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Is There an Increased Risk of Stroke Associated with Oral Contraceptives?

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Abstract

In the last few years several studies were published about the relationship between oral contraceptive use, estrogen dose, different types of progestogens, cigarette smoking and the risk of stroke.

There is a persistent association between the use of oral contraceptives containing more than 50μg of ethinylestradiol and the risk of stroke. Also, cigarette smoking seems to be a strong additive risk factor, especially in women >35 years old even with lower doses (≤30μg) of estrogen.

Unlike oral contraceptives containing >50μg of estrogen, currently there is no convincing evidence that the use of oral contraceptives containing <50μg in the absence of smoking is associated with any meaningful increase in the risk of ischaemic or haemorrhagic stroke.

Progestogen-only pills are not associated with an increased risk of stroke. A specific type of progestogen in combined pills was associated with an increased risk of stroke in a few studies. Data regarding this issue is, however, inconsistent and controversial and needs further investigation.

There were few if any studies that have addressed the effects of new types of progestogens (i.e. norgestimate, norgestrel or gestodene) and formulations containing 20μg of ethinylestradiol. At the present time we find no reason to alter the current practice in prescribing oral contraceptives. We do concede, however, that there might be a slight causal relationship between use of oral contraceptives containing <50μg of ethinylestradiol and stroke that did not reach statistical significance. This relationship is rare and should be viewed in context with the many benefits of oral contraceptives. Underlying risk factors for stroke such as factor V Leiden mutation and other thrombophilias might explain the role of oral contraceptive–induced stroke.

A stroke signifies the abrupt impairment of brain function caused by a variety of pathological changes involving 1 or several intracranial blood vessels. Two types of strokes have been described, namely, ischaemic and haemorrhagic.[1] 80% or more of strokes are caused by ischaemia due to decreased blood flow (i.e. ischaemic stroke). Decreased arterial perfusion can occur due to multiple causes including atherosclerosis with superimposed thrombosis, emboli, vasculitis, haematological disorders, drugs including oral contraceptives and general causes of decreased perfusion such as heart failure. Although considerably less common, venous occlusion can also cause ischaemic strokes

by reduction of capillary blood flow. The remaining 20% of strokes are haemorrhagic and are equally divided between parenchymatous haemorrhage into brain tissue due to rupture of a vessel within the brain and subarachnoid haemorrhage due to rupture of a superficial vessel with bleeding into the subarachnoid space. Although the incidence of stroke has been decreasing in the last few decades (it has stabilised at approximately 0.5 to 1 per 1000 population in the US), it is still a major cause of death and neurological morbidity in developed countries.[1]

The primary treatable risk factor for stroke is hypertension (table I).[2] Hypertension is associated with cerebrovascular atherosclerosis, thromboembolic stroke, and in many cases coronary artery disease. Improved management of high blood pressure may be 1 of the reasons for the decline in incidence of stroke in the last 2 decades. Hypertension is also the cause of more than 70% of strokes due to intracranial haemorrhage.[1-5] A history of pregnancy-induced hypertension or hypertension induced by oral contraceptives was linked to the occurrence of stroke in some studies.[6,7] Smoking is also a serious preventable risk factor and might play an important role in causing strokes in persons under 45 years old. Cigarette smoking is strongly associated with stroke in oral contraceptive users.[1,3,5,8] It is also an important factor in coronary heart disease. Other factors include migraine headaches, acute alcohol intoxication and risk factors for atherosclerosis like hyperlipidaemias and diabetes mellitus.[1,3-5,9-11]

In young adults, nontreatable disorders that are associated with hypercoaguable states include sickle cell disease, antithrombin III deficiency, and protein S and protein C deficiencies (table I).[12,13] Factor V Leiden mutations which also cause protein C resistance and prothrombin-gene mutations are strongly associated with stroke due to cerebral venous thrombosis.[14-20] Actually, 10 to 15% of cases of cerebral venous thrombosis are caused by congenital thrombophilias and factor V Leiden mutation is associated with 20% of cases of deep vein thrombosis.[15,16] More recently, mutations in the prothrombin-gene have been shown to be highly associated with individuals affected with cerebral thrombosis.[14] The use of oral contraceptives in such individuals further increases the risk of morbidity and might be important in younger patients affected by strokes.[18] In a recent case-control study, deBruijn et al.[21,22] demonstrated an increased risk of cerebral venous thrombosis with oral contraceptive use in patients with thrombophilic coagulation defects. The presence of antiphospholipid antibodies is another disorder associated with thrombosis and cerebral ischaemia.[23,24] Other nontreatable risk factors include age since the incidence of stroke strongly correlates with advancing age.[1] The incidence of stroke is also greater in men than women and in African-Americans compared to Caucasians.[1,25,26]

Table I. Risk factors for ischaemic stroke

Nontreatable	Treatable
Older age	Arterial hypertension
Race	Diabetes mellitus
Gender	Transient ischaemic attack
Family history	History of prior stroke
Thrombophilic coagulation defects	Cardiac disease
	Lipoprotein abnormalities
	Smoking
	Alcohol consumption
	Oral contraceptive use
	Obesity

1. Oral Contraceptives and Stroke

The incidence of stroke in women in the reproductive age period between 18 and 44 is low (4 to 11 per 100 000 women years).[1,2] But the importance of such strokes is underscored by the increase in cost of the resulting disability and morbidity. Oral contraceptive use is one of the commonly cited risk factors in younger women. Actually, the association between oral contraceptives and venous thrombosis, cardiovascular disease and stroke has been strongly debated over the years.

The low incidence of stroke in the reproductive age group of women together with varying steroid doses and progestational preparations increase the

difficulty in making a definite conclusion about an association between oral contraceptive use and stroke. Current ongoing investigations are directed towards the effect of the lower dose estrogen preparations and the new class of progestational agents. This manuscript reviews past and recent studies regarding the association of oral contraceptive use and stroke.

1.1 Past Studies

A short period after introduction of oral contraceptive pills, investigators like Lorentz in 1962 raised the possibility that strokes might be associated with pill usage.[27] Subsequent epidemiological studies conducted in the 1960s and 1970s showed an increase in the incidence of stroke associated with oral contraceptives containing >50μg of ethinylestradiol. Among other reasons, the increased risk of myocardial infarction, stroke and venous thrombosis lead to the development of lower dose oral contraceptives and of new progestogens over the last 3 decades.[28-31] The consensus of opinion seems to be that today's contraceptives pills are safer than the previous higher dosage pills, although questions regarding the effect of new progestogens on thrombotic events are still debated.

The association between low dose oral contraceptives and the occurrence of strokes has been addressed many times, but the low incidence of stroke in women in the reproductive age group, together with changes in doses and types of steroids used in oral contraceptive pills over the years makes an evaluation of this association difficult. Furthermore, the ability to design the definitive study is nearly impossible as stated previously.

1.2 Recent Epidemiological Studies

The Royal College of General Practitioners' study,[32] which was a nested case-control analysis of data collected during the prospective Royal College of Practitioners oral contraception study, reported an increased risk of stroke for ever and current oral contraceptive users including an increased incidence of fatal events even in former users. There also was an increased risk with higher doses of progestogens and with norethisterone (norethindrone acetate), lynestrenol and etynediol (ethynodiol diacetate) containing pills when compared with levonorgestrel or other progestogens. They could not show, however, an increased risk with the use of ethinylestradiol at doses of less than 50μg [adjusted odds ratio = 0.6; 95% confidence interval (CI) 0.1 to 2.9]. The number of cases reported with the lower dose pills, however, was low. There was a strong association with smoking in current and former users.

In the Oxford Family Planning Association Contraceptive Study,[33] no thrombotic strokes were reported in women using contraceptive pills containing <50μg of estrogen compared with 13 thrombotic strokes in women using formulations containing ≥50μg of estrogen. This prospective study included more than 17 000 participants.[33]

The results of a case-control study from Denmark reported by Lidegaard[34] showed an overall odds ratio of 3 for thromboembolic strokes among current oral contraceptive users compared with nonusers. There was an increased risk even with the use of preparations containing <50μg of estrogen (odds ratio 1.8; 95% CI 1.1 to 2.9). The lowest dose formulations containing 20μg of ethinylestradiol were not studied. Use of progestogen-only oral contraceptives was not associated with an increased risk.

Pettiti et al.,[35,36] in population-based, case-control studies performed between the years of 1991 and 1994, reported no increased risk of stroke with the use of oral contraceptives. The odds ratio for the occurrence of ischaemic stroke associated with oral contraceptive use was 1.18 and that for haemorrhagic stroke was 1.14, neither was statistically significant. Participants in this study only used oral contraceptive preparations containing <50μg of estrogen.[35] The study included 408 confirmed strokes during 3.6 million years of observation. The incidence of stroke in this young study population was low for both ischaemic and haemorrhagic stroke, namely 5.4 and 5.6 per 100 000 woman-years of observation, respectively.

4.1 Pharmacokinetics

The pharmacokinetic properties of tacrine have been studied following the administration of a single dose and after long term treatment.[40-48] Interindividual variations in tacrine pharmacokinetic parameters have been reported.[30] The bioavailability of tacrine has been found to range from 17 to 37%[41,43,45,48] (table II). Time to reach maximal plasma concentration (t_{max}) in the blood was 1 to 2 hours following oral administration of tacrine 10 to 50mg to patients with Alzheimer's disease.[40,43-46] The absorption is decreased by concomitant intake of food. The elimination half-life for tacrine is 1.3 to 7 hours in patients with Alzheimer's disease.[40,41,43,45]

A positive correlation has been observed between tacrine concentration and cholinesterase inhibition in plasma.[40] The therapeutic window for tacrine has been suggested to range between 7.5 and 20 μg/L.[49] Tacrine has been shown to be 75% bound to plasma albumin. It is metabolised in the liver by the cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP11D6 and 5 metabolites have been found in serum and urine.[30,50] The major metabolite is 1-hydroxy-tacrine, which is present in plasma and CSF at a concentration that is 10 times higher than that of tacrine.[9] This metabolite can inhibit cholinesterase and exerts clinical effects on its own.[51]

Higher plasma concentrations of tacrine have been reported in women[49] compared with men. This difference might be due to the lower activity of the CYP1A2 isoenzyme in women. A lower tacrine concentration has been reported in smokers compared with nonsmokers and this might be explained by the fact that smoking induces CYP1A2 activity.[50]

4.2 Administration Regimens

Tacrine is usually administrated 4 times daily starting at an initial dosage of 40 mg/day and increased every 6 weeks up to a maximal dosage of 160 mg/day. New labelling for the agent indicates that the dosage of tacrine can be increased after 4 weeks at each dosage level. Since some patients may not be able to tolerate the highest dosage of tacrine, titration to their maximum tolerated dosage is recommended.[50,52]

4.3 Interactions

Theophylline is metabolised via CYP1A2 and concomitant administration of tacrine and theophylline results in a 2-fold increase in theophylline concentration.[30,50] Cimetidine inhibits the metabolism of tacrine in the elderly and increases the plasma concentration of tacrine.[30,50]

Table I. A comparison of cholinesterase inhibition and percent of cholinergic adverse events between different cholinesterase inhibitors (see sections 3 to 11 for details and references)

Cholinesterase inhibitors	Cholinesterase inhibition (AChE vs BuChE)	Maximal inhibition of RBC AChE (%)	RBC AChE inhibition (%) achieved with therapeutic dosages	Administration (times/day)	Cholinergic adverse events (% of treated patients)
Tacrine	BuChE = AChE	60	30	4	10-30
Donepezil	AChE >> BuChE	90	64	1	10
Galanthamine	AChE > BuChE	30-60		3	4-20
Metrifonate	AChE = BuChE	62-72	50-70	1	7-18
Physostigmine	AChE > BuChE	70		2	7-40
Eptastigmine	BuChE = AChE	18-44	38	2 or 3	34
Rivastigmine	AChE > BuChE	40[a]		2	<20

a 62% CSF AChE inhibition.

AChE = acetylcholinesterase; **BuChE** = butyrylcholinesterase; **RBC** = red blood cell; **=** = equal inhibition; **>** = stronger inhibition; **>>** = much stronger inhibition.

showed a significant association between oral contraceptive use and thromboembolic stroke (relative risk 4.6; 95% CI 2.9 to 10.7; $p < 0.01$) as compared with nonusers. There were also 6 cases of cerebral venous thrombosis that were all reported in oral contraceptive users. There was a strong association between venous thrombi and coagulation defects in this study group.

In a recent thrombotic stroke population based case-control study from Washington State by Schwartz et al.,[40] in women between the age of 18 and 44 years, the incidence of ischaemic and haemorrhagic stroke was 4.3 and 6.4 per 100 000 women-years. The study included 69 women with ischaemic stroke and 102 with haemorrhagic strokes. After adjustment for risk factors for stroke, women who used oral contraceptives had an estimated odds ratio of 0.89 (insignificant) for ischaemic stroke and 0.93 (insignificant) for haemorrhagic stroke. The study results, however, showed an elevation of risk for haemorrhagic stroke, (odds ratio 3.23; 95% CI 1.24 to 8.41) with the use of low dose oral contraceptives containing norgestrel or levonorgestrel.

Haapaniemi et al.,[3] in a case-control study assessing the life-style associated risk factors for acute brain infarction, identified current use of oral contraceptives as an independent risk factor for stroke ($p = 0.01$). However, the dose of estrogen was not indicated. This study included 140 women between 16 and 60 with an acute, first ever, symptomatic brain infarction and 126 control individuals. Heinemann et al.,[41,42] in a matched case-control study demonstrated a small increased risk of occlusive stroke in healthy women using oral contraceptives. There was no statistical difference between the risk with oral contraceptives of the second or third generation or between third generation oral contraceptives and levonorgestrel-containing pills. The first generation oral contraceptives seemed to be associated with a higher risk compared with second and third generation pills.

The WHO Technical Report on Cardiovascular Disease and Steroid Hormone Contraception in 1998[43] reviewed the current data on cardiovascular disease and use of oral contraceptives and this included the effect of oral contraceptive use on stroke. In this report it was concluded that although the relative risk of both ischaemic and haemorrhagic stroke associated with the use of oral contraceptive decreased in recent years, there was still about a 1.5-fold increase in relative risk of ischaemic stroke in oral contraceptive users who are normotensive and do not smoke. Furthermore, smoking, hypertension and older age increased the relative risk of both types of stroke and this effect was compounded by the use of oral contraceptive. There was insufficient data to allow any conclusions about the effect of progestogen-only containing oral contraceptive on either type of stroke.

2. Conclusion

Most of the epidemiological studies could not document an association between oral contraceptive use and stroke in the absence of smoking and hypertension in women <35 years old. However, even in the absence of other risk factors there is probably a small proportion of cases of stroke attributable to oral contraceptive use in women in the reproductive age period of between 18 and 44 years old. The incidence of altered laboratory coagulation factors associated with oral contraceptive use and their contribution to thrombotic strokes with oral contraceptives is still unknown and might help us understand how genetic factors and oral contraceptive use may lead to stroke. Congenital thrombophilias such as mutations in factor V Leiden and prothrombin-gene are probably, however, risk factors that cause unexpected morbidity in oral contraceptive users and the effect might still be present even with low dose oral contraceptives. This information should be, however, interpreted keeping the benefits of oral contraceptives in mind and at this time no change in prescribing habits of oral contraceptives is recommended. Risks of stroke with oral contraceptives containing 20μg of estrogen or the effect of different progestogens is still unclear and needs further study. Developing screening strategies for thrombophilic coagulation defects and for newly identified risk

factors might also make contraceptive pill use safer even in young women.

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