

Effects of different hormonal contraceptives in women's blood pressure values

Efeitos dos diferentes anticoncepcionais hormonais nos valores de pressão arterial da mulher
Efectos de los distintos anticonceptivos hormonales en los valores de presión arterial de la mujer

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How to cite this article:

Ribeiro CCM, Shimo AKK, Lopes MHBM, Lamas JLT. Effects of different hormonal contraceptives in women's blood pressure values. Rev Bras Enferm [Internet]. 2018;71(Suppl 3):1453-9. [Thematic Issue: Health of woman and child] DOI: <http://dx.doi.org/10.1590/0034-7167-2017-0317>

Submission: 06-14-2017

Approval: 09-01-2017

ABSTRACT

Objective: To identify evidence in the literature of the relationship between the use of different hormonal contraceptive methods and alterations in women's blood pressure values. **Method:** This is an integrative literature review, consisting of ten scientific articles published in PubMed and BVS, between 2012 and 2016, selected by keywords, available fully and free of charge, in English, Portuguese, or Spanish. **Results:** The articles showed that exogenous estrogen helps in the activation of the renin-angiotensin-aldosterone system causing hypertensive effects even in small doses; and that combined use with drospirenone reduces these effects. Routes of administration without passage through the liver and use of isolated progestin showed promising results in reducing the effects on blood pressure. **Conclusion:** There is evidence in the literature of pressure alterations associated with different hormonal contraceptives and that personal history of morbidities are to be considered in an attempt to reduce the effects on the cardiovascular system.

Descriptors: Female Contraceptives; Oral Hormonal Contraceptives; Female Contraceptive Devices; Intrauterine Devices; Blood Pressure.

RESUMO

Objetivo: Identificar na literatura evidências sobre a relação entre o uso de diferentes métodos anticoncepcionais hormonais e as alterações nos valores de pressão arterial em mulheres. **Método:** Trata-se de revisão integrativa da literatura, constituída por dez artigos científicos publicados no PubMed e BVS, entre 2012 e 2016, selecionados por meio de palavras-chave, disponíveis na íntegra, gratuitos, em inglês, português ou espanhol. **Resultados:** Os artigos mostraram que o estrogênio exógeno contribui na ativação do sistema renina-angiotensina-aldosterona causando efeitos hipertensores mesmo em pequenas dosagens; e que o uso combinado com a drospirenona reduz esses efeitos. Vias de administração sem passagem pelo fígado e uso do progestágeno isolado mostraram resultados promissores na redução dos efeitos sobre a pressão. **Conclusão:** Há evidências na literatura de alterações pressóricas associadas a diferentes anticoncepcionais hormonais e de que antecedentes pessoais de morbidades devem ser considerados na tentativa de reduzir os efeitos sobre o sistema cardiovascular.

Descritores: Anticoncepcionais Femininos; Anticoncepcionais Orais Hormonais; Dispositivos Anticoncepcionais Femininos; Dispositivos Intrauterinos; Pressão Sanguínea.

RESUMEN

Objetivo: Identificar en la literatura evidencias sobre la relación entre el uso de distintos métodos anticonceptivos hormonales y las alteraciones en los valores de presión arterial en mujeres. **Método:** Se trata de la revisión integrativa de la literatura, constituida por diez artículos científicos publicados en PubMed y BVS, entre 2012 y 2016, seleccionados por medio de palabras-clave, disponibles en su totalidad, gratuitos, en inglés, en portugués o en español. **Resultados:** Los artículos han enseñado que el estrógeno exógeno aporta en

la activación del sistema renina-angiotensina-aldosterona causando efectos hipertensivos aunque en pequeñas dosificaciones; y que el uso combinado con la drospirenona reduce esos efectos. Vías de administración sin pasaje por el hígado y el uso del progestágeno aislado han enseñado resultados promisorios en la reducción de los efectos sobre la presión. **Conclusión:** Hay evidencias en la literatura de alteraciones presóricas asociadas a distintos anticonceptivos hormonales y de que antecedentes personales de morbilidades deben ser considerados en el intento de reducir los efectos sobre el sistema cardiovascular.

Descriptores: Anticonceptivos Femeninos; Anticonceptivos Orales Hormonales; Dispositivos Anticonceptivos Femeninos; Dispositivos Intrauterinos; Presión Sanguínea.

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INTRODUCTION

In Brazil, in 2015, 79% of women used some sort of contraceptive method as family planning, representing an index 28% greater than the registered in 1970. Of this group, hormonal contraception (reversible), such as contraceptive pills, was the first choice of most women, second place only for fallopian tubes ligation (irreversible)⁽¹⁾.

This type of medication is a formulation combining estrogen and progestogen or simple presentations of isolated progestogen. It can be found in several formulations (concentration of hormones) and different routes of administration (oral, intramuscular, subdermal implants, transdermal, vaginal, and associated with the intrauterine system). It acts with the purpose of blocking ovulation and changing the conditions of the uterus and the fallopian tubes, thus hindering fertilization⁽²⁾.

Due to the presence of estrogen and progesterone receptors in all constituent layers of the blood vessels, the effects of female sex hormones contained in contraceptives on the cardiovascular system has been subject of scientific interest⁽³⁾. Older studies have showed that the use of contraceptive pills potentialized the increase in systolic blood pressure (SBP) in groups of women who usually presented higher pressure levels⁽⁴⁾. Recent studies also highlight that combined hormonal contraceptives (CHC), for containing ethinylestradiol (EE), always change the blood pressure (BP), even at low doses. Despite not causing clinical repercussions in healthy women, they should be avoided by women with high blood pressure⁽³⁾.

The substances present in these contraceptives attempt to reproduce the properties of endogenous steroids. However, EE, due to its biological potency compared to estradiol (1,000 times more potent), intensifies the production of hepatic angiotensinogen, which, in its turn, causes elevation of blood pressure by the renin-angiotensin-aldosterone system (RAAS)⁽⁵⁾. In addition, progestogen associated with the EE present in CHCs, although similar, does not reproduce all characteristics of natural progesterone⁽⁶⁾.

The first formulations containing high hormone doses, used in the 1960s and 1970s, were associated with the increase not only of incidence of hypertension, but also of risk of venous thromboembolism (VTE), acute myocardial infarction (AMI), and hemorrhagic and ischemic cerebrovascular accident (CVA). Due to these events and reduction of side effects, in the early 1980s, new formulations of CHC with smaller dosages

of EE and new progestogens with reduced androgenic action were introduced⁽⁷⁻⁸⁾. First generation pills containing 150 µg of estrogen began to have concentrations smaller than 20 µg in the fourth generation. Also, progestogen more similar to endogenous ones, such as those presenting antiminerlocorticoid effect were introduced to the market.

Despite the reduction in the concentration of the components and the emergence of formulations closer to the natural hormone, the widespread use of CHC still deserves attention during prescription due to the effects caused on the cardiovascular system. Therefore, there is a need to further investigate what are the effects on women's blood pressure of the different hormonal contraceptives available, with the aim of alerting which formulations or routes of administrations are safer for women with previous morbidities as well as healthy women.

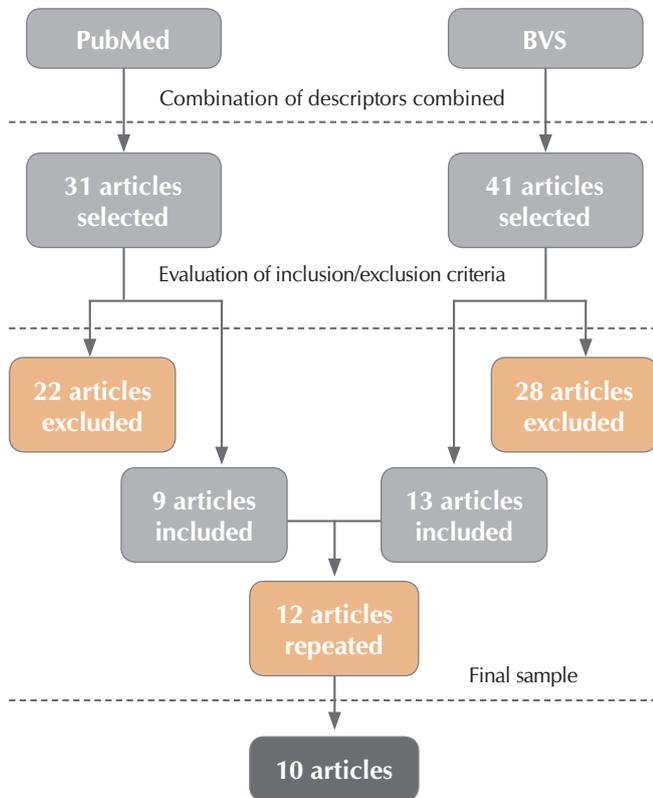
OBJECTIVE

To identify evidence in the literature of the relationship between the use of different hormonal contraceptive methods and alterations in women's blood pressure values.

METHOD

This is an exploratory research of bibliographic character developed based on previously prepared material, consisting of scientific articles. The literature search was conducted using the following descriptors: *Anticoncepcionais Femininos* (Contraceptive Agents, Female), *Anticoncepcionais Oraís Hormonais* (Contraceptives, Oral, Hormonal), *Anticoncepcionais Hormonais Pós-Coito* (Contraceptives, Postcoital, Hormonal), *Dispositivos Intrauterinos* (Contraceptive, Devices, Intrauterine), *Pressão Sanguínea* (Blood Pressure), *Hipertensão* (Hypertension). Those keywords were searched (in Portuguese) on the databases PubMed and Virtual Health Library (BVS), respecting the limits of publication between 2012 and 2016, in English, Portuguese, and Spanish.

The following inclusion criteria was established: articles that described the effects of hormonal contraceptives on the blood pressure values of women who used this type of medication. Exclusion criteria were: not meeting the criteria above; being published over five years; not having full text available and/or free access; and being written in a language other than English, Portuguese, and Spanish.



Note: BVS - Biblioteca Virtual em Saúde (Virtual Health Library)

Figure 1 – Articles selection process through the combination of descriptors and use of the filters “language”, “year of publication”, and “full text available”, Campinas, São Paulo, Brazil, 2016

RESULTS

Of the 72 articles found, 50 were excluded for not having full text available and/or not contemplating in the abstracts the relationship between the hormonal contraceptive method and blood pressure and other 12 were excluded due to repetition in the databases. Ten articles were selected for the sample. The data are presented in Chart 1.

Chart 1 – Description of the articles selected in the PubMed and Virtual Health Library databases by descriptors, Campinas, São Paulo, Brazil, 2016

Title	Year/ Language	Design	Methodology	Outcome
Transdermal contraception and the renin-angiotensin-aldosterone system in premenopausal women ⁽⁹⁾	2015 English	Prospective, non-randomized Premenopausal women (N = 30).	Application of negative pressure chamber into three groups: control (10), using contraceptive pill (10), and using contraceptive patch (10), for activation of RAAS and observation of systemic changes.	The results suggest that the use of contraceptives in the form of patches is associated with a low RAAS activation and low response by this system to caused orthostatic stress. The hypothesis is: the absence of estrogen (contained in the patch) passing through the liver reduces the production of angiotensinogen.
Modification of 24-h ambulatory blood pressure and heart rate during contraception with the vaginal ring: a prospective study ⁽¹⁰⁾	2013 English	Cross-sectional Healthy women (N = 18).	Blood pressure was monitored every 30 minutes for 41 hours, with an oscillometric device. Each participant used vaginal rings for six cycles, and pressure measurements were taken in the last days of the sixth cycle.	The results showed increased values in the 24h monitoring for diastolic pressure and average pressure. Even the smaller dose of estrogen, as contained in the vaginal ring, can stimulate the synthesis of angiotensinogen.

To be continued

DISCUSSION

Previous studies already indicated that the presence of exogenous estrogen in the body, contained in CHCs, stimulated the RAAS and caused increased systolic and diastolic pressures due to water and sodium retention, especially in hypertensive women⁽⁴⁾. Four articles included in this study⁽¹²⁻¹⁵⁾, two being reviews⁽¹²⁻¹³⁾, indicated as result the significant increase in blood pressure by use of CHC, both in hypertensive⁽¹³⁾ and normotensive^(12,14-15) women. In addition, two articles linked the extended time of use of medication to the prevalence of hypertension^(13,15); and one⁽¹⁸⁾ found high rates of hypertension in the user population of this type of medicine.

It is not known so far whether CHCs cause hypertension or simply bring out the high blood pressure that already exists and that would eventually appear spontaneously. In the article by White et al.⁽¹⁸⁾, the hypothesis for a high number of hypertensive women was developed due to the older age of the participants and not exclusively due to the use of the medication. On the other hand, the study by Kharbanda et al.⁽¹⁷⁾, observing the cardiovascular effects of CHCs in adolescents, found no changes in blood pressure.

The evaluation of the previous history of hormonal contraceptive use in postmenopausal women and its relationship with the development of hypertension, of an Australian study, did not find an association between the events in different age groups above 45 years old. This finding was common for both use and time of use, the latter divided into 0 to 5 years; 5 to 10 years; and more than 10 years⁽¹⁹⁾.

The fact is that the mechanism of development of hypertension induced by the medication is still unknown, although hemodynamic changes in the RAAS, on insulin sensitivity, and erythrocyte-cation transport have already been identified⁽²⁰⁾. The correlation between exogenous hormones and regulation of blood pressure by the sympathetic nervous system, was also studied by Harvey et al.⁽²¹⁾ and, although the results did not show changes in muscle sympathetic activity between users of CHC and non-users, in low-dose hormonal phases, placebo and follicular phase of the menstrual cycle, respectively, the average blood pressure was higher in the first group (89 ± 1

Chart 1

Title	Year/ Language	Design	Methodology	Outcome
Effects of progestin-only long-acting contraception on metabolic markers in obese women ⁽¹¹⁾	2013 English	Prospective, non-randomized Obese women, with no previous use of contraceptive pills (N = 25).	The participants were divided into three groups: non-hormonal contraceptive (8), subdermal implant (8), and Mirena IUD (9). Three visits (0, 3, and 6 months) were carried out to collect laboratory tests and perform clinical evaluations. Non-change of life habits (diet and physical activity) was guaranteed during the research.	No statistically significant differences were observed in the pressure values of the groups and in the periods of data collection.
Our Own Worst Enemy: Pharmacologic Mechanisms of Hypertension ⁽¹²⁾	2015 English	Literature review	Broad categorization of different drugs and topical discussion of the effects of each one on blood pressure and emergence of hypertension.	The articles show that the endogenous estrogen of hormonal contraceptives activates the RAAS, producing angiotensinogen by the liver and contributing to the retention of sodium and water. New generation medications, with smaller amounts of hormones, increase in 8 and 6 mmHg the systolic and diastolic pressures, respectively, when compared to non-users of hormonal contraceptives. Another conclusion taken from other articles is that hypertension is found in up to 2.8% of users.
Women-specific factors to consider in risk, diagnosis and treatment of cardiovascular disease ⁽¹³⁾	2015 English	Literature review	Discussion in topics of the biological mechanisms of the different sexes, followed by the specifically female conditions, such as the use of hormonal contraceptives.	The chronic use of combined oral contraceptives (COCs), regardless of the concentration of estrogen, can increase blood pressure values both in normotensive and hypertensive women (8 mmHg). In addition, some articles have shown that the use of COCs may increase the risk of venous thrombosis, heart attack, and CVA.
Associations between oral contraceptive use and risks of hypertension and prehypertension in a cross-sectional study of Korean women ⁽¹⁴⁾	2013 English	Retrospective and observational Women, selected from a database (N = 3,356).	Information on sociodemographic characteristics and use of oral contraceptive were collected, including time of use. Blood pressure was measured while the women were in a sitting position with their back supported, after 5 minutes of rest. A mercury gauge was used in the right arm, and three measurements were carried out. The final value was the average of the last two measurements.	The average of systolic and diastolic pressures was higher in participants who have been using oral contraceptive for longer periods. In addition, there was a significant relationship between time of use of contraceptives and prevalence of hypertension: 34.8% in the group of users for more than 24 months, against 18.1% in the group of non-users. The same relationship was observed for the prevalence of prehypertension.
Appropriate follow up to detect potential adverse events after initiation of select contraceptive methods: a systematic review ⁽¹⁵⁾	2013 English	Systematic review Articles (N = 15)	From the selected articles via PubMed, five approached incidence of SAH and use of CHC, seven of pelvic inflammatory disease and IUD, and three on weight gain and use of medroxyprogesterone. We did not find any studies on migraine and CHC.	Regarding the use of CHC and SAH: the articles, in general, showed a small percentage of women who developed high blood pressure after use for 24 months of combined contraceptives. The evidence from the study were limited, as some of the studied articles did not use the recommended methodology for pressure measurement, and one of them had a small sample size.
Effects of a contraceptive containing drospirenone and ethinylestradiol on blood pressure, metabolic profile and neurohumoral axis in hypertensive women at reproductive age ⁽¹⁶⁾	2014 English	Prospective and controlled Controlled hypertensive women (N = 56).	The participants were divided into two groups: volunteers (30) to use combined hormonal contraceptives (20mcg ethinylestradiol and 3 mg drospirenone) and volunteers (26) to use non-hormonal contraceptives. All evaluations were made in the same menstrual period. Blood pressure was measured by the auscultation method following the current recommendations, with a calibrated mercury sphygmomanometer.	Regarding blood pressure: there were no significant changes in systolic and diastolic blood pressure after 6 months in any of the groups.

To be continued

Chart 1 (concluded)

Title	Year/ Language	Design	Methodology	Outcome
Initiation of Oral Contraceptives and Changes in Blood Pressure and Body Mass Index in Healthy Adolescents ⁽¹⁷⁾	2014 English	Observational. Adolescents (N = 1,422).	The participants, selected through a medication dispensing system, were divided into two groups: using COC (510) and not using hormonal methods (912). Considering the baseline, the measures of weight, height, and blood pressure were taken in the first month of medication dispensing, and other measurements were taken during the medical visits performed after starting the medication (every 3 months). Blood pressure measures were taken in accordance with the recommendations, by trained professionals and properly calibrated instruments.	There was no statistically significant difference in systolic and diastolic blood pressure among adolescents using COC and the control group in the 3 rd , 6 th , and 12 th month of follow-up.
Hypertension among Oral Contraceptive Users in El Paso, Texas ⁽¹⁸⁾	2013 English	Prospective cohort. Women (N = 941).	The participants were divided into two groups: those who received the pills from USA clinics and those who received them from Mexican pharmacies. Four interviews were conducted, with three-month intervals between them, two (first and fourth) in person and two (second and third) by phone. Information on demographic data, history of use of contraceptive pills, presence of hypertension, and blood pressure measurement values were collected. In the last interview, blood pressure was measured.	Seven per cent of the women who took pills from the USA clinics had hypertension, against 10.5% of those who got their medication from Mexican pharmacies. The conclusion of the study was that there was a high prevalence of hypertension in women who used oral contraceptives compared to other studies, regardless of where they got their medication. In addition, the authors associated this result to the older age of the women who participated in the study.

Observation: CVA – Cerebrovascular Accident; CHC – Combined Hormonal Contraceptives; COC – Combined Oral Contraceptives; SAH – Systemic Arterial Hypertension; RAAS – Renin-Angiotensin-Aldosterone System.

mmHg) comparing to the second (85 ± 1 mmHg), reinforcing the hypertensive effects of the medication for other causes.

Even with the reduction in the concentration of ethinyl-estradiol in new-generation contraceptives and in the creation of different routes of administration for the medication, the effects on blood pressure are still being observed. The article by Cagnacci et al.⁽¹⁰⁾ showed that administration in low concentration (15 mcg/day) and via vaginal ring, whose pharmacokinetics is completely different, was able to stimulate the synthesis of angiotensinogen and increase SBP and diastolic blood pressure (DBP), with this result being observed in 24-hour monitoring of blood pressure.

The article by Oduyayo et al.⁽⁹⁾, comparing the response of the cardiovascular system to the use of oral and patch contraceptives, found a low, but present, activation of RAAS by the dermal route when stimulating orthostatic stress. The hypothesis raised by the authors was based on the absence of passage of the medication through the liver, due to its presentation, reducing the production of angiotensinogen.

In addition to the change of the route of administration, the isolated presence of progestogen, as happens in the Mirena IUD (levonorgestrel) and subcutaneous implant (etonogestrel), has also been studied as minimizer of cardiovascular effects in women. Bender et al.⁽¹¹⁾, studying the use of simple progestin

contraceptives in healthy and obese women, found no statistically significant increase of pressure values.

The results of these three studies can be based on the theory that the progestogens of second and third generations, as cited above, probably do not present a significant sodium retainer effect, however are devoid of antiminerlocorticoid action. Therefore, they are able to, in isolation, maintain the pressure values; but, in combination, are unable to control the sodium retention caused by EE, even if in small doses^(5,22).

With that in mind, drospirenone, a synthetic progestogen similar to endogenous progesterone, began to be prescribed, first as hormone replacement therapy and subsequently as birth control, due to its antiminerlocorticoid properties and anti-adrenergic activities⁽²³⁾. This drug has the effect not only of neutralizing the RAAS induction caused by estrogen, but also of blocking receptors for testosterone, reducing the androgenic effects in women⁽²⁴⁻²⁵⁾. De Moraes et al.⁽¹⁶⁾, in their study with hypertensive women undergoing regular treatment with antihypertensive drugs and combined EE contraceptives and drospirenone, observed this neutralizer effect when they were unable to find any significant changes in the blood pressure values of the participants.

Despite this and the use for decades of this combination of hormones, drospirenone, as well as other progestins,

maintains an increased risk of thrombolytic effects in the body. Data from the Dutch study MEGA (Multiple environmental and genetic assessment of risk factors for venous thrombosis-study), published in 2009, revealed risk for VTE of approximately four times for combinations containing levonorgestrel regarding risk for non-users. The risks increased about six to seven times for other progestin: gestodene, desogestrel, cyproterone acetate, and drospirenone⁽²⁶⁾.

A Danish cohort study published in the same year presented similar numbers, i.e., the relative risk of VTE in users of pills of 30 mg of ethinylestradiol and levonorgestrel was 2.9, about two times lower than the observed for desogestrel (6.6), gestodene (6.2), and drospirenone (6.4)⁽²⁷⁾.

These findings reinforce the health field concern with the increased risk of cardiovascular diseases, not just the VTE, but also CVA and AMI in women users of combined oral contraceptives⁽²⁸⁾. Thus, various aspects have been discussed as risk factors in studies, including the high doses of ethinylestradiol contained in various formulations, the androgenic properties of different types of progesterone of the various generations developed over the years, hypertension, smoking, hypercholesterolemia, diabetes mellitus, migraines, diseases background, and age (especially after 35 years old), among others⁽²⁰⁾.

It is important to emphasize that, despite the new generations of medication with reduced concentrations of hormones and the creation of new routes of administration, choosing the best medication to be prescribed must be associated with complete anamnesis and clinical evaluation, taking into consideration the personal history of morbidities and the risk-benefit of the treatment⁽²⁸⁻²⁹⁾. Hypertension is the first risk factor

for cardiovascular diseases, and its prevention and control are priority issues for public health.

Study limitations

The limitations of the study are related to the exclusion of incomplete articles, abstracts, and those in languages other than English, Portuguese, and Spanish.

Contributions to the field of nursing, health, or public policies

Studies like this contribute to the understanding of the effects of synthetic hormones in women's blood pressure values, aiding health workers in the search for better practices and correct therapies.

CONCLUSION

We conclude that there is evidence in the literature of pressure changes associated with different combined hormonal contraceptives. The presence of exogenous estrogen in the bloodstream, regardless of concentration, activates the RAAS and causes water and sodium retention. Progestogen, in its turn, is not capable of, in isolation, causing the same effects on blood pressure and, when its formulation has antiminer-alcorticoid properties, it is able to neutralize the effect of the estrogen administered in combination.

Despite the evolution in the formulation of the medication, they still must be prescribed in accordance with the personal history and presence of morbidities, in an attempt to reduce the effects on the cardiovascular system concerning the incidence of diseases such as hypertension.

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