Review Article

Long-Term Impact of Oral Contraceptive Use in Adult Life on Postmenopausal Hypertension

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ABSTRACT

Oral contraceptive pills (OCP) are widely utilized globally for both contraceptive and non-contraceptive purposes, with combined oral contraceptive pills being the more commonly prescribed type compared to progestin-only pills. Despite their efficacy, OCPs are associated with various adverse effects, including the development of hypertension. Hypertension, a prevalent condition among older women, particularly those over 60 years of age, has been linked to prior OCP use, potentially contributing to an elevated risk of cardiovascular and cerebrovascular disorders. The mechanisms underlying OCP-induced hypertension include activation of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, vascular remodeling, inflammation, and oxidative stress. Evidence suggests that estrogen-containing OCPs can exert long-term effects on blood pressure regulation, increasing the likelihood of hypertension, particularly with prolonged use or higher estrogen doses. However, newer formulations with lower estrogen doses have been shown to mitigate this risk. Additionally, certain progestins, such as drospirenone, may exert protective effects by reducing blood pressure. Ongoing research and vigilant monitoring are essential to further elucidate these associations and optimize OCP formulations for safer use.

Key words: Oral Contraceptive Pills, Hypertension, Estrogen, Postmenopausal Hypertension, Contraceptives

Oral contraceptive pills (OCPs) were introduced in the 1960s as a reversible method of contraception and are now widely used, with over 150 million users globally by 2019 **[1]**. In the United States, approximately 65.3% of reproductive-age women use contraception, with 14% choosing OCPs **[2]**. OCPs are divided into combined oral contraceptives (COCs) and progestin-only pills (POPs). COCs, the most common type, are available in monophasic, biphasic, and triphasic formulations, with modern preparations containing lower estrogen doses (20–35 mcg) compared to earlier versions **[3]**. **Figure 1** illustrates different types of oral contraceptive pills, their mechanism of action, and the subsequent risk of causing hypertension **[3, 4, 5]**. Beyond contraception, approximately 18% of women use OCPs for managing menstrual disorders, dysmenorrhea, and hyperandrogenism-related symptoms and for their protective effects against endometrial, ovarian, and colorectal canc ers **[6]**. However, OCPs can have side effects, including headache, nausea, and mood changes, as well as more serious complications such as venous thromboembolism and hypertension.

Prolonged oral contraceptive pill (OCP) use has been linked to elevated blood pressure (BP), particularly in women with pre-existing risk factors like smoking or obesity. Hypertension is a significant public health concern, affecting 45% of adults worldwide and 75% of women aged 60 and older in the United States **[7]**. Defined by the American Heart Association (AHA) as BP ≥130/80 mmHg, it is a leading risk factor for cardiovascular disease (CVD) **[8]**. Hypertension may be primary (essential) or secondary, with secondary hypertension accounting for approximately 10% of cases and often linked to identifiable causes, including OCP use **[9]**. **Table 1** shows categories of blood pressure in adults - AHA

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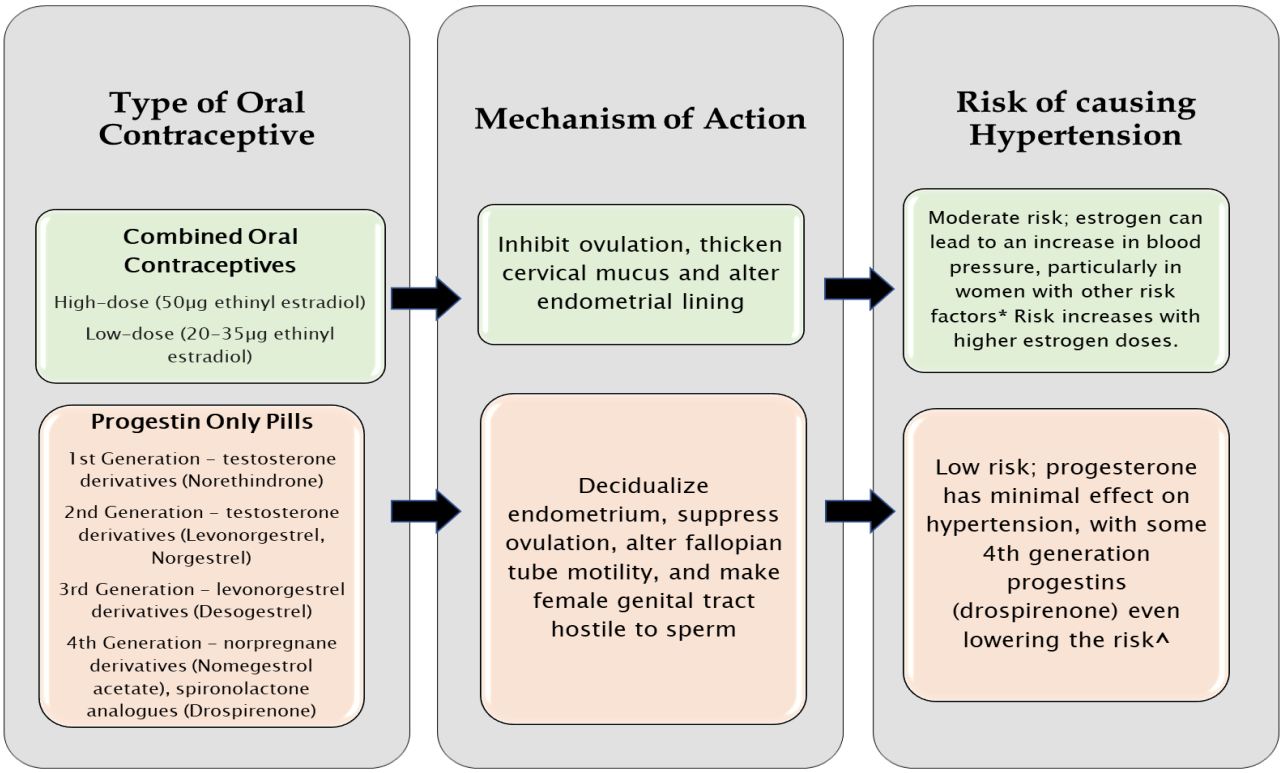
classification **[8].** Postmenopausal hypertension is a complex multifactorial phenomenon that can involve interactions between genetic polymorphisms, aging, oxidative stress, obesity, arterial stiffness, and changes in sex hormones **[4]**.

The results of an epidemiological study have emphasized that hypertension is more prevalent in men than women in the early adulthood period. At the same time, the situation reverses after menopause, especially for ages≥65 years **[10]**. Another study highlighted that a higher prevalence of HTN in postmenopausal women when compared to premenopausal women can be explained by confounding risk factors like high BMI, dyslipidemia, and endothelial dysfunction **[11]**. Although multiple factors can influence the risk of developing HTN in postmenopausal women, those who had a history of OCP use showed significant elevations in their blood pressure **[12]**. Various cross-sectional studies have established that women who use OCPs for a longer duration have higher chances of developing hypertension, with risk as high as twofold in women who used it for more than 24 months **[13]**.

Considering the risk of HTN and subsequent CVD associated with OCP use, the American College of Obstetricians and Gynecologists recommends blood pressure monitoring both before and after its initiation, with regular follow-up visits for women who had no history of HTN and close monitoring for those who had well-controlled HTN **[1]**. In this review, we aim to discuss the interplay of various mechanisms implicated in the development of postmenopausal hypertension after long-term OCP use by women in their reproductive years while also providing evidence of association using well-established literature.



*Smoking, obesity, and pre-existing hypertension. ^Drospirenone exhibits anti-androgenic and anti-hypertensive properties

Figure 1: Different types of Oral Contraceptive Pills, their mechanism of action, and subsequent risk of causing hypertension. Derived from the data of [3, 4, 5].

Table 1: Categories of Blood Pressure in Adults - AHA Classification [8]

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Pathophysiology: Oral contraceptive pill (OCP) use throughout reproductive life may contribute to the development of hypertension in postmenopausal women through a variety of hypothesized mechanisms. It is broadly accepted that the estrogenic component found in oral contraceptive pills demonstrates a relationship with the occurrence of hypertension, while the role of progesterone is ambiguous; however, the mechanisms that lead to this specific phenomenon are considered to be complex **[12].**

Renin-Angiotensin-Aldosterone System Activation

The Renin-Angiotensin-Aldosterone System (RAAS) is the main regulator of blood pressure because it maintains the extracellular fluid volume, sodium balance, and total peripheral resistance. Renin, angiotensin II, and aldosterone all function together to raise blood pressure when RAAS is activated. This complex pathway is activated in response to renal afferent arteriolar hypotension, decreased salt delivery to the distal convoluted tubule, and activation by the sympathetic nervous system **[14]**. Synthetic estrogen-containing oral contraceptive pills activate RAAS by increasing hepatic angiotensinogen synthesis **[15]**. OCP use also leads to elevated plasma renin levels, leading to hypertension **[16]**. However, endogenous estrogen reduces sympathetic tone and vasoconstrictive effects of angiotensin II, thereby decreasing blood pressure **[17]**.

Furthermore, through the PI3K/cPLA2/p42/44 MAPK signaling pathways, endogenous estrogen regulates the activity of the sodium-potassium pump (Na+, K+-ATPase), which affects vascular tone **[18]**. Estrogen has also been shown to counteract the vasoconstrictor effects of serotonin via src kinase inhibition **[19]**. In the postmenopausal state, reduced levels of endogenous estrogen lead to increased sympathetic activity, increased RAAS activation sodium imbalance, and vascular hyperactivity contributing to hypertension. While there exists some uncertainty, it has also been postulated that polymorphisms in genes associated with the Renin-Angiotensin-Aldosterone System (RAAS) may play a significant role in hypertension that is related to the use of oral contraceptive pills (OCPs), as these contraceptives influence the modulation of the RAAS effects **[20]**.

Vasodilator-Vasoconstrictor imbalance

Estrogen has been shown to increase vasodilation by upregulating endothelial nitrogen oxide synthase through the cytosolic estrogen receptor-mediated effect, leading to activation of the phosphatidylinositol 3-kinase/ cyclic adenosine monophosphate pathway. Estrogen can also lead to increased nitric oxide production independent of the endothelium directly in the vascular smooth cells. Estrogen can achieve this by decreasing intracellular calcium levels, leading to increased vascular smooth muscle relaxation **[21]**. In postmenopausal women, endogenous estrogen deficiency leads to reduced production of nitric oxide (NO) and thus increases vascular resistance leading to hypertension. There is a significant correlation between estrogen levels and NO content in hypertensive postmenopausal women, indicating that reduced estrogen levels contribute to decreased NO availability and increased blood pressure **[22]**.

OCP use in women has also been linked to higher serum uric acid concentrations, which have a detrimental effect on the NO signaling mechanism that is dependent on the endothelium. This can cause endothelial dysfunction ultimately leading to hypertension **[23]**. Moreover, progesterone in oral contraceptives can lead to increased expression of aminopeptidase P protein. This can lead to increased degradation of the vasodilator peptide bradykinin, leading to elevated blood pressure **[24]**.

Oxidative Stress and Inflammation

Decreased estrogen levels in the postmenopausal state lead to increased levels of circulating inflammatory markers such as soluble intracellular adhesion molecule-1 (sICAM), vascular cell adhesion molecule (VCAM), and E- and P- selectins and also lead to increased production of reactive oxygen species, contributing to vascular damage and hypertension **[25][26]**. Additionally, OCP use leads to increased levels of high-sensitivity C-reactive protein (hs-CRP) and increased levels of pro-inflammatory marker plasminogen activator inhibitor-1**,** leading to a chronic inflammatory state which can ultimately lead to hypertension and increased risk of other cardiovascular diseases in women **[27][28]**.

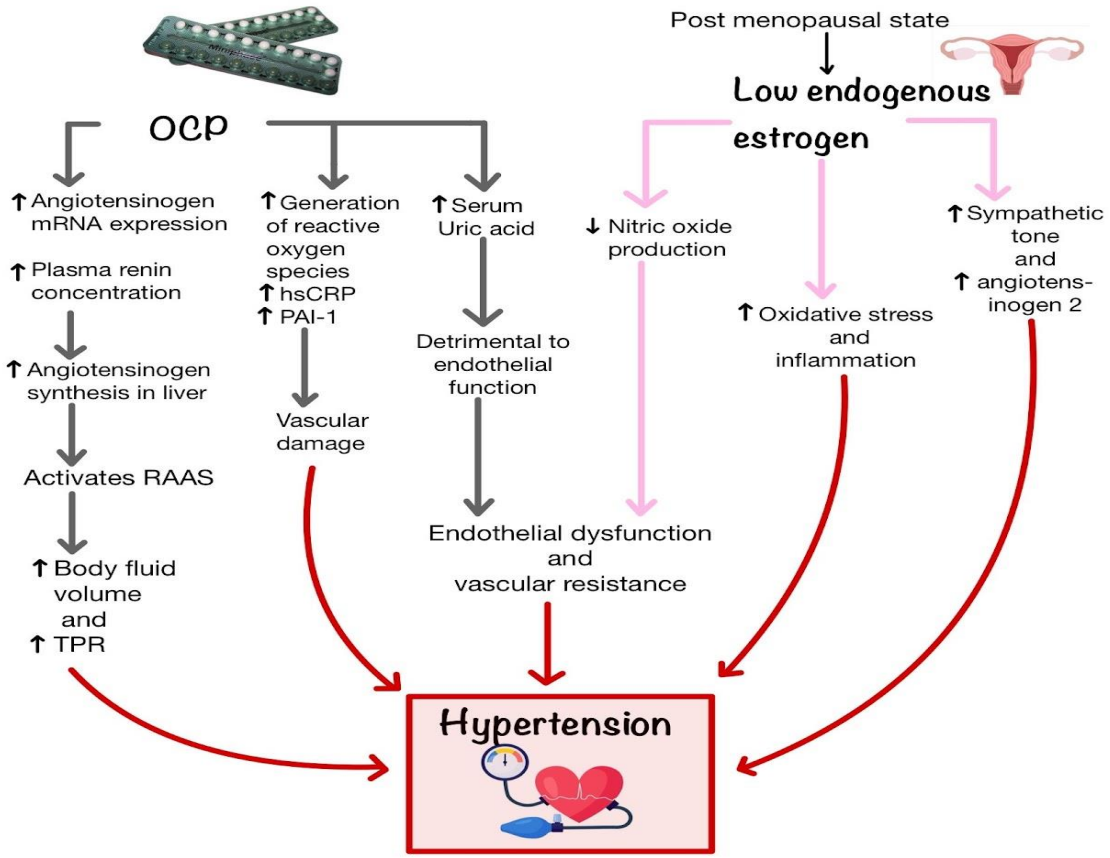
Sympathetic Nervous system role

Long-term OCP use may contribute to increased sympathetic tone in postmenopausal women due to its effects on protective mechanisms **[20]**. In young women, the presence of endogenous estrogen supports β-adrenergic receptor activity, which blunts vasoconstrictor effects by offsetting sympathetic nerve activity. This protective mechanism reduces the risk of hypertension and high sympathetic tone in premenopausal women **[29]**. However, OCP use has been associated with limitations in baroreflex sensitivity, potentially reducing the ability to suppress sympathetic activity effectively. After menopause, the loss of estrogen further diminishes β-adrenergic receptor activity, leaving postmenopausal women more susceptible to elevated muscle sympathetic nerve activity (MSNA), increased total peripheral resistance (TPR), and blood pressure **[30]**.

Racial factor/ Genetic factor

Racial and ethnic disparities exist in Hypertension prevalence as well as outcomes among US women. It is more common in ethnic minorities such as African-American and Hispanic women. This can be attributed to existing gaps in awareness and treatment of Hypertension **[31]**. The 235T allele of the angiotensinogen gene is more frequently found in those with hypertension attributable to OCP usage **[1]**. Single nucleotide polymorphisms(SNPs) in the angiotensin-converting enzyme 2 (ACE2) gene that has been linked with an increased risk of developing hypertension include rs2106809, rs4646155, and rs2074192. These point mutations lead to the abnormal expression of the ACE2 gene with increased activity or resistance to degradation **[32]**. Additionally, genetic polymorphisms on the estrogen beta receptor gene may augment the effects of combined hormonal contraceptives **[33]**. All these polymorphisms in the angiotensinogen and

ACE2 genes influence sodium retention, SNS, and RAAS in OCP users and contribute to hypertension **[1, 32]**. **Figure 2** suggests the underlying mechanisms related to hypertension development in postmenopausal women who used oral contraceptives during reproductive years.



(mRNA: messenger ribonucleic acid, RAAS: renin-angiotensin-aldosterone system, TPR: total peripheral resistance, hsCRP: high-sensitivity C-reactive protein, PAI-1: plasminogen activator inhibitor-1)

Figure 2: Suggested underlying mechanisms related to Hypertension development in postmenopausal women who used oral contraceptives during reproductive years

DISCUSSION

There is significant concern associated with the long-term effects of OCP use on blood pressure due to their widespread use in recent times. Multiple studies have tried to investigate this complex topic to look for a correlation between the duration of oral contraceptive use and the development of hypertension in the postmenopausal phase. A cross-sectional study utilized data from the Fifth Korea National Health and Nutrition Examination Survey of postmenopausal women to establish an association between long-term use of OCPs and the subsequent development of hypertension. It reported that the group using OCPs for more than 30 months had a higher odds ratio (OR) of 2.11 for developing hypertension when compared to the control group. However, for those who used OCPs for a shorter duration (less than 30 months), OR (1.05) did not show statistical significance **[34]**. Two additional cross-sectional studies investigated the association between the duration of OCP use and the development of hypertension. One study conducted on women registered in the Tabari cohort concluded that the women who used OCP for 61–120 months, as well as those who used it for more than 120 months, had a significantly 39% and 47% higher chance of developing hypertension compared to the control group **[35]**.

Similarly, Park et al. discovered that using oral contraceptives for more than 24 months led to about a twofold increase in the risk of developing hypertension, with no significant risk of disease for those who used it for a shorter duration **[11]**. According to a meta-analysis conducted by Hui Lui et al. based on 24 studies, including 270 284 participants, a linear relationship was found between the duration of oral contraceptive use and the risk of hypertension. The risk of hypertension increased by 13% (relative risk, 1.13) for each additional 5 years of OCP use **[13]**. According to the findings of another study, women who ever used contraceptives, including current and past use, had a significantly higher risk of developing hypertension than women who have never used

them, with an OR of 1.23 (1.18–1.28) **[36]**. In contrast, many studies have found no link between previous use of contraceptives and hypertension. Farahmand et al. reported no significant link between OCP use under 36 months and cardiometabolic parameters **[37]**.

Likewise, the duration of OCP use had no impact on hypertension development in Australian women **[38]**. Some recent studies have provided significant evidence of the role of the estrogen component of OCPs in hypertension. A cohort study done with women ages ≥ 45 years in 2008 -2019 concluded that a higher dose of estrogen, irrespective of the route of administration, had a higher risk of hypertension [Relative Risk (RR), 1.19]. Furthermore, in comparison to estradiol, conjugated equine estrogen was found to be associated with an increased risk of hypertension. (RR, 1.08) **[39]**. Similarly, Oral conjugated equine estrogen plus progestogen users had a greater incidence of hypertension than non-users (SMD = 0.60 mm Hg, 95% CI = 0.19 to 1.01), but according to a meta-analysis, there was no significant effect on DBP. Additionally, it was shown that oral or transdermal use of estradiol plus progestogen or estradiol alone had no significant impact on SBP or DBP **[40]**.

According to a meta-analysis of 15 international studies, OCP users had significantly higher levels of cardiovascular disease (CVD) risk variables, such as hypertension [(SMD) = 0.73, (0.46, 0.99)] than non-OC users [SMD = -0.11, (-0.81, 0.60)]. The largest impact size [SMD = 1.86, (-0.31, 4.04)] for CVD risk among OCP users was found in North America **[41]**. In another study, older OCP formulations, mainly first and second-generation formulations with high estrogen and progesterone doses, were found to be associated with increased hypertension risk by Angela Boldo et al. Hence, newer third and fourth-generation oral contraceptive preparations containing lower estrogen and progestin doses have been developed to reduce the hypertensive effect associated with older first and second-generation pills **[42]**. Contrary to the above, a study by Cagnacci et al. demonstrated that even administration of low-dose (15 mcg/day) estrogen orally and via vaginal ring stimulated angiotensinogen synthesis and elevated both systolic and diastolic blood pressure **[43]**.

The influence of oral contraceptives on the pathophysiology of hypertension represents a multifaceted phenomenon, especially when accounting for constituents beyond estrogen, including progestins. While estrogen frequently receives emphasis for its association with elevated blood pressure levels, progestins also play some role in this phenomenon. Franceschini et al. examined the effects of non-hormonal versus hormonal contraceptive methods in healthy women. Within the latter group, one subgroup received 30 mcg of ethinyl estradiol with 3 mg of chlormadinone acetate(EE+CMA), while another subset received 30 mcg ethinyl estradiol with 150 mcg of levonorgestrel (EE+LNG). Systolic blood pressure rose in the EE+CMA group after 6 months but declined in the EE+LNG group **[44]**.

The type and dosage of progestin may also affect hypertension rates, yet progesterone-only users exhibit a minimal rise in blood pressure. Drospirenone, a novel fourth-generation progestin with diuretic properties, appears to lower BP when used with estrogen. In a randomized control trial, 80 participants received either drospirenone 3 mg with varying ethinylestradiol doses of levonorgestrel 150 µg with ethinylestradiol 30 µg over six cycles. Systolic and diastolic BP decreased by 1–4 mmHg for drospirenone combinations, while levonorgestrel combinations led to a 1–2 mmHg increase **[45]**. The International Active Surveillance study "Safety of Contraceptives: Role of Estrogens" (INAS-SCORE) examined 50,203 women to assess cardiovascular risks linked to a combined oral contraceptive (COC) with dienogest and estradiol valerate (DNG/EV) versus established OCPs commonly used in clinical practice. The findings of the study indicated that users of DNG/EV had a significantly reduced risk of experiencing severe cardiovascular incidents in comparison to alternative combined hormonal contraceptives **[46]**.

According to the results of another study, people who used ethinyl estradiol and gestodene for more than six months had an increase in blood pressure. On the other hand, women who received OCP containing ethinyl estradiol and chlormadinone for more than 24 months saw a decrease in blood pressure. The study found that for women who are at a high risk of developing hypertension, OCP containing ethinyl estradiol combined with either drospirenone or chlormadinone acetate may be a more suitable choice **[47]**. A study compared the blood pressure of OCP users with non- OCP users during different phases of the menstrual cycle. The results revealed that, in comparison to non-OCP users, systolic blood pressure (SBP) was significantly higher during the lower hormone phases (119.3 (8.3) vs. 110.2 (8.3) mmHg, P = 0.02); however, no significant difference was observed during the higher hormone phase. In conclusion, the effects of endogenous and exogenous hormones on blood pressure were comparable; however, the intake of exogenous hormones resulted in elevated blood pressure during all phases of the menstrual cycle **[48]**.

Postmenopausal hypertension is a complex condition influenced by various factors beyond contraceptives and estrogen. Although contraceptive use is a significant factor, lifestyle and physiological factors play important roles in the development and management of hypertension in postmenopausal women. Additionally, hypertension could be influenced by vascular aging and hormonal changes. Therefore, addressing these factors is important when evaluating hypertension in them **[49]**. Furthermore, women with a familial history of hypertension and those with a history of hypertension during pregnancy exhibit an elevated

risk of developing hypertension during the postmenopausal period **[50]**. Oxidative stress and inflammatory processes are significantly exaggerated in postmenopausal women suffering from hypertension. The decrease in the activity of antioxidant enzymes, including catalase, and the increase in lipid peroxides highlight the important role of oxidative stress in the development of postmenopausal hypertension **[51]**. **Table 2** explains the different types of studies that were analyzed and their results for evaluating the impact of oral contraceptive use in adult life on hypertensive risk in postmenopausal women. In conclusion, future studies are important to understand further the mechanisms that link long-term oral contraceptive use during adult life to an increased risk of hypertension after menopause while also exploring the development of safer OCP formulations that alleviate this risk for individuals seeking contraception.

Table 2: Types of studies that were analyzed and their results for evaluating the impact of oral contraceptive use in adult life on hypertensive risk in postmenopausal women.

Study	Type of Study	Results
JungJu Lee et al. **(2022)**	Cross-sectional study	The group using OCs for more than 30 months had a higher odds ratio (OR) of 2.11 for developing hypertension when compared to the control group. For those who used OCs for a shorter duration (less than 30 months), OR (1.05) did not show statistical significance.
Mahdi Afshari et al. **(2021)**	Cross-sectional study	Women who used OCP for 61–120 months, as well as those who used it for more than 120 months, had a significantly 39% and 47% higher chance of developing hypertension compared to the control group.
Hyejin Park et al. **(2013)**	Cross-sectional study	Using OCs for more than 24 months led to a twofold increase in the risk of developing hypertension, with no significant risk of disease for those who used it for a shorter duration.
Hui Lui et al. **(2017)**	Meta-analysis	A linear relationship was found between the duration of oral contraceptive use and the risk of hypertension. The risk of hypertension increased by 13% (relative risk, 1.13) for each additional 5 years of OCP use.
Farahmand et al. **(2015)**	Case-control study	Reported no significant link between OCP use under 36 months and cardiometabolic parameters.
Chiu CL et al. **(2015)**	Observational cross-sectional study	The duration of OCP use had no impact on hypertension development in Australian women.
Kalenga CZ et al. **(2023)**	Cohort stud	A higher dose of estrogen, irrespective of the route of administration, had a higher risk of hypertension (RR, 1.19). Conjugated equine estrogen was associated with increased hypertension risk in comparison to estradiol (RR, 1.08)
Angela Boldo et al. **(2011)**	Cohort study	Older-generation OCs, mainly first and second-generation formulations with higher doses of estrogen and progesterone, were associated with an increased risk of hypertension.
Cagnacci et al. **(2013)**	Observational study	Administration of low-dose (15 mcg/day) estrogen orally and via vaginal ring stimulated angiotensinogen synthesis and elevated both systolic and diastolic blood pressure.
Franceschini et al. **(2013)**	Randomized control trial	Systolic blood pressure rose in the group that was given 30 mcg of ethinyl estradiol with 3 mg of chlormadinone acetate(EE+CMA) after 6 months but declined in the group with administration of 0 mcg ethinyl estradiol with 150 mcg of levonorgestrel (EE+LNG).
Pimenta E. et al.	Randomized control trial	Systolic and diastolic BP decreased by 1–4 mmHg for the group that

(2011)		received drospirenone 3 mg with varying ethinylestradiol doses, while levonorgestrel 150 µg with ethinylestradiol 30 µg led to a 1–2 mmHg increase.
Dinger J et al. **(2016)**	Prospective, noninterventional cohort study	The users of dienogest and estradiol valerate (DNG/EV) had a significantly reduced risk of experiencing severe cardiovascular incidents in comparison to established combined hormonal contraceptives.

CONCLUSION

Postmenopausal hypertension, a complex condition, is influenced by various factors, namely lifestyle, physiological factors, vascular aging, oxidative stress, and inflammatory changes. Hormonal influence due to physiological causes or the concomitant use of OCPs plays a significant role in hypertensive changes in the postmenopausal state. This multifaceted phenomenon has been widely studied due to substantial health adversity and disease burden. Some studies indicate an association between long-term use of OCP and the development of hypertension, particularly with older generations (first and second) of OCPs containing high doses of estrogen and progesterone. However, the recent use of newer generations of OCPs, namely the third and fourth generation, with lower doses of estrogen and progesterone, has less impact on blood pressure regulation.

While estrogen has been implicated as the main culprit in the development of hypertension and the associated risk of stroke and myocardial infarction, progesterone, such as drospirenone, may protect by reducing blood pressure. Yet, this needs to be further studied to understand this phenomenon in its fullest form. Hence, even though newer, low-dose estrogen and progestin formulations have reduced these risks, caution must be exercised, especially for women over the age of 35 or those with additional cardiovascular risk factors. Regular blood pressure surveillance during the use of OCPs can nip it in the bud. Further research into this complicated relationship can aid in guiding future contraceptive recommendations for women.

Ethics Statement

This study is a narrative review and does not involve human or animal subjects; therefore, it does not require approval from an institutional review board or ethics committee.

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