Hormonal Contraception and Cardiovascular System

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Abstract

Hormonal contraception is the most widely used method to prevent unplanned pregnancies. The literature has shown an association between cardiovascular risk and use of hormone therapy. With the purpose of providing better guidelines on contraception methods for women with risk factors for cardiovascular disease, we have reviewed the literature on the subject. This review describes the latest data from the scientific literature concerning the influence of hormonal contraceptives on arterial thrombosis, venous thrombosis and systemic high blood pressure, which are diseases that have become increasingly prevalent among young females.

Introduction

Hormonal contraception is the reversible method most widely used by the Brazilian female population (± 25%) for family planning[1]. The method comprises a combination of estrogen (usually ethinylestradiol) and progestogen; or the progestogen-only contraceptive, without the estrogen component. Hormonal contraceptives are available in various dosage forms and for different routes of administration (oral, intramuscular, vaginal, transdermal, subdermal implants and associated with the intrauterine system). Their purpose is to block ovulation by inhibiting the secretion of follicle-stimulating hormone and luteinizing hormone; they thicken the cervical mucus, which makes it difficult for the sperm to pass; they cause the endometrium to be unreceptive to implantation; they alter the secretion and peristalsis of the fallopian tubes[2].

Scientists have been very interested in the effects of female sex hormones on the cardiovascular system, because such effects target blood vessels, since there are estrogen receptors and progesterone receptors in all layers that make up blood vessels.

Keywords

Contraception; contraceptive agents / contraindications familyplanning (public health); cardiovascular diseases; venous thrombosis.

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Several epidemiological studies have shown a clear association between the use of combined oral contraceptives (COC) and an increased risk of venous and arterial thrombosis[3-5]. Even though there are some common risk factors for arterial thrombosis and venous thrombosis, blood stasis and hypercoagulability are known to be the main etiopathogenic factors for the onset of venous thromboembolism (VTE), while endothelial injury is the main determinant of arterial thrombosis (AT). It is worth highlighting that, during the reproductive life span, AT is less common than VTE (one case of AT for each 5-10 cases of VTE)[6].

The purpose of this review is to discuss the main effects of sex steroids on risk factors for cardiovascular disease and expose available scientific evidence for prescribing hormonal contraceptives to women with arterial and venous thrombosis and systemic high blood pressure. Most of the published articles on contraception and cardiovascular diseases refer to observational studies or clinical trials on intermediate outcomes. This makes the evidence of recommendations less strong, but, currently, this is the best evidence available to guide the clinical practice. It is imperative that cardiologists be aware of such information, because they are often the ones who say, at the request of gynecologists, whether or not patients that are likely to develop cardiovascular diseases should use hormonal methods. This matter will be addressed according to the eligibility criteria established by the World Health Organization (WHO)[7] in July (table 1).

Hormonal contraception and venous thrombosis

Ethinylestradiol (EE) induces significant changes in the coagulation system, leading to increased generation of thrombin. There is also an increase in coagulation factors (fibrinogen, VII, VIII, IX, X, XII and XIII) and a reduction in natural coagulation inhibitors (protein S and antithrombin), which produces a mild procoagulant effect[8,9]. These effects can be seen more clearly in tests that assess the overall hemostasis. In addition, the effects show the acquired resistance to protein C and increased generation of thrombin[10].

The risk of VTE is dependent on the EE dosage. The high dose of EE (≥ 50 mcg) is associated with a twofold increase in risk of VTE when compared to a low dose of this hormone (<50 mcg)[9,11,12]. Recently, it was said that formulations containing 20 mcg of EE were associated with lower risk of thrombosis (OR: 0.8; 95% CI: 0.5-1.2) when compared to preparations with 30 mcg of EE, but without any significant difference[11].

Initially, it was thought that thrombosis was the result only of the estrogen dose used, which led to the reduction

Table 1 – Medical eligibility criteria for contraceptive use according to the World Health Organization

Category	Classification	Clinical Judgment
1	Condition for which there is no restriction on the use of the contraceptive method.	Use the method in any circumstances
2	Condition where the advantages of using the method generally outweigh theoretical or proven risks.	Generally use method
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method.	Use of method not usually recommended unless other more appropriate methods are not available or not acceptable.
4	Condition that represents an unacceptable health risk if the contraceptive method is used	Do not use the method

Adapted from WHO[7].

in the EE dose of contraceptives (150 mcg for 15-20 mcg). However, in 1995, it was demonstrated that COCs containing third generation progestogens (gestodene, desogestrel) were associated with risk of thrombosis two times higher than those containing second generation progestogens (levonorgestrel)[4,13]. Thus, the type of progestagen associated with estrogen, and not just the dose of the latter, became the subject of studies on the role of progesterone in hemostasis and in the determination of thrombosis.

Despite having the common characteristic of binding with progesterone receptors, progestogens are a group of steroids that have different systemic effects and which are mediated not only by the affinity with progesterone receptors, but mainly by the ability to bond with receptors of other steroids such as estrogens, androgens, glucocorticoids and mineralocorticoids[14]. This ability to bond with other steroid receptors and the affinity for each one of these receptors can result in different risks levels for thrombosis, depending on the progestogen associated with estrogen.

Oral contraceptives combined with third-generation progestogens are associated with the development of more accentuated "acquired activated-protein-C resistance"[15], as well as with a tendency to produce higher levels of coagulation factors and lower levels of natural anticoagulants, when compared to COC containing second generation progestogen[10,16,17]. These findings could explain the epidemiological observations of increased VTE risk in users of COCs containing third generation progestogens, because (acquired or hereditary) resistance to the action of protein C is an important marker for increased risk of VTE[18]. Another finding is that hyperfibrinolysis is less marked in users of COCs with third generation progestogens than in users of COCs with second generation progestogens[16]. Other progestogens have also been studied in relation to the risk of thrombosis when combined with EE. The most recent study, coordinated by the University of Leiden, in the Netherlands, conducted to evaluate the different progestogens and risk factors for venous thrombosis (Multiple Environmental and Genetics Assessment of Risk Factors for Venous Thrombosis [MEGA])[11], confirmed the association between the type of progestagen and the risk factor for thrombosis, but it showed a difference less marked than previously described between different progestogens. However, some formulations included a small sample for a definitive conclusion. Compared to non-users of hormonal contraceptives, COC containing levonorgestrel was associated with four-times higher risk factor for venous thrombosis (OR: 3.6; 95% CI: 2.9-4.6). Levonorgestrel was the progestogen associated with the lowest risk factor for thrombosis, followed by gestodene (OR: 5.6; 95% CI:3.7-8.4), drospirenone (OR: 6.3; 95% CI: 2.9-13.7); cyproterone acetate (OR: 6.8; 95% CI: 4.7-10); desogestrel (OR: 7.3; 95% CI: 5.3-10). Thus, considering the VTE risk, levonorgestrel offers the lowest risk, while the other progestogens seem to show similar risk levels, higher than the association with levonorgestrel. This happens probably because the latter is more androgenic than the others, as androgenic progestogens (levonorgestrel) are associated with lower protein C resistance than those with less androgenic potency (gestodene and desogestrel) and antiandrogens (cyproterone acetate and drospirenone)[19].

The data presented do not mean that you should not always recommend the use of COC containing levonorgestrel. It is important to know the VTE risks, as well as the added benefits of each progestogen, for a proper prescription, according to the expectations and clinical characteristics of patients[20]. Moreover, there is a higher risk of VTE in pregnancy-childbirth cycle than in any contraceptive formulation presented[21]. However, when it is estimated that approximately 100 million women worldwide use hormonal contraception[22], the awareness of less thrombogenic options becomes very important, especially among women with other associated risk factors for the development of VTE.

When administered separately (progestogen-only contraceptives), progestogens have a very little impact on the coagulation system. A small and insignificant increase in the risk of VTE has been reported in users of contraceptive pills containing only progestogen (PP)[23,24]. Progestogen-only contraceptives are not associated with marked changes in parameters of coagulation or fibrinolysis. Therefore, progestogens may be prescribed for patients at risk of VTE[7].

A randomized, double-blind study compared the effects on the hemostasis of two PP (desogestrel versus levonorgestrel) and showed that both had a favorable effect on it[25]. Another recent study also showed favorable results in the hemostasis in users of PPs (desogestrel versus levonorgestrel), with reduction in activated protein C resistance and increase in protein S[15]. Thus, the negative effects dependent on the type of progestogen, caused by the COCs on coagulation and anticoagulation parameters, were not evident with the use of PPs (levonorgestrel or desogestrel).

Over the past 20 years, subdermal implants that keep releasing low doses of progestogens have been developed. In Brazil, there is the etonogestrel-releasing implant (Implanon®, NV Organon, Oss, The Netherlands). In the haemostatic variables examined, there was either no change or very small changes, always within normal values for the tests done[26-29].

With respect to the route of administration, even though the transdermal route in users of hormone replacement therapy (HT) during menopause does not seem to increase the risk of VTE[30], these data cannot be extrapolated to contraception, especially because EE is used in contraception, and the potency of EE is greater than the potency of estrogens used in HT. In November 2005, the U.S. Food and Drug Administration (FDA) issued a statement that the patch containing 0.75 mg + 6 mg norelgestromin (Ortho-Evra®, 20 mcg of EE + 150 mg norelgestrolmin/day) released 60% more than the total amount of EE available in a "35 mcg EE" COC[31], which could change the frequency of serious adverse events such as VTE. Subsequently, a study showed that the patch that released 20 mcg of EE on a daily basis has incidence of VTE that is similar to that of a COC with 35 mcg of EE. This means that we should not use this method for patients at high risk of VTE, unlike the transdermal HT[32]. Other combined non-oral hormonal contraception methods, such as the vaginal ring and monthly injectable contraceptives, were tested for their effects on hemostasis. The ring (15 mcg of EE + 120 mcg of etonogestrel/day) was compared to COC containing 30 mcg EE + 150 mcg levonorgestrel. The result showed similar changes in hemostasis[33]. A recent study compared the effect of combined oral and vaginal contraception on hemostatic variables, and it showed a procoagulant effect due to EE, regardless of the route of administration[34]. However, further studies are needed to assess the risk of VTE with this vaginal contraceptive. Combined injectables had a smaller impact on hemostasis than oral preparations[35], unlike other non-oral formulations (patch and ring), probably because they contain natural estrogens (estradiol valerate or estradiol cypionate) in their composition, instead of EE. In terms of risk of thrombosis, a study with a small sample for this outcome showed little or no risk of VTE, AMI (acute myocardial infarction) and CVA (cerebral vascular accident)[36], but there is no definite answer to whether or not combined injectables do not pose any risk of VTE.

Typically, thromboembolic events occur within the first year of use of hormonal contraceptives, especially four months after the beginning of use[3,9,11]. But after a year, the time of COC use does not alter the risk of VTE[3,9].

In short, for patients with prior thrombosis or thrombophilia (inherited or acquired) the use of combined hormonal contraception is proscribed, regardless of the route of administration. On the other hand, progestogen-only contraceptives (in any route of administration) and non-hormonal methods (condoms and intrauterine device with copper) are allowed, according to the WHO's criteria (table 2). In patients at risk of venous thrombosis (obese patients, patients with metabolic syndrome, smokers, patients over 40 years-old and family history of thrombosis), the use of progestogen-only contraception is preferable, although the use of EE is allowed (except for smokers aged ≥ 35 years). In such patients at risk, it is better to use combined contraception with levonorgestrel, as this progestogen is the one with the lowest risk of VTE when it is associated with EE.

Hormonal contraception and arterial thrombosis

Even though the occurrence of AT is infrequent among young women, the behavioral changes – low frequency of high-fiber foods, increase in the proportion of saturated fat and sugar in the diet - together with a sedentary lifestyle, have increased the risks of AT during the reproductive life span[37]. Thus, in women with risk factors for cardiovascular disease (CVD) (such as smokers, obese women, women suffering from high blood pressure, hypercholesterolemia or diabetes mellitus), hormonal contraceptives should be prescribed with caution.

Just like for VTE, the use of COC is also associated with increased risk of AT[38-40]. This risk is directly related to the dose of the estrogen component, but even in users of low-dose pills (EE<50 mcg), there was an increase in this risk[41].

With the use of low-dose COC (EE <50 mcg), the risk of arterial thrombosis is approximately two times higher among users of the method, even after the correction of confounding variables for risk factors for cardiovascular disease[42]. Unlike VTE, the type of progestagen associated with EE does not significantly change the risk of AT[38,40,41].

The risk of AMI among users of COC increases with the coexistence of risk factors for CVD such as smoking, and this effect is more evident among women that are more than 35 years-old. For women under 35 and users of COC, the incidence of AMI among smokers (≥ 20 cigarettes / day) is 10 times higher than among nonsmokers (3.5 per 100,000 versus 0.3 per 100,000, respectively)[38]. For women that are more than 35 years-old and use COC, the risk of AMI is significantly higher both among smokers (40 per 100,000) and nonsmokers (3 per 100,000)[38]. Thus, age over 35 years and smoking always deserve special attention when one has to choose the contraceptive. Like age and smoking, other diseases that increase the risk of CVD (such as diabetes, high blood pressure) also increase the risk of AMI among users of combined hormonal contraception.

Thus, at the moment, when one thinks about not causing any significant increase in the risk of AMI, the dose of EE has to be smaller than 50 mcg and it is important to identify risk factors for CVD, before prescribing the contraception method[7,38-41].

Cerebrovascular accident (CVA) is another very rare blood disease among women at the reproductive age[43]. However, there is a higher incidence of cases among users of COC compared to non-users[44,45]. When Heinemann[46] examined epidemiological articles published, it was possible to conclude that high doses of EE (≥ 50 mcg) were associated with increased risk of stroke compared to formulations with 50 mcg of EE (OR:5.3; 95% CI: 2.6-11 versus OR: 1.53; 95% CI: 0.71-3.31)[47]. However, the studies showed no difference between the formulations of second generation progestagen and third generation progestagen[47,48], as for AMI.

More recently, a multicenter, case-control study was published. It involved 1,182 healthy women aged 18 to 49 years old. The study estimated that the risk of stroke was 2.3 times higher among users of COCs containing <50 mcg of EE (OR: 2.3; CI 95%: 1.6-3.3) compared to users of non-

Table 2 – Use of hormonal contraceptives in women at risk for CVD and/or DVT

Condition	Only-Progestogen		Combined contraceptive	
	Oral Implant LNG-IUS	Injectable	Oral Vaginal Transdermal	Injectable
DVT / PE				
a) History of DVT / PE	2	2	4	4
b) Acute DVT/PE	3	3	4	4
c) DVT/PE in use of OAC (oral anticoagulants)	2	2	4	4
d) Family history	1	1	2	2
e) Major surgery I. With prolonged immobilization	2	2	4	4
II. Without prolonged immobilization	1	1	2	2
f) Minor surgery without immobilization	1	1	1	1
Ischemic heart disease (current or previous)	2 if B	3	4	4
	3 if C			
CVA	2 if B	3	4	4
	3 if C			
Obesity (BMI ≥ 30 kg/m^2)	1	1	2	2
Smoking				
a) Age <35 years	1	1	2	2
b) Age ≥ 35 years	1	1	3 / 4 *	3
Headache				
a) No migraine (mild or severe)	1	1	1 if B/ 2 if C	1 if B / 2 if C
b) Migraine				
Without aura Age <35 years	1 if B / 2 if C †	2	2 if B / 3 if C	2 if B / 3 if C
Age ≥ 35 years	1 if B / 2 if C †	2	3 if B / 4 if C	3 if B / 4 if C
With aura	2 if B / 3 if C	2 if B / 3 if C	4	4
Multiple risk factors for CVD	2	3	3/4	3/4
SHBP				
a) History of Systemic HPB, when BP cannot be measured	2	2	3	3
b) Controlled systemic high blood pressure, when BP can be measured	2	1	3	3
c) High levels of blood pressure (mmHg):				
SBP: 140-159 or DBP:90-99	1	2	3	3
SBP ≥ 160 or DBP ≥ 100	2	3	4	4
d) Vascular disease	2	3	4	4
e) History of systemic high blood pressure during pregnancy	1	1	2	2

*(Adapted from WHO[7,33]. ; DVT - deep vein thrombosis; EP - pulmonary embolism; LNG-IUS - levonorgestrel-releasing intrauterine system; OAC - oral anticoagulant; CVA – Cerebrovascular Accident; SHBP – systemic high blood pressure, BP - blood pressure, C - continuity, B - beginning; * Switch to category 4 if patient smokes ≥ 15 cigarettes/day; † Etonogestrel implant is classified as category 2 both for beginning and continuing the method.*

hormonal methods[40]. The risk of stroke, as in previous studies, was not related to the associated progestagen[40,45].

Studies show that migraine with aura doubles the risk of stroke compared to migraine without aura[49]. As it is common among women during the reproductive period[50], it is important to be alert to the presence of this disease (table 2). After the neurologist defines the neurological manifestations that characterize migraine, if there is an aura, EE-containing

contraceptives are contraindicated at any age of the woman's reproductive life. With respect to progestogen-only contraceptives and migraine, there are very few studies and most of them do not distinguish between the oral formulations, that is, they do not say whether the contraceptives are combined or progestogen-only pills[51]. However, in the absence of other risk factors for stroke, WHO allows it to be used by women with migraine, except for those that have the disease during the use of this contraceptive. In such case, the use should be discontinued[7] (table 2).

Despite the low incidence of AT during the reproductive life, which makes it difficult to reach reliable conclusions on the studies available, there are no data that indicate the safest route[52].

In the case of progestogen-only contraceptives, WHO is cautious in prescribing their injectable version to women with previous AT (table 2). The depot medroxyprogesterone acetate (DMPA) inhibits ovulation and causes a decline in estradiol levels, thereby inducing hypoestrogenism[53]. So, when it is administered for a long time, it can alter the vascular function[54,55]. In addition, longitudinal and cross-sectional studies noted the increase in LDL levels and reduction in HDL cholesterol among DMPA users, which are changes that are epidemiologically linked to CVD. However, these changes in lipid profile were not related to adverse clinical events[56]. As for implants, the levonorgestrel-releasing intrauterine system and PP were not associated with adverse effects on the lipid profile[7,57-59].

Another rare vascular/arterial complication during the reproductive life span, but with a bad prognosis, is the peripheral arterial disease (PAD), with high incidence of vascular occlusion, amputation and death. There was a risk three times higher of DPA among COC users compared to non-users (OR:3.8; CI 95%: 2.4-5.8)[60]; and this risk was greater, as in other arterial diseases, in the presence of other risk factors for CVD. When each one of the three generations of contraceptive pills was compared to non-users of hormonal contraceptives, we found a very high risk in formulations with first-generation progestogens (norethisterone and lynestrenol) (OR:8.7, CI 95%:3.6-21.3) and three times more risk for second-generation progestogens (OR: 2.6; CI 95%: 1.4-4.9) and third-generation progestogens (OR:3.0, CI 95%: 1,4-6,6)[60].

It seems that the PP does not increase the risk of CVD[61,62]. A recently published meta-analysis found no significant association between contraceptives containing only progestogens and EVA (Encephalic Vascular Accident) (OR: 0.96; CI 95%: 0.70-1.31), despite the low quality of the articles selected[62].

Thus, for women with ischemic heart disease, EVA, migraine with aura or with multiple risk factors for CVD (>35 years of age, suffering from diabetes, high blood pressure and smokers), one should opt for non-hormonal contraceptive methods or progestogen-only contraceptives (table 2). Among the latter, the best ones are the PPs, etonogestrel-releasing implant and levonorgestrel-releasing intrauterine system.

Hormonal contraception and systemic high blood pressure (SHBP)

The substances contained the COCs try to reproduce the properties of endogenous steroids. However, the EE, due to its high biological potency, compared to estradiol (a thousand times more potent), exacerbates the production of hepatic angiotensinogen, which in turn causes the renin-angiotensin-aldosterone system to increase blood pressure[63]. Moreover, the progestagen associated with the EE contained in the COC is similar, but it does not reproduce all the characteristics of the natural progesterone[64].

Despite the development of new progestogens, only drospirenone keeps the antimineralocorticoid effect[65] of the natural progesterone. Even so, it is still not possible to determine the beneficial effects of this contraceptive formulation on the blood pressure of users with high blood pressure[66]. This conclusion differs from that reached for HT in postmenopausal women, in which the compound (drospirenone and estradiol) was associated with decreased blood pressure in women that suffer from high blood pressure[67]. This does not apply to the association of drospirenone with EE in contraception. In contraception, an article on people with normal blood pressure showed that the blood pressure decreased 4 mm Hg, in users of EE+drospirenone in a specific evaluation after six months of medication use[68]. Another article also on a specific evaluation of 160 women with normal blood pressure compared COCs containing drospirenone to COCs containing gestodene. It showed a drop in blood pressure in the drospirenone group throughout the study, but without any difference between the groups in the final evaluation, after 12 months[69]. However, there are no safety data on the use of this contraceptive by women with high blood pressure. Thus, drospirenone is best for PA, but its use with EE lacks safety data for women suffering from high blood pressure. We can conclude that, to date, there is no difference in terms of safety between the progestogens with respect to blood pressure in contraception.

In a cross-sectional study, Lubianca et al[70] evaluated 171 women diagnosed as having high blood pressure and noted an increase in diastolic blood pressure (DBP), even after correction of confounding variables[70]. The same authors mentioned above conducted a study in which they followed up a cohort, so as to evaluate whether discontinuation of COC use interfered in blood pressure levels. They found a decline in SBP (- 15.1 ± 2.6 mmHg) and DBP (- 10.4 ± 1.8 mmHg), after six months of suspension of COC, that was significantly higher when compared to women who continued to use the combined contraceptive[71].

The route of administration in hormonal contraception does not interfere with blood pressure[7]. Unlike what was noted for hormone therapy in postmenopausal women, where there is no negative change in blood pressure levels of hypertensive menopausal women that use transdermal HT, compared to placebo[72].

Even though COCs cause an increase in BP levels that ranges from 2 to 3 mmHg, on average, in healthy women,

the antihypertensive therapy is unnecessary in most cases[73]. However, in women previously diagnosed with high blood pressure, the prescription of contraceptive containing EE must be avoided, since the prognosis of the disease may worsen and there may be an increase in the risk of AT.

There are few studies designed to evaluate changes in blood pressure and progestogen-only contraceptives, but there is consistent evidence that there is no association between their use and high blood pressure in healthy women during a two-year follow-up[7,74].

In short, for women suffering from high blood pressure, we should recommend the use of non-hormonal contraceptive methods, or hormonal contraceptives containing only progestogen (table 2). Combined contraceptives, by any route, interfere with blood pressure and increase the risk of AT in patients that are already predisposed to such disease. In well-controlled patients with high blood pressure, under the age of 35, one can use the combined contraceptive, but according to WHO criteria, there is more scientific evidence that backs the previous options and they are safer[75].

Summary of recommendations

The benefits of using hormonal contraceptives outweigh the risks associated with these drugs. Good guidance on what contraceptive women should use must include all the beneficial aspects and possible adverse events, so as to allow, in this context, an informed choice that is more appropriate for each case. The following is the summary of recommendations that we should always take into consideration when we choose the contraception method for women with risk factors for CVD:

- COCs increase the risk of venous and arterial thrombosis, even in healthy women, but this risk is low;
- The preparations currently available (EE < 50 mg) are considered to pose a low risk of venous and arterial thrombosis to patients that are not at risk;
- The combined progestin component changes the risk of VTE for a COC. Current evidence suggests that those containing levonorgestrel pose the lowest risk of VTE. For arterial thrombosis, the type of progestogen does not alter the risk of thrombosis, so in healthy women, there is not an option that poses less risk;
- Progestogen-only and non-hormonal contraceptives are not associated with increased risk of VTE. Therefore, they are suitable for patients at risk of VTE or with previous history of VTE;
- In patients with previous history of AT or multiple risk factors for AT, one should opt for non-hormonal contraceptives or progestogen-only contraceptives (except for quarterly injections);
- The AT or VTE risk does not depend on the route of administration of the combined hormonal contraceptive;
- Since combined hormonal contraceptives contain ethinyl estradiol, they always change the blood pressure, even at low doses. This change has no clinical repercussions for healthy women, but its use in women with high blood pressure shall be avoided. Thus, in women with high blood pressure, it is better to use non-hormonal contraceptives or progestogen-only contraceptives, because EE enhances the risk of arterial thrombosis and changes the control of blood pressure in these patients.

Potential Conflict of Interest

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