Venous and arterial thrombosis during oral contraceptive use

Rosendaal, F.R.

Venous and Arterial Thrombosis during Oral Contraceptive Use: Risks and Risk Factors

Bea C. Tanis, M.D.,[1] and Frits R. Rosendaal, M.D., Ph.D.[1,2]

ABSTRACT

Since the introduction of oral contraceptives, their use has been associated with an increased risk of both venous and arterial thrombosis. Pulmonary embolism, myocardial infarction, and stroke are serious disorders with a considerable risk of mortality. Because worldwide over 100 million women use oral contraceptives, issues of drug safety are of great importance. The risk of venous thrombosis during low-dose oral contraceptive use is three- to sixfold increased compared with that of nonusers. The association is not only attributed to the estrogen component of the pill: the risk is twice as high for desogestrel and gestodene (third generation) containing oral contraceptives as for levonorgestrel (second generation) containing oral contraceptives. The risk of venous thrombosis is highest in the first year of use and in women with genetic or acquired risk factors for thrombosis. Both venous or arterial thrombosis are unrelated to duration of use or past use of combined oral contraceptives. The risk of myocardial infarction and stroke during low-dose oral contraceptive use is two- to fivefold increased relative to that of nonusers. The risk of arterial thrombosis induced by oral contraceptive use is more pronounced in smokers and women with hypertension, diabetes, and hypercholesterolemia. All types of thrombosis have strongly age-dependent incidences, and therefore in absolute figures the risks and effects of risk factors increase with age. The lowering of the estrogen dose in combined oral contraceptives from 50 μg to 20–30 μg in the last decade did not clearly reduce the risk of venous thrombosis, myocardial infarction, stroke, or peripheral arterial disease. For stroke and peripheral arterial disease no difference in risk was found between second and third generation oral contraceptives. For myocardial infarction study results are conflicting, and a small benefit of third- over second-generation oral contraceptives cannot be ruled out. However, this is unlikely to counterbalance the adverse effect of third generation contraceptives on venous thrombosis.

KEYWORDS: Oral contraceptives, estrogens, progestagens, venous thrombosis, arterial thrombosis, epidemiology

Educational Objectives: Upon completion of this article, the reader will be able to (1) summarize the most important determinants of venous and arterial thrombosis, and ascertain whether a putative interaction with oral contraceptive use is present (2) comprehend the latest developments in understanding the possible mechanisms underlying an increased thrombotic risk for both venous and arterial thrombosis by oral contraceptive use, and (3) explain how second and third generation oral contraceptives differ from each other in influencing coagulation and lipid levels

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Thrombosis, venous as well as arterial, is the most frequently occurring serious side effect of combined oral contraceptives (OCs). Millions of women all over the world use OCs for many years and therefore side effects are highly relevant. Even a small increase in risk will lead to disease in a large number of women who are often healthy and young. Most women use OCs as a method for birth control; OCs are more rarely used for other reasons such as acne and dysmenorrhea.

For almost 40 years it has been known that OC use is associated with an increased risk of cardiovascular disease. A boost in understanding the pathogenesis of *venous* thrombosis came when we became aware of the gene-environment interaction in which OC use coincidences with heritable clotting defects leading to a disbalance of hemostatic factors. The identification of new risk factors (apart from the classical ones, i.e., deficiency of antithrombin, protein C, or protein S) for venous thrombosis, that is, factor V_{Leiden}, prothrombin 20210A, high levels of factor VIII, IX, and XI, thrombin-activatable fibrinolysis inhibitor (TAFI), and hyperhomocysteinemia, has greatly improved insight into the etiology of venous thrombosis and especially resistance to activated protein C (APC resistance) in the understanding of the role of OCs.[1]

For *arterial* thrombosis, however, the role of hemostatic risk factors is less clear.[2] Although numerous studies have been published on the role of genetic risk factors for myocardial infarction, studies are limited by their sample size, which was mostly insufficient to establish the risk of a single polymorphism in a complex disease.[3,4]

Thrombosis is a multicausal disease in which acquired and genetic causes interact.[5] The effects of OCs on venous thrombosis, myocardial infarction, and ischemic and hemorrhagic stroke are strongly influenced by other risk factors for thrombosis, which are different for venous and arterial thrombosis. Venous thrombosis is an acute event in contrast to most types of arterial thrombosis, which predominantly occurs in vessels with preexistent atherosclerotic disease. Table 1 summarizes the main risk factors for both types of thrombosis.

In this article, we evaluate the epidemiology of venous and arterial thrombosis during OC use. We restrict ourselves predominantly to the studies of combined OCs from the last decade and give a summary of the studies that also focus on differences between OCs, that is, the dose of estrogen and the different types of progestagens.

COMPOSITION AND MODE OF ACTION OF ORAL CONTRACEPTIVES

Most OCs contain an estrogen and a progestagen (monophasic preparations). In biphasic and triphasic combinations, the content of the pills during one cycle varies, with more estrogen in the early phase of the cycle and more progestagen in the later phase of the cycle. OCs act by preventing ovulation through the action of progestagen, which suppresses luteinizing hormone. Some formulations contain only a progestagen, and these cause a higher frequency of breakthrough bleedings. The major role for the estrogen component in the pill is to prevent

Table 1 Inherited and Acquired Risk Factors for Venous and Arterial Thrombosis

Inherited*	Venous Thrombosis Acquired/Mixed	Arterial Thrombosis Acquired/Mixed
Antithrombin deficiency	Oral contraceptives, age	Oral contraceptives, age
Protein C deficiency	Hormone replacement therapy	Smoking
Protein S deficiency	Previous venous thrombosis	Previous cardiovascular event
Factor V Leiden	Immobilization	Systolic and diastolic hypertension
Prothrombin 20210A	Major surgery and trauma	Diabetes
Dysfibrinogenemia	Pregnancy, puerperium	Hyperlipidemia, hypercholesterolemia
	Obesity	Obesity
	Antiphospholipid syndrome	Antiphospholipid syndrome
	Hyperhomocysteinemia	Hyperhomocysteinemia
	High levels of factor VIII	Inactivity
	High levels of factor IX	Sex
	High levels of factor XI	Left ventricular hypertrophy
	High levels of fibrinogen	High levels of fibrinogen
	APC resistance in absence of FVL	
	High levels of TAFI	
	Myeloproliferative syndrome	
	Malignancy	
	Elevated D-dimers	

*These genetic defects are clear risk factors for venous thrombosis, their role in arterial disease is less clear and much less pronounced

breakthrough bleeding and spotting by organizing the endometrium. With optimal compliance the failure rate is less than 1%.

During the past four decades the hormonal contents of combined OCs have changed. The estrogen dose has been reduced from 150 μg mestranol or ethinylestradiol to 20–30 μg ethinylestradiol, the so-called low-dose formulations. Ethinylestradiol is a synthetic estradiol, which is active when metabolized in the liver.

Progestagens are grouped into "generations" based historically on when they were first produced because of the absence of a formal classification system. OCs from the 1960s contained a first-generation progesteron (norethisterone, lynestrenol), and from the 1970s onward the second generation (levonorgestrel, norgestrel, norgestrione) was used. To minimize the androgenic side effects third-generation progestagens (desogestrel, gestodene) have been developed, and these have been used from the early 1980s in Europe and since the 1990s in the United States. Norgestimate, also marketed since the 1980s, is partly metabolized into levonorgestrel, so it cannot be readily categorized. In this system of generations, cyproterone acetate and drosperinone are not classified.

ASSOCIATION BETWEEN ORAL CONTRACEPTIVES AND THROMBOSIS

The clinical observations linking OC use with venous thombosis,[6] ischemic stroke,[7] and myocardial infarction[8] were made shortly after their introduction in the early 1960s, including fatal cases from thromboembolic disease. In subsequent studies the death rate from all types of cardiovascular events during OC use appeared to be five times that of control women who had never used OCs, and the risk did not differ between the older formulations with high (≥ 50 μg) estrogen dose and the newer low-dose (< 50 μg) OCs from the 1970s.[9,10] If the risk went down over the years, it may have been the result of more careful prescription of OCs.[11]

Age is an important risk factor for thrombosis. Thrombosis rarely occurs before puberty, after which the annual incidence progessively increases. Incidences of cardiovascular disease and mortality data during the reproductive age are summarized in Table 2. Until age 40, venous thrombosis is the most common form of thrombosis with a low mortality. After age 30, however, mortality is higher for arterial than for venous thrombosis and increases exponentially through the reproductive age periods. Today, women tend to start OC use earlier and use them for a longer period.[12]

Venous Thrombosis

Venous thrombosis occurs most often as deep vein thrombosis of the leg and pulmonary embolism. Although only 10% of patients with deep vein thrombosis have symptoms indicative of pulmonary embolism, half of the patients have unequivocal evidence of asymptomatic pulmonary emboli.[13,14] Mortality is higher for pulmonary embolism than for deep vein thrombosis because the diagnosis can be easily missed in previously healthy women. Relative risks for fatal pulmonary embolism associated with OC use were found to be the same for older formulations and currently available combined OCs.[15,16]

The first case-control study on venous thrombosis reported a threefold increased risk in OC users compared with nonusers,[17] which was soon confirmed by other studies.[18–21] In the early 1970s estrogens were found to be responsible for the increased risk of thrombosis,[22] but certain discrepancies in the data already suggested that the dose of estrogen could not be the only factor related to the risk of thrombosis.[23]

Table 2 Incidence of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke and Incidence of Death at Young Age[178]

	Incidence per 100,000 per Year		
Age	Venous Thrombosis	Myocardial Infarction	Ischemic Stroke
15–24	20 2	0 7	1 9
25–39	39 3	18 6	6 6
40–54	74 2	175 6	45 4
Age	**Mortality per 100,000 per Year**		
15–24	0 3	0 3	0 1
25–39	0 4	3 0	0 4
40–54	1 1	31 5	3 6

ESTROGENS AND PROGESTAGENS

Studies performed between 1967 and 1993 did not show a substantial risk reduction for venous thrombosis despite the lowering of the estrogen dose in the 1970s and the introduction of new progestagens in the 1980s.[24,25] The newest progestagens (so-called third generation progestagens) were introduced after studies with intermediate endpoints in young healthy women (e.g., blood pressure, lipid and glucose levels, and various coagulation and fibrinolysis parameters).[26] Although third-generation progestagens seemed to influence lipid and carbohydrate metabolism less than the older formulations, adverse side effects on the hemostatic system have been underestimated. Despite some reports of severe thrombogenic episodes and fatal pulmonary embolism during third-generation OC use,[27,28] only a few studies reported on hemostatic adverse effects in depth.[29] This was probably due to the absence of knowledge of which parameters were important, and it lasted 25 years before the effect of progestagens on clotting was recognized. Unexpectedly, therefore, in 1995 and 1996, a further twofold increased risk of venous thrombosis was reported in

several studies including OCs containing desogestrel and gestodene (third generation) compared with OCs with previous generations of progestagens.[30–33] Subsequent studies confirmed these findings and also showed a higher risk of fatal pulmonary embolism during third-generation OC use.[16,34]

A recent meta-analysis of the risk of third-generation OCs and the risk of venous thrombosis showed an overall adjusted odds ratio of 1.7 (95% confidence interval [CI] 1.4–2.0) relative to the use of second-generation OCs.[35] In a subgroup analysis, the odds ratios differed between studies sponsored by the pharmaceutical industry (OR 1.3; 95% CI 1.0–1.7) and non–industry-sponsored studies (OR 2.3; 95% CI 1.7–3.2), according to an earlier comment on the influence of competing interest.[36] After the medical alert in 1995, changes have occurred in OC prescriptions according to recommendations from health authorities.[37,38] Consistency of the study results thereafter, reasonable certainty about the absence of bias as well as confounding, and a remarkable start in understanding biological plausibility may contribute to the appreciation of a causal relationship between third-generation OCs and venous thrombosis.[39–48]

MAGNITUDE OF RISK OF VENOUS THROMBOSIS

Women who take low-dose OCs still have a risk of venous thrombosis that is increased three- to sixfold compared with that of nonusers.[49–51] The majority of women who use OCs remain free of thrombotic events, but in combination with other acquired risk factors and particularly in women with genetic thrombophilic defects OC use will often trigger thrombosis.[52–56]

The absolute risk of venous thrombosis among OC users has been estimated at 2.0 and 3.0 per 10,000 users per year,[46,52] compared with 0.8 per 10,000 per year in nonusers.[52] Given the steep age dependence of the thrombosis incidence, absolute risks are considerably lower in the youngest and considerably higher in the older users. For venous thrombosis, the risk is highest in the first 6 months of OC use.[57] This does not indicate an effect of duration but risk stratification between users: those with a high "thrombotic potential" (for instance, due to prothrombotic mutations) will develop thrombosis shortly after being exposed to an additional risk factor such as OCs. Analogous results have been found for postmenopausal hormones and myocardial infarction.[58]

The case-fatality rate for venous thromboembolism is slightly lower than for arterial diseases and is assumed to be about 2–5%.[59,60] Workers from New Zealand reported seven cases of women who used third-generation OCs and died from pulmonary embolism.[16] The absolute risk of fatal pulmonary embolism in this study was estimated to be 10 per million women-years.

Duration of OC use does not effect the risk estimates of venous thrombosis, nor does lifetime duration of use.[42,49] The risk increase disappears within 3 months after stopping OCs; that is, the risk is immediate, reversible, and does not accumulate.

UNCOMMON FORMS OF VENOUS THROMBOSIS

A strong association has been found between cerebral sinus thrombosis and OC use and in synergy with factor V_{Leiden} and prothrombin 20210A.[61–64] The increased risk for third-generation OCs compared with other OCs was also found for cerebral venous sinus thrombosis.[65] Several case reports have highlighted the association between retinal vein occlusion and OCs,[66,67] but in a population-based study this association has not been confirmed.[68] OC use has been associated with Budd-Chiari syndrome in case reports.[69,70] In a multicenter case-control study, Budd-Chiari syndrome and portal vein thrombosis were found to be multicausal diseases. In a third of these patients concurrent acquired or genetic risk factors for thrombosis were present, but OCs were not found to be an important risk factor.[71]

The post-thrombotic syndrome is a chronic consequence of deep venous thrombosis that has received little attention to date. Few studies have looked at the relation with OC use.[72] This syndrome occurs in almost 30–60% of the patients with deep venous thrombosis and is strongly related to ipsilateral recurrent deep venous thrombosis but is not directly related to the extent of the thrombosis.[13] Superficial thrombophlebitis has also been associated with OC use in older reports but in recent studies failed to be significant.[73]

Arterial Thrombosis

Myocardial infarction and ischemic stroke are due to cell necrosis after reduced blood flow related to occlusion of one or more coronary arteries in the case of myocardial infarction or occlusion of the intracranial or extracranial arteries in the case of ischemic stroke. Hemorrhagic stroke is caused by an arterial rupture. Spasm or dissection of the blood vessels has also been associated with endogenous (pregnancy, puerperium) and exogenous sex hormones. Coronary thrombosis is usually precipitated by endothelial denudation or plaque fissuring or rupture. Occluding thrombi often occur at sites with angiographically minimal or absent underlying stenosis. Patients with cerebral thrombosis present with clinical symptoms reflecting the size and location of the artery involved. Large artery occlusions may present in a sudden or gradual or stepwise fashion, with or without a prior transient ischemic attack. Thrombosis without underlying atherosclerotic disease may occur in patients with coagulation disorders, especially in young patients without conventional stroke risk factors and with recurrent unexplained episodes of thrombosis.[74]

Peripheral arterial occlusive disease is rare in young women but carries a poor prognosis with a high incidence of vascular graft occlusion and amputation and therefore high morbidity.[75,76] In older reports, a causative relation-

ship between early localized arteriosclerosis in the distal aorta in women of reproductive age with intermittent claudication and long-term OC use has been suggested,[77] for example, mesenterial thrombosis,[78] and thrombosis of the digital vessels.[79] There are no studies available on the association between OC use and these rare manifestations of arterial thrombosis, which may simply reflect their low incidence.

Myocardial Infarction

The introduction of newer low-dose OCs over time has coincidenced with a reduction in the incidence of myocardial infarction.[80] This may point to lower thrombogenicity of these OCs but could also be explained by secular trends in the post–World War II epidemic of cardiovascular disease. In the MONICA study, the estimated incidence rates ranged from 0 to 3 per 100,000 women-years in the age group 25–34 years and 6 to 14 per 100,000 women-years in the age group 35–44 years.[81] Mortality from myocardial infarction is low, < 0.4 per 100,000 women-years at age 15–24 and 2–7 per 100,000 women-years at age 35–44 years. In the United States similar risks were found, 1–2 per 100,000 women-years in women younger than 35 years, 4.1 per 100,000 women-years in women aged 35–39 years, and 10–21 per 100,000 women-years for women in their 40s. Most of the risk is confined to women with additional risk factors such as smoking, hypertension, diabetes, hyperlipidemia, and obesity. Estimates of fatality rates for myocardial infarction differed between studies, countries, and age groups between 8 and 50%. The 28-day case-fatality rate in women aged 15–44 years was between 20 and 30%.[60]

RISK AND RISK FACTORS

Among the studies on the association between myocardial infarction and OCs, few data are available on the currently used low-dose OCs. More recent studies showed a small increased risk for nonsmoking OC users but still a high risk for smokers.[82–84] The results of the five studies on first myocardial infarction and low-dose OCs are summarized in Table 3.[82,83,85–87] Myocardial infarction was defined by electrocardiographic changes, increased cardiac enzymes, and the presence of chest pain. The overall estimated risk associated with low-dose OC use is a twofold increase. In Europe, but not in developing countries, relative risks associated with estrogen dose did not differ between higher and low-dose OCs. Among women who used OCs and had additional risk factors, the risk of myocardial infarction increased to 6-fold for hypertensive OC users, 13-fold for smoking OC users, 17-fold for diabetic OC users, and 24-fold for hypercholesterolemic OC users.[87]

Five studies have been published that presented a direct comparison of third- and second-generation OCs in relation to the risk of myocardial infarction. These studies were heterogeneous with respect to case and control selection as well as to the outcome. Overall there was a slight but not significant lower risk of myocardial infarction for third- compared with second-generation OCs (Table 4). The World Health Organization (WHO) study, however, found no difference in risk between second- and third-generation OCs in women who have had a blood pressure check.[85] In a recent study the risk of death within 1 month after myocardial infarction was increased for second-generation OCs compared with no use (OR 2.9; 95% CI 1.2–6.8) but not for other types of

Table 3 Adjusted Odds Ratios for Myocardial Infarction in Current Oral Contraceptive Use versus No Use

Author (Reference)	Number of Cases	Number of Controls	Number of Exposed Cases	Number of Exposed Controls	Odds Ratio (95% CI)
WHO, 1997[85]					
Developing countries	170	461	39	41	4 8 (2 5–9 1)
≥ 50 µg EE			26	18	77 (3 3–18 0)
< 50 µg EE			13	22	2 9 (1 2–70)
Europe	198	480	62	78	5 0 (2 5–9 9)
≥ 50 µg EE			31	43	4 5 (2 0–10 0)
< 50 µg EE			28	33	4 7 (2 0–10 9)
Lewis, 1997[86]	153	498	57	156	2 4 (1 4–3 9)
Sidney, 1998[82]	267	991	12	87	0 9 (0 4–2 2)
Dunn, 1999[92]	448	1728	62	261	1 4 (0 8–2 5)
Tanis, 2001[87]	248	925	99	348	2 1 (1 5–3 1)
50 µg EE			4	10	2 0 (0 6–73)*
30 µg EE			37	94	2 6 (1 6–4 2)*

*Analyses were restricted to OCs with 50 µg ethinylestradiol (EE) and 125 µg levonorgestrel and OCs with 30 µg ethinylestradiol and 150 µg levonorgestrel

Table 4 Relative Risk of Myocardial Infarction in Current Users of Low-Dose (<50μg of Estrogen) Combined Oral Contraceptives Containing Different Types of Progestagen, Compared with Nonusers or Users of Low-Dose Combined Oral Contraceptives Containing Levonorgestrel

Author (Reference)	Type of Progestagen	Number of Cases	Number of Controls	Number of Exposed Cases	Number of Exposed Controls	Relative Risk (95% CI) Compared with	
						Nonusers	Users of Low-Dose Pills Containing Levonorgestrel
Jick, 1996[179]	Levonorgestrel	75	300	5	18	—	1 0
	Desogestrel/ gestodene			1	5	—	0 7 (0 1–8 2)
				1	6	—	0 6 (0 1–6 4)
WHO, 1997[85]	Levonorgestrel	368	941	13	17	1 6 (0 5–5 5)*	—
	Desogestrel/ gestodene			3	5	1 0 (0 1–70)*	—
Lewis, 1997[86]	Levonorgestrel	153	498	22	57	3 0 (1 5–6 1)	1 0
	Desogestrel/ gestodene			7	49	0 8 (0 3–2 3)	0 3 (0 1–0 9)
Dunn, 1999[92]	Levonorgestrel	448	1728	20	119	1 1 (0 5–2 3)	1 0
	Desogestrel/ gestodene			20	61	2 0 (0 9–4 4)	1 8 (0 7–4 8)
Tanis, 2001[87]	Levonorgestrel	248	925	59	173	2 5 (1 5–4 1)	1 0
	Desogestrel/ gestodene			20	110	1 3 (0 7–2 5)	0 5 (0 2–1 1)

*In women with a blood pressure check prior to prescription, odds ratios were 1 0 for second and third generation oral contraceptives

contraceptives.[88] However, this conclusion was based on only 3 deceased patients and 17 patients who stayed alive after myocardial infarction.

Duration of OC use has not been proved to be important in the relation to the risk of myocardial infarction,[59,85] and no evidence was found that long duration of OCs adversely affects long-term risk of mortality due to myocardial infarction.[89]

Lack of an effect of past use of OCs for coronary disease is well documented,[90] and more recent studies also failed to show an increased risk among past users of OCs.[84,85,91,92]

It has been hypothesized that myocardial infarction during OC use is a separate disease entity, as completely normal coronary angiographies have been found in women with thrombotic coronary occlusions.[93,94] This suggests that the effect of OCs, also on arterial disease, is thrombotic rather than atherogenic and is in accordance with an immediate, reversible, noncumulative effect. If this hypothesis is true, the theoretically beneficial effect of the third generation on the lipid profile may not lead to a lower risk of myocardial infarction. In addition to OCs, smoking cigarettes is particularly a risk factor for acute coronary thrombosis in women.[95]

Stroke

The incidence of fatal ischemic and hemorrhagic stroke is very low in women of reproductive age but increases exponentially with age.[96] In the MONICA project the incidence of ischemic stroke was 73.1 per 100,000 women aged 15 to 55 years.[97] Incidence of ischemic stroke was estimated between 4.1 and 11.3 per 100,000 women-years in women between 15 and 44 years of age in a population from the United States.[98–100] Case-fatality rates for stroke differed in different studies but have been reduced in recent years to 5–20% of ischemic strokes.

RISK OF ISCHEMIC STROKE

In studies before 1990 combined OCs were found to be associated with a three- to fourfold increased risk of first ischemic stroke.[101–103] The results of the eight recent studies on ischemic stroke are summarized in Table 5. Stroke was defined by the presence of specific symptoms and the results of imaging procedures.Current use of low-dose combined OCs is still associated with ischemic stroke with relative risk estimates varying from 1.2 to 3.1.[98,104–107] Migraine, particularly with aura, during OC use has been described as an additional risk factor for ischemic stroke.[108,109]

Four studies investigated the risk of ischemic stroke according to progestagen type; these studies are summarized in Table 6. The overall odds ratios were quite similar and no differences between second- and third-generation OCs were found.

The risk of stroke among past users of OCs was not increased in the majority of the studies.[98,106] In both older[15,20,102,110] and recent studies, duration of OC use was without influence on the risk of stroke and the odds ratios were constant over the age bands.[106] Increased risk in long-term (> 6 years) users has been found but can also be related to OC-induced hypertension.[104] A seem-

Table 5 Adjusted Odds Ratios for Ischemic Stroke in Current Oral Contraceptive Use versus No Use

Author (Reference)	Number of Cases	Number of Controls	Number of Exposed Cases	Number of Exposed Controls	Odds Ratio (95% CI)
Tzourio, 1995[108]	72	173	47	63	3 1 (1 2–8 2)
50 μg EE			8/41	7/62	4 8*
30–40 μg EE			30/41	46/62	2 7*
20 μg EE			2/41	5/62	1 7*
WHO, 1996[104]					
Europe	141	373	52	87	3 0 (1 7–5 4)
≥ 50 μg EE			32	35	5 3 (2 6–11 0)
< 50 μg EE			20	52	1 5 (0 7–3 3)
Developing countries	556	1579	109	163	2 9 (2 2–4 0)
≥ 50 μg EE			44	69	2 7 (1 8–4 2)
< 50 μg EE			63	89	3 3 (2 2–4 9)
Pettiti, 1996[98]					
Ischemic	144	774	17	43	1 2 (0 5–2 6)
Hemorrhagic	151	774	21	50	1 1 (0 6–2 2)
Schwartz, 1997[100]	60	485	6	49	0 9 (0 3–2 9)
Heinemann, 1998[105]	220	775	127	289	3 6 (2 4–5 4)
Lidegaard, 1998[106]	219	1041	68	207	
50 μg EE			10	15	2 7 (1 1–6 3)
30–40 μg EE			43	163	1 6 (1 1–2 4)
20 μg EE			5	22	1 6 (0 6–4 6)
Kemmeren, 2002[107a]	203	925	102	348	2 1 (1 5–3 1)
50 μg EE			3	10	2 3 (0 6–9 0)†
30 μg EE			28	94	2 4 (1 4–4 1)†

*No confidence intervals were provided in the original paper
†Analyses were restricted to OCs with 50 μg ethinylestradiol (EE) and 125 μg levonorgestrel and OCs with 30 μg ethinylestradiol and 150 μg levonorgestrel

ingly similar but different observation was made in relation to recency of use.

RISK OF HEMORRHAGIC STROKE

The risk of hemorrhagic stroke associated with OC use is less well established than that of ischemic stroke. The overall relative risk for hemorrhagic stroke associated with OCs from three recent studies was estimated to be 1.5-fold (95% CI 1.1–1.9) increased compared with that of nonusers[98,100,111] but increased substantially in cigarettes smokers (3-fold) and in women with hypertension (10- to15-fold).[98,111] The risk of hemorrhagic stroke in OC users was not elevated in women younger than 35 years, but in women older than 35 it was estimated to be elevated 2.2-fold compared with that of nonusers. Smoking increased the risk further.[60] For hemorrhagic stroke there is no evidence that there is a difference in risk between second- and third-generation OCs.[107,112]

Peripheral Arterial Occlusive Disease

A unique pattern of localized aortoiliac atherosclerosis in the distal aorta in young women with intra-arterial thromboembolic events at presentation has been described, but the role of OCs in premature arteriosclerosis has not been investigated.[75,77] In an animal model, however, no increase of arterial thrombosis was found after 30 months of OC treatment.[113]

In a population-based case-control study among young women all types of OC use were associated with a 3.8-fold risk (95% CI 2.4–5.8) of peripheral arterial disease. There was no difference in risk between 50 and 30 μg ethinylestradiol–containing combined contraceptives or between second- and third-generation OCs.[114] The odds ratio for second-generation OCs was 2.6 (95% CI 1.4–4.9) and for third-generation OCs was 3.0 (95% CI 1.4–6.6).

INTERACTION WITH OTHER RISK FACTORS DURING ORAL CONTRACEPTIVE USE

A positive interaction between cigarette smoking and current OC use with high risks of myocardial infarction was already recognized in the 1970s.[115] Several studies confirmed a higher risk than expected for myocardial infarction in OC users who smoked in comparison with nonsmokers for both high-dose and low-dose formula-

Table 6 Relative Risk of Ischemic Stroke in Current Users of Low-Dose (<50 μg of Estrogen) Combined Oral Contraceptives Containing Different Types of Progestagen, Compared with Nonusers or Users of Low-Dose Combined Oral Contraceptives Containing Levonorgestrel

Author (Reference)	Progestagen	Cases (N)	Controls (N)	Number of Exposed Cases	Number of Exposed Controls	Relative Risk (95% CI) Compared with Nonusers
Heinemann, 1998[105]	Levonorgestrel	220	775	58	144	3.4 (2.1–5.5)
	Desogestrel/ gestodene			45	92	3.9 (2.3–6.6)
Lidegaard, 1998[106]	Levonorgestrel	219	1041	22	56	2.4 (1.4–4.2)
	Desogestrel/ gestodene			24	118	1.3 (0.8–2.2)
Poulter, 1999[107]	Levonorgestrel	122	191	52	87	2.7 (1.8–4.1)
	Desogestrel/ gestodene			8	15	1.8 (0.6–5.2)
Kemmeren, 2002*[107a]	Levonorgestrel	203	925	52	173	2.4 (1.4–4.1)
	Desogestrel/ gestodene			32	110	2.2 (1.2–3.9)

*Direct comparison between 30 μg ethinyestradiol–containing formulations only.

tions.[85,87,116] Smoking is by far the most important risk factor for the occurrence of arterial cardiovascular disease in young women.[117] For myocardial infarction the relative risks ranged from 11- to 22-fold, and higher risks were found with increasing number of cigarettes.[85–87] For ischemic stroke the relative risk ranged from 4 to 7 as compared with nonusers who did not smoke.[104]

OCs are a risk factor for myocardial infarction especially when there are other cardiovascular risk factors, that is, hypertension, diabetes, hypercholesterolemia, and obesity, and these risk factors increase with age.[118,119] As the absolute risk of myocardial infarction is highly age dependent, OCs will have the most impact in older women. Unfortunately, in many studies of the association between OCs and cardiovascular disease, patients with conventional risk factors have been excluded, resulting in a lack of data on combinations of risk factors.

In contrast to the progress that has been made in understanding the genetic contributions to venous thrombosis, much still remains to be studied on the genetic base of arterial thrombosis. A major complication in the study of gene-environment interaction for arterial disease is that this has a chronic process of atherosclerosis compounded by an acute thrombotic event, in contrast to venous thrombosis, which is due to acute clot formation. Despite the documentation of associations between several genetic polymorphisms and plasma coagulation factor levels, consistent associations with arterial thrombotic disease have not been found.[3,4]

The influence of genetic defects on myocardial infarction and stroke has been investigated since 1995 with varying outcomes. Different results on the contribution of genetic defects seem to depend on the type of population that has been studied. Positive associations between prothrombotic mutations (i.e., factor V_{Leiden}, prothrombin 20210A) and the risk of myocardial infarction were found among young women, particularly smokers and women with other cardiovascular risk factors[120,121] or patients with normal angiographies.[74] The risk of myocardial infarction was similar among women who used OCs whether or not they had a prothrombotic mutation.[87] Data on the effect of prothrombotic mutations and stroke are controversial. Most studies in women did not find an increased risk of stroke in the presence of prothrombotic mutations.[122,123]

EFFECTS OF ORAL CONTRACEPTIVES ON THE COAGULATION SYSTEM

Changes of Coagulation Factors

Elevations of the procoagulant factors fibrinogen, prothrombin, and factors VII, IX, X, and XII and decrease of the anticoagulant factors protein S and antithrombin are consistent effects of OCs on the hemostatic system.[124–126] Women differ in the extent of these changes, and it has been suggested that so-called high responders have the highest risk.[127] The underlying mechanisms of this response are unknown. Upon cessation, coagulation parameters returned to normal within 3 months.[128]

Acquired Activated Protein C Resistance

APC resistance is defined as an impaired plasma anticoagulant response to APC in vitro. After the discovery of inherited poor anticoagulant response to APC as a risk factor for familial venous thrombosis,[129] factor V_{Leiden} was found as the most common cause of inherited APC

resistance.[130,131] Factor V_{Leiden} is caused by a single base mutation (G1691→A) in the factor V gene resulting in the replacement of Arg^{506} by Gln at the predominant cleavage site for APC. Besides inherited APC resistance, other coagulation disorders are associated with APC resistance, that is, antiphospholipid antibodies and elevated factor VIII levels. Acquired APC resistance without the presence of factor V_{Leiden} was recognized in OC users[132–137] and is one of the major epidemiologic observations explaining the increased risk in OC users.[1,138,139] It is more pronounced in women using third-generation OCs than in second-generation OC users.[140–143] Acquired APC resistance is best measured with a APC sensitivity assay based on the endogenous thrombin potential (ETP), in which coagulation is initiated through the extrinsic pathway, which proved to be more sensitive to exogenous factors than the commonly used activated partial thromboplastin time (aPTT)–based test.[144] Women who used third-generation OCs had almost the same degree of APC resistance as carriers of factor V_{Leiden} without OC use.[145] In addition, women with APC resistance related to factor V_{Leiden} are most susceptible to acquired APC resistance associated with OC use, probably due to a gene-environment interaction. Moreover, a dose-response relationship between the severity of APC resistance and the risk of venous thrombosis has been observed with a fourfold increased risk for values in the lower quartile compared with those in the highest quartile.[146]

Acquired Decreased Levels of Protein S and Antithrombin

During OC use protein S and antithrombin levels decrease.[53,125,147] Women with inherited antithrombin deficiency developed venous thrombosis during OC use or pregnancies earlier in life than women with inherited protein S deficiency.[148]Antithrombin levels decrease more with gestodene-containing OCs than with levonorgestrel-containing contraceptives.[149,150] In a randomized controlled trial both free and total protein S in plasma from users of desogestrel-containing OCs were more decreased than in plasma from users of levonorgestrel-containing OCs.[143]

Fibrinolytic Factors

OCs induce changes in fibrinolytic parameters, but changes in the fibrinolytic system have not been associated with venous thrombosis. High levels of TAFI have been found to be a mild risk factor for venous thrombosis.[151] TAFI levels increase during OC use, inducing a hypofibrinolytic state, which is more pronounced with third- than with second-generation OCs.[152] This can be one of the mechanisms by which OCs contribute to the thrombotic risk.

Fibrinogen increases considerably by 10 to 20% during OC use, which may contribute to the increased cardiovascular risk,[153] possibly in particular to the risk of arterial disease. Rise of fibrinogen was dependent on estrogen dose and smoking.

EFFECTS OF ORAL CONTRACEPTIVES ON THE CARBOHYDRATE AND LIPID SYSTEM

OCs can induce substantial changes in plasma glucose and lipoprotein levels similar to those associated with an increased risk of cardiovascular disease, including increased levels of glucose and insulin, increased levels of triglycerides and low-density lipoprotein (LDL), decreased levels of high-density lipoprotein (HDL),[154] and increases in systolic and diastolic blood pressure.[116] Generally, all low-dose combined OCs produce a slight increase in insulin resistance and a decrease in glucose tolerance. Modifications in lipoprotein parameters may depend on the estrogen or progestagen content of each formulation.[155] In most comparative studies these changes were moderate and reported as staying within normal limits.[156–159]

PROGESTAGEN-ONLY FORMULATIONS

Progestagen-only contraceptives are used by only a small percentage of women. In the past, progestagen-only preparations have been used by women for whom combined OCs were contraindicated. Changes in lipid parameters have been observed with progestagen-only preparations, which showed a decrease in total cholesterol, HDL cholesterol, and triglycerides. Changes in LDL cholesterol were dependent on the type of progestagen; an increase was found with levonorgestrel-only and a decrease with desogestrel-only preparations.[160] The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception found no increased risk of myocardial infarction and stroke and an unclear effect with regard to venous thromboembolism.[161] However, among women with hypertension, progestogen-only contraceptives increased the risk of stroke. In a more recent study there was no effect on venous thrombosis with progestagens alone used for contraception,[162] but a substantial association has been found with higher dose progestagens for other indications, that is, menstrual disorders.[163]

CLINICAL RECOMMENDATIONS

Screening

Routine screening of all women for genetic risk factors before prescription of an OC is not cost effective. In addition, it would deprive a large number of women of the safest method of contraception because a growing number of genetic risk factors for venous thrombosis have been discovered. Moreover, it would prevent only a small number of deaths due to pulmonary emboli.[164] Finally, it would imply population genetic screening, which has many ethical and social drawbacks.[165]

Assessing the family history for thrombophilic defects in identifying women at risk of venous thrombosis during OC use may be worthwhile. In some studies the positive predictive value of a family history of thrombosis in a first-degree relative was rather low: 14% and 12% for women with and without previous thrombosis, respectively,[166] confirmed in a small study with a sensitivity of 16% in first and second degree family history and 11% in first degree only.[167] Underestimation of the importance of the family history in these studies, however, was probably due to the selection of the subjects.[168]

The annual incidence of venous thromboembolism in factor V_{Leiden} carriers is low[169–171] and does not justify universal screening for this mutation.[172] In case of selective screening in high-risk patients, ethnic-specific prevalence rates should also be taken into account in the decision regarding screening for specific defects.[173,174] Obviously, individual counseling is needed when family members of a proband with a genetic defect ask for screening before prescription of an OC.[175,176]

Prescription

In patients with a previous venous thromboembolism, myocardial infarction, stroke, or peripheral arterial occlusive disease, OCs should not be used except for women receiving anticoagulation therapy or having specific individual circumstances. Because all monophasic combined OCs are equally effective for birth control, the safest brand should be chosen. Previous studies have shown that the relative risk of venous thrombosis is particularly elevated by OC use in young users and that third-generation OCs led to higher risks of venous thrombosis than second-generation OCs: sevenfold higher among women aged 15–19 and fourfold among women aged 20–24.[32] Among young women, venous thrombosis is more common than arterial disease. Formulations with low-dose ethinylestradiol ($\leq$ 30 μg) and a second-generation (levonorgestrel) progestagen should therefore be preferred to minimize the risk of venous thrombosis. The effect of age should be taken into account,[177] and conventional risk factors for cardiovascular disease should be identified in individual women before prescription of OCs. At older ages the risk of cardiovascular disease increases exponentially, especially in combination with other risk factors. Therefore, women over 35 to 40 years and women with a genetic defect should be informed about alternative methods of contraception. Before prescription of OCs special attention should be give to conventional risk factors. Women who refrain from smoking, who have normal blood pressure, and who have no diabetes of hyperlipidemia have no or a minimally increased risk of myocardial infarction regardless of their age. OC use should not be discouraged in all women with familial thrombophilia, as the risk of an unplanned pregnancy also brings an increased risk of thrombosis, which may be higher than that during OC use. It is most important to make these women aware of the possible symptoms of a thrombotic manifestation and the need for a diagnostic work-up in case of complaints.

CONCLUSIONS AND FUTURE PERSPECTIVES

Multiple prospective and case-control studies have shown that current available OCs are still associated with venous and arterial thrombosis. Venous thrombosis is a more common disease than arterial thrombosis, especially in the younger age groups, but arterial events are slightly more frequently lethal. The relative risk is about fourfold increased for venous and twofold increased for arterial thrombosis. The risk of venous thrombosis in OC users becomes high in women with genetic risk factors for thrombosis, and the risk of arterial thrombosis becomes high in women with classical cardiovascular risk factors. Venous thromboembolism recurs in about a third of surviving patients within the next decade. In addition, in about one third of the patients venous stasis syndrome or venous ulcers will occur within 20 years and continue to develop even after 20 years. Improved strategies for appropriate prophylaxis in high-risk situations and prevention of venous stasis syndrome should be created from ongoing studies. The small but definite increased risk of both venous and arterial thrombosis indicates that a history of a thrombotic event is a contraindication to using OCs (and hormone replacement therapy) in the future. Although the absolute risk of a thrombotic event during OC use is low, the reduction of known risk factors for cardiovascular disease, in particular smoking and hypertension, should be emphasized. All patients with a previous arterial thrombotic event should be monitored periodically by their physcian for optimal management of conventional risk factors. Most of the genetic defects associated with thrombosis are still unknown, and the mechanisms by which OCs induce thrombosis are poorly understood. It will be a challenge to determine these defects and to reveal the mechanisms in the near future.

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