fulfillment of the commitments made to the registration system, as well as the assurance of the veracity of the realization of each step and, the

due consideration of the task performed by the different authors who are members of the research team during its construction process.

3. Results

3.1. Selection of studies

Of the 1596 references found in the databases, 132 underwent comprehensive analysis, resulting in the inclusion of six for systematic review. Additionally, three articles were included through snowball searching in the references of the selected articles (Fig. 1). Two independent reviewers analyzed the risk of bias using the Cochrane tool, resolving any discrepancies with the involvement of a third reviewer. In total, the study included data from n = 515 women. The methodological quality of the included studies was summarized in a table (Fig. 2).

3.2. Characteristic of the studies

RCTs evaluating the use of ethinylestradiol, drospirenone, chlormadinone acetate, gestodene and levonorgestrel-releasing intrauterine device (LNG-IUD) were selected for inclusion in the analysis. The results are presented in Table 1.

3.3. Primary results

Figs. 3 and 4 show the comparison of mean differences in blood pressure changes based on treatment type, with non-hormonal contraceptives serving as the control and any hormone-containing contraceptive formulation as the intervention. The analysis revealed a significant increase in both systolic (p = 0.02) and diastolic (p = 0.004) blood pressure among users of cyclic oral contraceptives when compared to the control group.
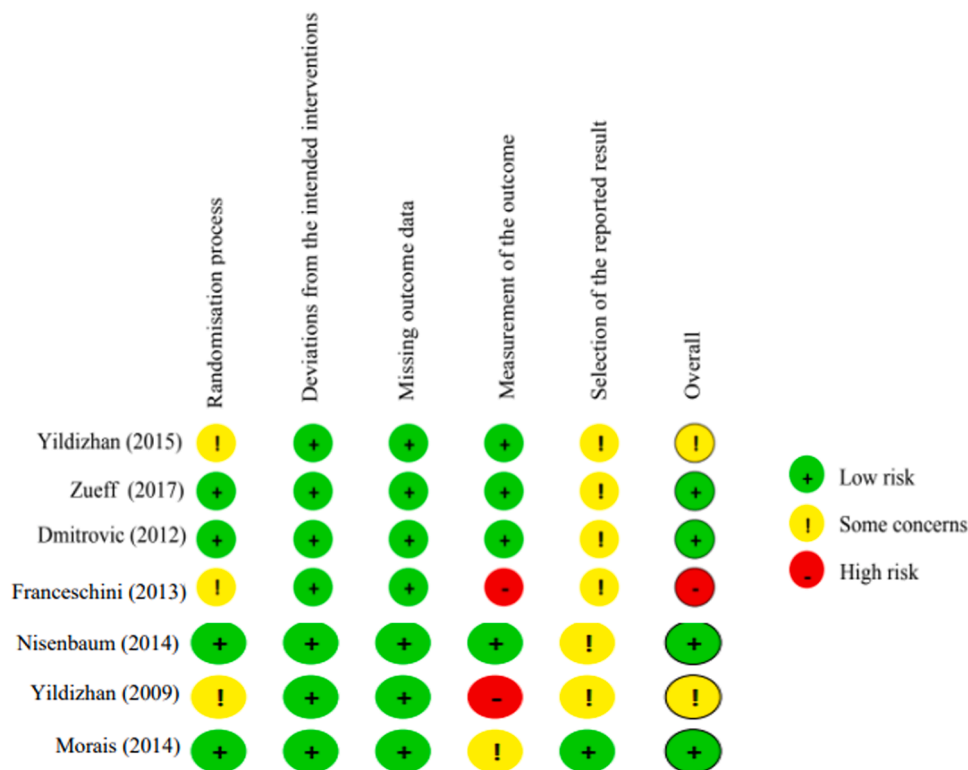

Fig. 2. Assessment of risk of bias by Risk of Bias 2 (RoB 2) tool - Cochrane Methods.
Source: Authors.

Table 1
Characterization of the studies included in the analysis.

AUTHOR	INTERVENTION Group A	n	Group B	n	GRADE	BASELINE Group A SBP	DBP	Group B SBP	DBP	OUTCOME 3 MONTHS Group A SBP	DBP	Group B SBP	DBP	12 MONTHS Group A SBP	DBP	Group B SBP	DBP	24 MONTHS Group A SBP	DBP	Group B SBP	DBP
1	Ethinylestradiol 0,03 mg +drospirenone 3 mg	56	Ethinylestradiol 0,03 mg + clormadinone 2 mg	50	Moderate	114,71 ±17.93	73.5 ±6.79	15,0 ±9.53	70,3 ±8.04	2.04 ±18.41	5.63 ±6.95	5.20 ±6.46	4.80 ±6.39	3.46 ±19.54	6.88 ±7.66	6.40 ±7.76	5.80 ±8.04	4.18 ±17.88	7.05 ±8.08	6.80 ±8.19	7.40 ±9.54
2	UID levonorgestrel	42	non-hormonal method of contraception	40	Moderate	125.5 ±9.6	83.4 ±8.2	126.9 ±12.7	83.4 ±8.2	-	-	-	-	5.20 ±10.6	4.38 ±8.4	-	-	-	-	-	-
3	Ethinylestradiol 20 mcg + Gestodene 0.075 mg cyclic	19	Ethinylestradiol 20 mcg + Gestodene 0.075 mg continuous	19	Low	101.8 ±8.1	60.6 ±7	107.2 ±6.7	65.3 ±6.1	10.5 ±2.72	11 ±3.01	2.4 ±2.6	3.1 ±2.9	-	-	-	-	-	-	-	-
4	Nonhormonal methods	64	Etinilestradiol 30 mcg + 2 mg clomadinone	22	Moderate	109.6 ±10.3	74.3 ±6.7	112.9 ±7.9	77.3 ±6.1	2.3 ±10.3	1.7 ±6.5	0.4 ±7.3	3 ±6.7	-	-	-	-	-	-	-	-
5	Ethinylestradiol 0.03 mg + 0.075 mg gestodene	71	Ethinylestradiol 0.03 mg +3 mg drospirenone	72	Moderate	109.27 ±9.99	74.18 ±5.25	109.19 ±9.94a	73.85 ±5.27	1.03 ±9.52	0.93 ±5.36	3.02 ±7.79	-1.42 ±4.97	0.52 ±9.65	-0.39 ±6.18	-5.79 ±13.10	-1.66 ±5.00	-	-	-	-
6	Non-hormonal method of contraception	30	Ethinylestradiol 20 mcg +3 mg drospirenone	30	Moderate	129.0 ±2.5	87.6 ±1.9	127.8 ±2.1	83.9 ±1.3	1.03 ±2.4	-0.6 ±1.4	-1.2 ±2.5	-0.2 ±1.8	-	-	-	-	-	-	-	-

(1) Yildizhan et al. (2015); (2) Zueff et al. (2017); (3) Dmitrovic et al. (2012); (4) Nisenbaum et al. (2013); (5) Franceschini et al. (2013); (6) Yildizhan et al. (2009); *Non-hormonal contraceptive method: non-hormonal copper intrauterine device (IUD), male condom, diaphragm, female condom; (SBP) systolic blood pressure; (DBP) Diastolic blood pressure

3.4. Clinically relevant outcomes (CRO)

In the control group, the change in blood pressure after 12 months of non-hormonal contraceptive use was − 0.9 mmHg (initial=126.9 mmHg and final=126 mmHg; systolic blood pressure) and − 0.5 mmHg for diastolic blood pressure (initial=83.4 mmHg and final=82.9 mmHg) (see Table 1; Fig. 3; Fig. 4). However, these changes were clinically not relevant, with systolic CRO at 0.9 % and diastolic CRO at 0.3 %. Table 2 presents the percentage of clinically relevant changes in blood pressure.

The mean relative blood pressure changes observed for the hormonal interventions, relative to baseline values, were consistently greater than 1 %. Specifically, endpoints deemed not clinically relevant (with relative changes <5 %) included levonorgestrel intrauterine system (LNG_IUS) at 12 months (2.4 % for systolic and 1.7 % for diastolic) and ethinylestradiol associated with gestodene continuously at 12 months (0.9 % for systolic and 1.3% for diastolic).

Clinically relevant outcomes (with relative changes falling between 5–10 %) were noted for ethinylestradiol associated with drospirenone (EE_DRSP) at 24 months (3.6 % for systolic and 9.6 % for diastolic) and ethinylestradiol associated with chlormadinone acetate (EE_CMA) at 6 months (5.6 % for systolic and 8.3 % for diastolic) and at 12 months (5.7 % for systolic and 8.3 % for diastolic).

Finally, endpoints classified as clinically relevant (relative changes >10 %) were identified for ethinyl estradiol associated with chlormadinone (5.9 % for systolic and 10.5 % for diastolic over 24 months) and cyclic gestodene associated with ethinyl estradiol over 6 months (10.3 % for systolic and 18.2 % for diastolic).

Furthermore, in cases where relative changes exceeded 10 % (representing highly clinically relevant outcome), the direction (positive or negative) of change varied. Specifically, a decrease in diastolic blood pressure was observed in the ethinylestradiol-associated chlormadinone intervention after 24 months, while conversely, an increase in both systolic and diastolic blood pressure was noted in the ethinylestradiol-associated cyclic gestodene intervention after 6 months.

4. Discussion

The apprehension surrounding the use of combined or uncombined hormonal contraceptives stems from concerns about potential side effects and associated risks, including breast cancer [17,18]. However, there are various combinations of estrogens and progestogens with different characteristics, some of which may present a more favorable profile for the cardiovascular system while other may pose increased risks.

Our findings suggest that the use of oral, cyclical ethinylestradiol associated with gestodene appears to exert the most negative impact on both systolic blood pressure (SBP) and diastolic blood pressure (DBP). Conversely, the association of ethinylestradiol and chlormadinone acetate exhibits the least impact on both systolic and diastolic blood pressure in the short term. Over the long term, spanning more than one year, ethinylestradiol combined with drospirenone and ethinylestradiol combined with chlormadinone acetate did not have adversely affect systemic blood pressure and even showed a reduction in blood pressure values over the course of the study. Therefore, the composition of hormonal contraceptive may play a crucial role in determining endothelial dysfunction and influencing the risk of systemic hypertension.

Orshal & Khalil [19] investigated the impact of estrogen on vascularization and concluded that estrogen receptors enhance nitric oxide availability, thereby contributing to the flow-mediated vasodilator (FMD) effect. Similarly, Dos Santos et al. [20] affirmed that estrogen attenuates vasoconstrictor responses to noradrenaline. However, when estradiol is combined progesterone at supraphysiological levels, endothelium relaxation may be inhibited, exacerbating the vasoconstrictor response of estrogen alone. Therefore, the effects of the contraceptives result from the combined actions of both hormones, impeding
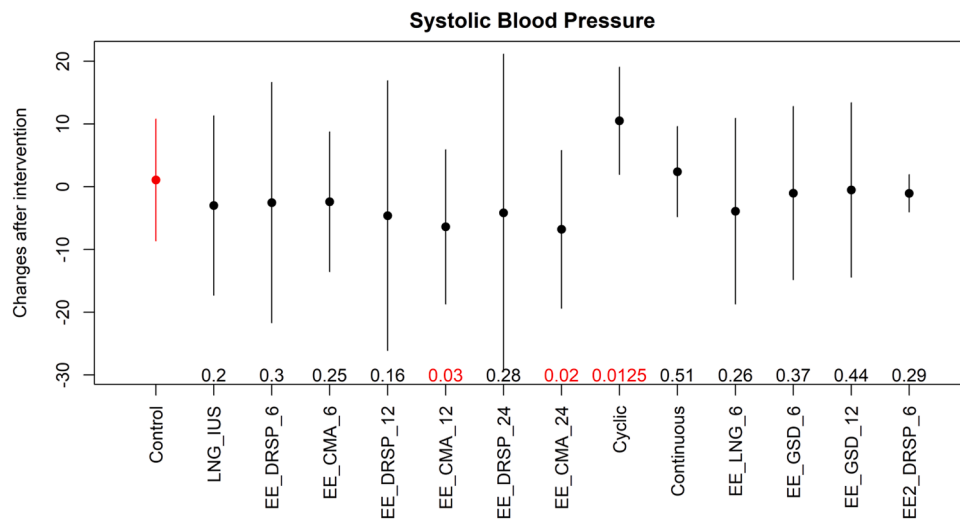
Systolic Blood Pressure

Fig. 3. Comparison of the mean difference in systolic blood pressure change based on treatment type. **Abbreviation:** (Control) Control group; (LGN_IUS) Levonorgestrel Intrauterine System; (EE_DRSP) ethinylestradiol associated with drospirenone in 6 months; (EE_CMA) ethinylestradiol associated with chlormadinone acetate in 6 months; (EE_DRSP) ethinylestradiol associated with drospirenone in 12 months; (EE_CMA) ethinylestradiol associated with chlormadinone acetate in 12 months; (EE_DRSP) ethinylestradiol combined with drospirenone at 24 months; (EE_CMA) ethinylestradiol combined with chlormadinone acetate at 24 months; (Cyclic) Group using ethinylestradiol combined with gestodene cyclically; (Continuous) Group using ethinylestradiol combined with gestodene continuously.

Dyastolic Blood Pressure

Fig. 4. Comparison of the mean difference in diastolic blood pressure change based on treatment type. **Abbreviation:** (Control) Control group; (LGN_IUS) Levonorgestrel Intrauterine System; (EE_DRSP) ethinylestradiol associated with drospirenone in 6 months; (EE_CMA) ethinylestradiol associated with chlormadinone acetate in 6 months; (EE_DRSP) ethinylestradiol associated with drospirenone in 12 months; (EE_CMA) ethinylestradiol associated with chlormadinone acetate in 12 months; (EE_DRSP) ethinylestradiol combined with drospirenone at 24 months; (EE_CMA) ethinylestradiol combined with chlormadinone acetate at 24 months; (Cyclic) Group using ethinylestradiol combined with gestodene cyclically; (Continuous) Group using ethinylestradiol combined with gestodene continuously.
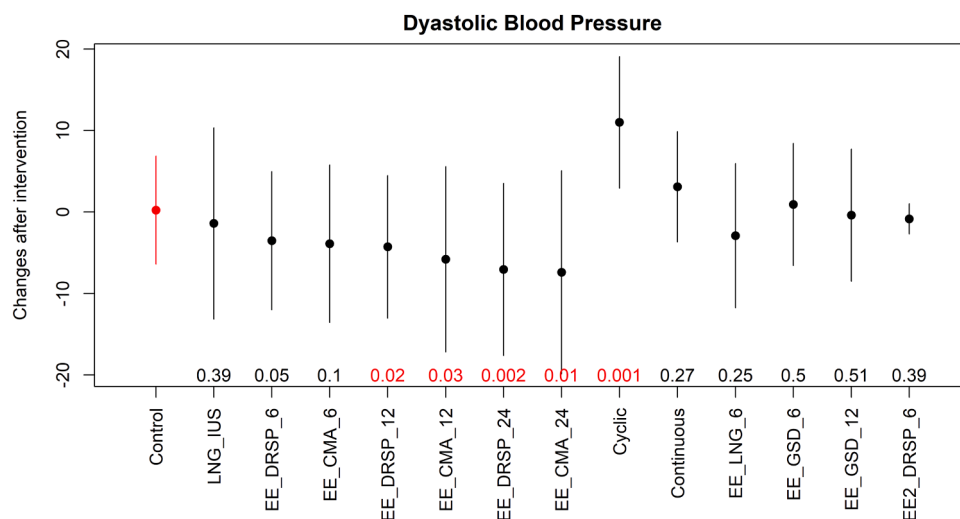
physiological vasodilation.

The estrogen can induce vasodilation by promoting nitric oxide synthesis and exerting a prostacyclin synthase effect on the endothelium. In addition, estrogen inhibits the growth and development of atherosclerosis, leading to an increase in vasodilator factors and subsequent reduction in blood pressure [21]. However, Ribeiro et al. [22], observed that estrogen also acts on aldosterone receptors, a key regulator of the Renin-Angiotensin-Aldosterone System (RAAS). The elevated plasma levels of aldosterone associated with hormonal contraceptives may disrupt vascular tone regulation and escalate oxidative stress. Therefore, this mechanism may further elucidate the observed effects of hormonal contraceptives on blood pressure regulation.

Cooper et al. [23] corroborated the involvement of estrogen in the modulation of RAAS, thereby contributing to elevated blood pressure levels. Moreover, estrogen was associated with increased oxidative

stress, vasoconstriction, and vascular remodeling. Xue et al. [24] also highlighted the role ovarian hormone signaling in RAAS-mediated hypertension.

Adler et al. [25] conducted a study investigating the impact of ethinyl estradiol on healthy women and those with mild hypertension and obesity. Their findings revealed that mild hypertension serves as a stronger predictor of endothelial dysfunction compared to obesity in otherwise healthy women without evident cardiovascular dysfunction. In contrast, Nisenbaum et al. [26] conducted a prospective controlled trial involving 69 women using contraceptive containing 20 mcg ethinylestradiol and 3 mg drospirenone. Their study did not observe significant changes in clinical, hemodynamic (blood pressure and heart rate) and autonomic parameters in healthy women.

One RCT found that an oral contraceptive (OAC) containing different dosages of ethinyl estradiol associated with progestin resulted in a

Table 2

Clinically relevant outcome (CRO) of interventions.

Groups	CRO systolic (%)	CRO diastolic (%)
Control	0,9	0,3
LNG_IUS	2,4	1,7
EE_DRSP_6	2,3	4,8
EE_CMA_6	2,1	5,3
EE_DRSP_12	4,1	5,8
EE_CMA_12	5,6	8,3
EE_DRSP_24	3,6	9,6
EE_CMA_24	5,9	10,5
EE_GTD_Cyclic	10,3	18,2
EE_GTD_Continuous	2,2	4,7
EE_LNG_6	3,4	3,8
EE_GSD_6	0,9	1,3
EE_GSD_12	0,5	0,5
EE2_DRSP_6	0,9	1,1

Abbreviation: (Control) Control group; (LGN_IUS) Levonorgestrel Intrauterine System; (EE_DRSP) ethinylestradiol associated with drospirenone in 6 months; (EE_CMA) ethinylestradiol associated with chlormadinone acetate in 6 months; (EE_DRSP) ethinylestradiol associated with drospirenone in 12 months; (EE_CMA) ethinylestradiol associated with chlormadinone acetate in 12 months; (EE_DRSP) ethinylestradiol combined with drospirenone at 24 months; (EE_CMA) ethinylestradiol combined with chlormadinone acetate at 24 months; (Cyclic) Group using ethinylestradiol combined with gestodene cyclically; (Continuous) Group using ethinylestradiol combined with gestodene continuously.

decrease in blood pressure and body weight. This suggests its potential use in women prone to weight gain and elevated blood pressure [27]. Furthermore, progestin alone as hormonal therapy reduced the risk of cardiovascular disease in early menopausal women with stage 1 hypertension. Significant reductions in body mass index, total cholesterol, low-density lipoprotein cholesterol and apolipoprotein B concentrations were observed, while concentrations of high-density lipoprotein cholesterol and apolipoprotein increased [28]. Another prospective study evaluated the contraceptive efficacy of drospirenone alone and demonstrated a decrease in blood pressure alongside effective contraception [27]. Our study corroborated a decrease in diastolic blood pressure in the EE_DRSP intervention after 24 months.

Franceschini et al. [29] conducted a study involving 64 healthy women, 21 of whom used non-hormonal contraceptive methods (control) and 43 used hormonal contraceptive pills. They observed an increase in systolic blood pressure among women who used EE_CMA after 6 months, whereas a reduction was noted in those using EE_LNG. However, diastolic blood pressure significantly decreased in women using EE_CMA after 6 months as well as in the EE_LNG group. Our study confirmed a clinically relevant decrease in DBP in women using EE_CMA over a 12-month period.

Regarding the mode of administration, Dmitrovic et al. [28] conducted a double-blind clinical trial. They concluded that continuous administration may offer benefits over cyclic administration in terms of pain reduction. However, they noted potential unpleasant side effects such as weight gain observed in the research.

Franceschini et al. [29] conducted a study involving healthy women using non-hormonal contraceptive method (control) and another group using hormonal contraceptive pills. Within the latter group, participants were randomized into two subgroups: one consuming 30 mcg of ethinyl estradiol associated with 3 mg of chlormadinone acetate, and the other receiving 30 mcg ethinyl estradiol associated with 150 mcg of levonogestrel. Systolic blood pressure increased among women who used EE_CMA after 6 months and decreased in women who used EE_LNG. However, DBP significantly decreased in women using EE_CMA after 6 months as well as in the EE_LNG group.

Nisenbaum et al. [26] confirmed that there were no significant differences in SBP or DBP values between groups. In our study, we observed a decrease in both DBP and SBP with EE_DRSP compared to other hormonal pills. Differently, in a randomized clinical trial by Yildizhan et al.

[30], who included 145 healthy women randomized between EE_GTD (n = 71) and EE_DRSP (n = 72) pills for 12 months, EE_DRSP showed favorable effects in decreasing both SBP and DBP. In contrast, the group using EE_GTD maintained mean SBP and DBP values. There were no clinically significant changes observed in cardiovascular risk markers among obese women 12 months after the placement of a levonorgestrel-releasing intrauterine system [31].

Yildizhan et al. (2009) [32] compared the effect of ethinylestradiol 0.03 mg/gestodene 0.075 mg (EE/GSD) with ethinylestradiol 0.03 mg/drospirenone 3 mg (EE/DRSP) on blood pressure (BP) and lipid metabolism in 160 healthy women. This study found that the EE/DRSP regimen provides good cycle control with reliable contraceptive efficacy and a low incidence of adverse events.

A RCT study conducted by Mansour et al. [33] evaluated the efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17beta-estradiol compared to EE_DRSP. The study involved 1552 women who completed the trial over 13 cycles. No significant differences in mean blood pressure values were observed between the two groups.

The "Safety of Contraceptives: Role of Estrogens" (INAS-SCORE) study, a cohort study, evaluated 50,203 users who were followed up for a mean of 2.1 years. This study investigated cardiovascular risks among users of dienogest and estradiol valerate (DNG_EV) based contraceptive pills compared to OACs commonly used in clinical practice. The study concluded that DNG_EV users experienced a twofold decrease in the risk of serious cardiovascular events compared to other combined hormonal contraceptives [34].

In another meta-analysis, researchers identified an association between duration of oral contraceptive use and risk of systemic hypertension. The findings demonstrated that the combined relative risk of hypertension for the highest versus the lowest category of oral contraceptive duration increased linearly. Specifically, the risk of hypertension increased by 13 % for every 5-year increase in oral contraceptive use [35].

4.1. Limitations and strength of the study

Since individual patient data were not available, we resampled the normal distribution of the population to include the values extracted from the clinical trials (mean, standard deviation, and sample size). This resampling was essential for applying the statistical tests, although it was not necessary for generating the figures. Resampling can yield reliable results. However, to complement and validate the statistical findings, we also applied a clinically relevant outcome approach.

Due to the heterogeneity of interventions (varying active ingredients, dosages, and administration methods), a meta-analysis could not be generated. Additionally, the limited number of trials necessitates caution when interpreting the results of such analyses, as they may have reduced statistical power.

The choice of contraceptive method (COC or non-hormonal) depends on many factors, in Brazilian research it is reported that COC is the contraceptive method most used by young women, with preferential use among low-income women starting contraception with this method [36, 37]. Another aspect to be considered is that the dosages of estrogen (ethinyl estradiol) were reduced over time [38] and the type of progestogen was changed with preference for progestogens with less cardiovascular effect [39], which may interfere in the comparison of results. In addition to the lake of prospective literature on the subject.

5. Conclusion

Our study identified minor fluctuations in blood pressure among different oral contraceptive formulations. However, these variations do not carry significant implications for clinical recommendations. Nonetheless, our findings suggest caution for individuals with hypertension regarding ethinyl estradiol, especially when administered cyclically

with gestodene, due to a potential risk of elevated blood pressure. Additionally, oral contraceptives containing ethinyl estradiol combined with chlormadinone acetate or drospirenone may be more preferable for individuals at higher risk of developing hypertension.

CRediT authorship contribution statement

Ingrid Soares de Souza: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **José Maria Soares Júnior:** Writing – review & editing, Validation, Supervision, Investigation. **Rodrigo Daminello Raimundo:** Visualization, Validation, Supervision, Methodology. **Gabriel Zorello Laporta:** Supervision, Software, Methodology, Formal analysis. **Juliana Zangirolami-Raimundo:** Supervision, Data curation, Conceptualization. **Isabel Cristina Esposito Sorpreso:** Writing – original draft, Validation, Supervision, Data curation, Conceptualization. **Heloisa Carla Lopes Silva dos Santos:** Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eurox.2024.100307.

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