Aetiology and treatment of venous thromboembolism

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Oral Contraceptives and Cardiovascular Disease

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Abstract

Combined oral contraceptives are increasingly used since they have been introduced. However, there are also data indicating that they are associated with cardiovascular disease.

Here we give an overview of the effects of oral contraceptives on the cardiovascular system. These effects are mostly type-dependent and they interact with individual characteristics of the users.

Third-generation oral contraceptives cause an increased risk of venous thromboembolism as compared to second-generation preparations, which is probably due to a stronger negative effect on the natural anticoagulant and antifibrinolytic system. This effect is even more pronounced in women with inherited thrombophilic factors that are associated with venous thromboembolism.

Oral contraceptives increase also risk for myocardial infarction and stroke. However, this risk seems to be limited to women with often other risk factors such as smoking and hypertension. Furthermore, the attributable risk of oral contraception on this risk is much lower than, for instance, smoking itself. Although third-generation oral contraceptives have a beneficial effect on lipid profiles, this does not seem to be translated into a lower increase in risk.

Benefits of use of oral contraceptives need to be balanced against the disadvantages of these drugs in order to decide whether they should be used.
Introduction
The introduction of oral contraceptives in the late 1950s has altered society and has even led to radical demographic alterations. Currently, combined oral contraceptives are the most effective and most easily reversible method of contraception. They have the best ‘pearl index’ (i.e., the number of pregnancies occurring despite the use of contraception in 100 women during one year) $^{1,2}$. Oral contraceptives are also used for other indications, such as treatment of menstrual disorders. The widespread use of oral contraceptives has given rise to concerns about possible side effects, especially cardiovascular disease. Initial case reports on fatal thromboembolic disease in young women who used oral contraceptives have led to a multitude of studies that have assessed the risk for venous and arterial disease in relation to the use of these drugs, as well as assessing the potential underlying hemostatic and metabolic mechanisms $^{3-5}$. This chapter reviews the epidemiology of cardiovascular disease in relation to the use of oral contraceptives, as well as the presently known underlying mechanisms of cardiovascular disease in oral contraceptive users.

Types of Oral Contraceptives
Hormonal contraceptives are female sex steroids. They can take the form of a synthetic estrogen combined with a synthetic progesteron (progestagen), or a progestagen only. They are mostly administered orally, but they are sometimes given intramuscularly. The combinations of estrogens and progestagens have their contraceptive effect by selective inhibition of pituitary function that results in inhibition of ovulation. The combined agents also produce a change in cervical mucus and in the motility and secretion in the tubes, decreasing the likelihood of conception and implantation. Use of progestagens alone does not always inhibit ovulation but does produce the latter effects.

Combined oral contraceptives are often classified according to the type of progestagens. The so-called first-generation pills contain norethisterone (acetate), lynesterol, ethynodiolacetate or norethynodrel; they are not used any more. The presently available oral contraceptives are second-generation pills, which contain norgestrel, levonorgestrel or norgestrinone, and third-generation combined oral contraceptives, which contain desogestrel, norgestimate or gestodene. The second- and third-generation progestagens are combined with 20 - 50 µg ethinyl estradiol (‘sub-50 pills’).
Epidemiology of Oral Contraceptives and Cardiovascular Disease

Oral Contraceptives and Venous Disease

Risk for Deep Venous Thrombosis and Pulmonary Embolism

Venous thromboembolism (VTE) is a common disorder with an overall annual incidence in Western populations of 2-3 per 1000 inhabitants, that increases with age.

In young women, VTE is the most common cardiovascular event. Its reported incidence varies between 0.4 and 1.5 per 10,000 women-years in women aged 25-29 years, and between 0.6 and 3.0 per 10,000 women-years in the age group of 40-44 years. Deep venous thrombosis of the lower limbs and pulmonary embolism are the most common presenting features, but a partial or complete occlusion of a vein by a thrombus may also occur at other sites.

Since the first report that suggested a relationship between oral contraceptives and the occurrence of VTE in a 40-year-old woman, many studies on this potential association have been performed. In Table 1, recent epidemiological studies of the risk for VTE in women who use the pill as compared to non-users are summarised. For users of first-generation pills, the risk for VTE is 3- to 6-fold increased. It has been consistently reported that the use of second-generation

<table>
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<th>Study</th>
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Table 1: Risk of venous thromboembolism in women using different generations of oral contraceptives versus non-users.
pills is associated with a 2- to 4-fold increase, while during use of third-generation pills this risk is increased 3- to 12-fold. The risk of VTE seems more enhanced by the use of third than by second-generation oral contraceptives, with reported odds ratio’s varying from 1.3 to 4.4. The absolute risk for VTE in women using second-generation or third-generation oral contraceptives is estimated to be between 1.6 and 3.1 per 10,000 women per year, and 2.9 and 5.0 per 10,000 women per year, respectively \(^9,10\). The increase in risk is most pronounced in ‘first-time’ users, and decreases over time \(^11,12\). There are no data available on the risk for recurrence of VTE in relation to continued use of oral contraceptives after a first episode.

The Risk for Oral Contraceptive-related Venous Thromboembolism in High-risk Women

Since the baseline risk for VTE in women with inherited thrombophilia is increased, it is important to estimate the additional increase in risk caused by the use of oral contraceptives in this population. The risk for VTE in women with heritable thrombophilic defects is found to be strongly enhanced by the use of oral contraceptives. Heterozygous factor V Leiden carriers who use oral contraceptives have an approximately 30-fold increased risk compared with women who do not carry the mutation and do not use the pill \(^13,15\). The same kind of interaction has been reported for women with deficiency of protein C, protein S, or antithrombin, and for heterozygous carriers of the prothrombin 20210A mutation, with odds ratio’s varying between 6.4 and 16.3 \(^16,17\). For women with increased levels of factor VIII, a known risk factor for VTE, increase of risk during the use of oral contraceptives has been found to be merely additive (as opposed to multiplicative), with an odds ratio of 10.3 as compared to women with normal factor VIII levels who did not use the pill \(^18\).

In terms of absolute risk, the incidence has been found to be between 0.5\% (95%CI 0.1-1.4) and 2.0\% (95%CI 0.3-7.2) per year of pill use in women with the factor V Leiden mutation, and 4.3 \% (95%CI 1.4-9.7) per year in women with deficiency of protein C, protein S or antithrombin \(^17,19\). At present, such absolute risk estimates are not available in women with the prothrombin mutation. In women with factor VIII levels above 150\% who use the pill, the absolute risk has been calculated to be approximately 6 in 10,000, based on a baseline estimate of 0.7 per 10,000 women \(^18\).
Risk for Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis is a very rare, but serious, potentially lethal disease with an estimated absolute risk in premenopausal women of 4 per 1,000,000.20. Best known risk factors are trauma, autoimmune diseases, pregnancy, puerperium, inherited thrombophilic risk factors and the use of oral contraceptives.20,21 Oral contraceptives increase the risk of cerebral vein thrombosis in women approximately 20-fold.20,21 As for deep venous thrombosis or pulmonary embolism, there appears to be a multiplicative interaction between use of oral contraceptives and hereditary thrombophilia. One study found an odds ratio of 34 for cerebral vein thrombosis in women with either factor V Leiden or protein C deficiency who also used the pill, whereas in another study an odds ratio as high as 149.3 (31.0-711.0) in women with the prothrombin mutation who used oral contraceptives has been reported (both studies provided a comparison with women without a defect who did not use the pill).20,21 Furthermore, women who use third-generation combined oral contraceptives have been found to be at an even higher (2-fold increased) risk of venous sinus thrombosis as compared with women who use second-generation preparations.21

Oral Contraceptives and Arterial Disease

Risk for Myocardial Infarction

Myocardial infarction is caused by irreversible necrosis of the heart muscle that results from prolonged ischemia. Nearly all cases of myocardial infarction are due to the formation of an acute thrombus that obstructs an atherosclerotic stenotic lesion. Men are affected more often than women (the overall ratio is 4:1). However, before the age of 40 years the ratio is about 8:1, whereas beyond the age of 50 years it decreases to 1:1.20,27 Next to the increase in age, cigarette smoking is an important risk factor for myocardial infarction in women.28 Although past use of oral contraceptives does not seem to increase the risk of this disease, many studies found a clear association between the current use of the pill and myocardial infarction.2,29-41 In women who use any types of low-dose oral contraceptives, the relative risk for myocardial infarction is 2.6 (1.7-3.8).35 Although some data indicate that the relative risk for myocardial infarction in third-generation oral contraception users versus non-users is not increased, this could not be established in two large case-control studies.34,36,37

There is an important interaction with other risk factors for arterial cardiovascular disease, such as smoking and hypertension, and the use of oral contraceptives in relation to the risk of MI. In a large multicenter case-control study in women
aged 35-44 years, the risk of death due to myocardial infarction was 69 per 100,000 in heavy smokers who used combined oral contraceptives versus 0.1 per 100,000 in non-smoking women who did not use oral contraceptives. However, the risk of myocardial infarction attributable to combined oral contraceptives alone is much lower than the risk attributable to smoking alone, or the combination of the two. Alternatively, oral contraceptives could make atherosclerotic coronary arteries more prone to arterial spasm. The use of progestagens alone is not associated with an increased risk of myocardial infarction.

**Risk for Ischemic Stroke**

The incidence of ischemic stroke in females aged 18-44 years is about 4.3 to 5.4 per 100,000 women years. A fatal ischemic stroke occurs in less than 0.5 per 100,000 for women under 45 years of age. Since the first case-report that raised this issue, many researchers have studied the association between ischemic stroke and use of oral contraceptives. One of the first case-control studies exploring the relationship between use of the pill and ischemic stroke found a relative risk for ischemic stroke of 3.1 (95%CI 1.1-8.6) in a population using high-dose estrogen pills. A worldwide study performed by the WHO revealed a relative risk of ischemic stroke in females who use oral contraceptives of approximately 3.0 (1.7-5.6) as compared to non-users, both in developed and developing countries. A recent meta-analysis of 16 adequate studies investigating the risk of ischemic stroke in low-dose oral contraception users calculated a relative risk of 1.9 (1.4-2.7) in studies that were controlled for smoking and hypertension. No significant difference in risk for ischemic stroke between women using second- or third-generation preparations could be detected. The use of progestagen-only contraceptives does not increase the risk for ischemic stroke.

**Risk for Hemorrhagic Stroke**

Approximately 10 percent of strokes are due to hemorrhages into the brain parenchyma, the subarachnoid space, or both, and another 10 percent are due to subarachnoid hemorrhage. The incidence of hemorrhagic stroke is higher in women than in men and is estimated to be 5.6 per 100,000 women-years in women aged 15-44 years. High-dose oral contraceptives have been reported to be associated with an
increased risk of intracerebral hemorrhage \cite{36-38}, although this risk seems to be lower or not increased at all in women using low-dose estrogen oral contraceptives (reported relative risks ranging from 1.14 to 2.5) \cite{39,41}.

The risk for hemorrhagic stroke may be higher among users of the pill who are already at higher risk for hemorrhagic stroke because of unruptured aneurysms, hypertension or smoking \cite{35,39,41,46,47}. Data on potential differences between the effects of second and third-generation pills on the risk of hemorrhagic stroke are not available.

**Potential Mechanisms of the Effect of Oral Contraceptives on Cardiovascular Risk**

**Effects of Oral Contraceptives on Hemostasis**

Hemostasis is mediated by the coagulation system, which leads to the production of fibrin, and the fibrinolytic system, which is responsible for its degradation. Within both systems, several regulating mechanisms are known to maintain an optimal balance between coagulation and fibrinolysis in different situations. Oral contraceptives influence the concentrations and activities of many factors of both coagulation and fibrinolysis \cite{40,41}.

Coagulation is initiated by the tissue factor (TF)-factor VIIa complex (the extrinsic pathway) which leads (by the activation of factor X) to the formation of the key enzyme thrombin. Thrombin activates factor XI which maintains coagulation, and catalyses the conversion of fibrinogen to fibrin. The extrinsic pathway is inhibited by tissue factor pathway inhibitor (TFPI). Furthermore, thrombin is generated via the intrinsic route, i.e. factors IXa and VIIIa (also called the tenase complex) and factors Xa and Va (also called the prothrombinase complex). The formation of thrombin (and thus fibrin) is regulated by natural anticoagulants, i.e. antithrombin, and the protein C pathway, consisting of protein C and protein S. Antithrombin is the primary inactivator of thrombin and factor Xa, but it also forms an irreversible complex with other activated coagulation factors. In the presence of thrombomodulin, thrombin activates protein C (APC), which together with its cofactor protein S, inactivates factors Va and VIIIa. This results in a downregulation of thrombin generation.

In the presence of fibrin, the fibrinolytic system is initiated when tissue plasminogen activator (t-PA) binds to plasminogen, which is then converted to its active form, plasmin. Plasmin catalyzes the degradation of fibrin, resulting in the dissolution of the clot. The activity of plasminogen activators is inhibited by
plasminogen activator inhibitors (PAI-1 and PAI-2). Furthermore, coagulation and fibrinolytic system are linked by thrombin-activatable fibrinolysis inhibitor (TAFI). Thrombin activates TAFI, which then downregulates fibrinolysis by inhibition of the binding between fibrin and plasminogen.

**Effects on Coagulation and the Anticoagulant System**

The concentrations of many clotting factors are increased during use of oral contraceptives, such as factors VII, VIII, X and fibrinogen. Moreover, prothrombin fragment 1+2, as a marker of thrombin formation, is known to increase during use of oral contraceptives.

In the natural anticoagulant pathway, the concentrations of protein S and to a lesser extent antithrombin are reduced in plasma of women using the pill.

Furthermore, the ability of activated protein C (APC) to downregulate coagulation by inactivation of factors V and VIII diminishes during use of oral contraceptives, as can be assessed by assays that measure APC resistance.

Although initially it was assumed that most of these effects are dose-dependent results of the estrogenic component of oral contraceptives, it is now clear that the progestagenic component importantly modulates this effect. In a crossover study, it was demonstrated that third-generation pills (containing desogestrel) induce greater increases in factor VII and prothrombin than second-generation oral contraceptives (containing levonorgestrel), and a more significant decrease in factor V. However, no difference in markers of thrombin generation was found between the two generations. Interestingly, there were clear differences between both pills with respect to their effects on the anticoagulant pathways. Both total and free protein S were markedly more decreased, and APC resistance more pronounced, with use of the third-generation oral contraceptives.

**Effects on the Fibrinolytic System**

Increased fibrinolytic activity is observed during the use of combined oral contraceptives, as measured by increased concentrations of plasminogen, tissue plasminogen activator, and plasmin-antiplasmin complexes and fibrin degradation products. Progestagens seem to modulate the fibrinolysis-enhancing effect of estrogens. However, in overall functional tests of the fibrinolytic system, no enhanced fibrinolysis is observed. This is probably attributed to a down-regulation of fibrinolytic activity by extra thrombin generation by the coagulation system via increased concentrations of TAFI. This inhibition of fibrinolysis is induced more by use of third-generation than second-generation oral contraceptives.
Effects on Risk Factors for Arterial Disease

Well-known risk factors for atherosclerosis include dyslipidemias, hypertension, cigarette smoking, diabetes mellitus, obesity and lack of physical activity. The use of combined oral contraceptives influences most of these factors.

Effects on Lipid Metabolism

In the exogenous pathway of lipid metabolism, absorbed cholesterol and triglycerides are incorporated into chylomicrons and transported into the venous circulation where they become hydrolysed by lipoprotein lipase, releasing fatty acids into muscle cells and adipose tissue. Metabolic remnants are absorbed by the liver, which can release it as free cholesterol or bile acids back into the intestine. In the endogenous pathway, very low density protein (VLDL) particles are released by the liver into the circulation. Assimilation of VLDL-residues result in cholesterol rich low density lipoprotein (LDL) that can be taken up by extrahepatic cells or by the liver. Cholesterol released into the circulation is transported by high density lipoprotein particles (HDL), which return cholesterol to the liver for excretion into the bile tract.

Elevated levels of triglycerides, carried mostly as VLDL, and elevated LDL levels promote atherosclerosis, while HDL is thought to protect against atherosclerosis. Estrogens and androgens have different effects on lipid metabolism. While estrogens lower LDL concentrations and elevate HDL and triglycerides, androgens and androgenic progestins do the opposite by reducing HDL and elevating LDL, mostly by interfering with hepatic lipase. In addition, low HDL levels seem to increase the atherosclerotic risk in women more than in men. Oral contraceptives containing third-generation progestagens, i.e. those with the lowest androgenic activity, are associated with a net beneficial lipid profile, i.e. lower LDL and higher HDL concentrations than in non users. In contrast, in women using second-generation combined oral contraceptives, the LDL concentration remains similar, but the HDL concentration is substantially reduced. The beneficial effect of third-generation oral contraceptives on the lipid profile was an important reason for developing and marketing these newer combined oral contraceptives.

Effects on Carbohydrate Metabolism

Diabetes mellitus is an important risk factor for atherosclerosis, although the effects of diabetes alone are difficult to assess. Many patients with diabetes also have secondary dyslipidemia and are often obese or hypertensive. Combined oral contraceptives increase levels of fasting insulin and C-peptide, as well as the
amount of insulin needed to cope with a standardized sugar load, indicating increased resistance to insulin. Insulin resistance has also been associated with an increased risk for coronary heart disease. The use of oral contraceptives does not lead to an increased risk for diabetes mellitus later in life.

**Effects on Blood Pressure**

Hypertension is associated with development of atherosclerosis, but also with premature deaths, non-lethal strokes, myocardial infarctions, retinal and kidney damage. Arterial pressure and blood flow to the tissues are controlled by cardiac output and vascular resistance, both of which are influenced by the sympathetic nervous system and the renin-angiotensin-aldosterone system. Hypertension may occur whenever there is an imbalance among the cardiac output, the volume of the vascular system and the vascular resistance. Oral contraceptives cause small increases in cardiac output, leading to higher systolic and diastolic blood pressure and increased heart rate. Hypertension is relatively unusual among users of oral contraceptives, although nearly 5 percent of women using (higher doses) oral contraceptives will develop hypertension. The effects are possibly dose-related and mainly induced by the estrogenic component which can affect levels of renin substrate, although the data are conflicting. Blood pressure rates usually normalises after discontinuation of oral contraceptives.

**Interaction Between Other Risk Factors and Oral Contraceptives**

Although smoking is not a risk factor for VTE, it is an important risk factor for arterial disease, especially in pill users who are over 35 years of age. These women have an increased risk of death from arterial cardiovascular events of up to 20 times as compared to women who do not use the pill and do not smoke. The attributable risk of oral contraceptives in non-smoking women is estimated to be 1.4 per 100,000, whereas it is 8.7 per 100,000 in women who smoke. Obesity is a risk factor for coronary artery disease. A modest weight gain is an adverse effect of oral contraceptives in clinical practice, in particular associated with the use of combined agents that contain androgen-like progestagens (second-generation oral contraceptives). Nevertheless, significant weight gain in combination with the use of oral contraceptives leading to an increase of arterial (and venous) disease has not been shown in studies. Weight gain can be controlled by changing to preparations that contain lower amounts of progestagens.
Clinical Implications

Clinical decisions on the use of oral contraceptives in women who are at a high risk for vascular disease should consider the benefits of these hormonal preparations (including better contraceptive qualities than other methods of contraception and beneficial effects on menstrual disorders) in relation to the documented risks and the preferences of the woman seeking advice.

For women with a past history of VTE, most clinicians will try to avoid the use of hormonal contraception and seek alternative contraceptive methods, such as the newest generation of intrauterine devices. For women without inherited thrombophilic conditions who had a first thrombotic event after a strong temporary risk factor such as trauma, surgery, and immobilisation, cautious use of oral contraceptives could be considered.

Whether female carriers of inherited thrombophilic factors who do not have a history of VTE are wise to use oral contraceptives remains a matter of individual counselling based on the known risk estimates. Use of second-generation combined oral contraceptives is definitely preferred to the use of third-generation preparations because of the higher risk of VTE during use of the latter. Since arterial cardiovascular diseases are relatively uncommon in premenopausal women, guidelines for prescription of combined oral contraceptives in women with arterial disease will be controversial. However, almost all women who develop arterial disease are older or have other risk factors such as smoking and hypertension. Thus, alternative contraceptive methods could be considered in these women. Since there is hardly any evidence that third-generation combined oral contraceptives induce a lower increase in the risk for arterial cardiovascular disease, there does not, at present, seem to be a strong indication to prefer these preparations in high-risk women.

In general, counseling women at increased risk for venous or arterial vascular diseases with regard to the use of oral contraceptives should be done individually and seems more important than an absolute 'yes' or 'no'.

Conclusions

In summary third-generation oral contraceptives cause an increased risk for VTE as compared to second-generation preparations, which is probably due to a stronger negative effect on the natural anticoagulant and antifibrinolytic system. This effect is even more pronounced in women with hereditary risk factors for VTE.
The use of combined oral contraceptives is also associated with an increased risk for arterial cardiovascular disease, in particular myocardial infarction and stroke. However, this risk seems to be limited to older women who also have other risk factors such as smoking and hypertension. Furthermore, the attributable risk of oral contraception on this risk is much lower than, for instance, smoking itself. Although third-generation oral contraceptives have a beneficial effect on lipid profiles, this is not translated into a lower increase in risk in most studies. In general, the increases in the risk of cardiovascular diseases associated with the use of oral contraceptives has to be balanced against the advantages of these drugs, especially in view of the absolute baseline estimates of cardiovascular diseases which are generally low in women of child-bearing age.

References


