SMOKING AND CONTRACEPTION

Timothy Rowe, MB BS, FRCSC,

Associate Professor,
Department of Obstetrics and Gynaecology,
University of British Columbia

ABSTRACT

Efforts by governments and public health bodies largely have been unable to reduce cigarette consumption by Canadians. Women who smoke (29% of women in the reproductive years) have reduced fertility and an increased risk of short-term and long-term cardiovascular disease. Women who have used oral contraceptive preparations in the past appear to have no increased cardiovascular risk, but current users carry an increased risk of thrombosis. The degree of risk is proportional to the estrogen dose of the preparation used. Women who smoke cigarettes and concurrently use oral contraceptives increase their risk of myocardial infarction beyond that of using either agent alone; the risk is increased in heavier smokers and in women over age 35. There is no effect of smoking on other forms of contraception.

RESUME

La plupart des efforts déployés par les gouvernements et les organismes de santé publique pour réduire la consommation de cigarettes des Canadiens se sont révélés vains. Les fumeuses (29 % des femmes en âge de procréer) présentent une fertilité réduite et un risque accru de maladie cardiovasculaire à court et à long terme. Dans le passé, les femmes ayant utilisé des préparations contraceptives orales ne semblaient courir aucun risque accru de maladie cardiovasculaire, mais les utilisatrices actuelles présentent un risque accru de thrombose. L'importance du risque est proportionnelle à la teneur en oestrogènes de la préparation utilisée. Les femmes qui fument la cigarette et utilisent simultanément des contraceptifs oraux courent un risque d'infarctus du myocarde plus élevé que si elles n'utilisaient que l'un ou l'autre de ces agents; le risque augmente chez les femmes qui fument beaucoup et chez celles qui ont plus de 35 ans. Le tabagisme est sans effet sur les autres types de contraception.

J SOC OBSTET GYNAECOL CAN 1997;19:1399-1403

KEY WORDS

Women, contraception, smoking, cardiovascular disease.

Received on April 20th, 1996. Revised and accepted on June 11th, 1996.

INTRODUCTION

The adverse effects and consequences of cigarette smoking are well recognized. For many years it has been known that male smokers had an increased risk of coronary heart disease and peripheral vascular disease. There is now clear evidence that women who smoke face the same increased risk.[1] Smoking women increase their risk of developing respiratory diseases and cancer,[2] and face the prospect of an earlier menopause[3] with attendant consequences. Smoking in both men and women is a major public health concern.

Yet the habit continues in Canada, despite substantial efforts by health bodies and medical associations to eliminate it. The federal government's efforts to reduce cigarette consumption in Canada by means of anti-smoking advertisements, compulsory warning labels on cigarette packages, and banning advertising have been largely unproductive. Twenty-nine percent of Canadian women between the ages of 20 and 44 smoke and 20 percent of teenaged girls and boys smoke.[4] The great majority of smokers become addicted in their teens, and efforts to reduce cigarette smoking have been aimed specifically at preventing teenagers from ever beginning

to smoke. How this can be done effectively remains a challenge for public health bodies, because it has been recognized that smoking is a device that young people choose to take on, often quite rationally, as they weather the challenges of adolescence. It is clear that the appeal of smoking to young people—that the act has meanings that help them craft a more powerful and engaging sense of self—is difficult to oppose or reduce.[5]

The manufacturers also have used shrewd methods to promote the use of cigarettes by women, emphasizing the potential for cigarette smoking to limit weight gain, and associating cigarette smoking (in women) with independence and emancipation. The purported association between cigarette smoking and weight control does in fact have supportive objective evidence. The body weight of smokers is on average 2.7 to 4.5 kg lower than that of non-smokers.[6] Such promotional methods account, at least in part, for the fact that the decline in the prevalence of smoking over the past three decades has been significantly greater in men than in women.

Most women in the reproductive age group, whatever their age and smoking status, will need to make contraceptive choices at some stage. For many women, the use of oral contraception (OC) is the best and preferred choice. The recent Canadian Contraceptive Study indicated that 84 percent of Canadian women aged 15 to 44 have used OC at some time.[7] The effectiveness of OC in preventing pregnancy is accepted universally, and the non-contraceptive benefits are recognized increasingly by consumers. Women who are smokers may be reluctant to trade off the contraceptive effectiveness and additional benefits of OC by using another method of contraception, because of the reported risks to their health of combining OC use and smoking. There are no known interactions or synergies between smoking and forms of contraception other than OC.

The observed risks to health arising from the combination of OC use and smoking relate to cardiovascular disease exclusively. These risks, and the pathophysiology involved, are discussed below.

CIGARETTE SMOKING AS A RISK FOR CARDIOVASCULAR DISEASE

There is now sufficient evidence in women to indicate that up to two-thirds of myocardial infarctions in women of reproductive age (under age 50) are attributable to the effects of cigarette smoking.[8,9] The level of cardiovascular risk from smoking has appeared to be smaller in women than in men, a difference which has been attributed to different inhalation habits.[10]

The level of risk to women increases with the number of cigarettes smoked. In the Nurses' Health Study,[1] women who smoked 45 or more cigarettes daily had a risk of fatal coronary heart disease and non-fatal myocardial infarction 11 times higher than that in women who had never smoked. Moreover, there appeared to be no safe level of cigarette consumption; women who smoked between one and four cigarettes daily still had a risk of the above conditions which was 2.5 times higher than in controls.

The association between cigarette smoking and cardiovascular disease appears to be mediated mostly by the effects of nicotine. Of the toxins present in tobacco smoke, carbon monoxide (constituting approximately 2.7 to 6.0% of smoke[11]) may also have pathological effects on cardiovascular fitness. But it is chiefly nicotine's effects which are invoked as the cause of cardiovascular disease.

Nicotine is a tertiary amine which binds stereotypically to acetylcholine receptors in autonomic ganglia, neuromuscular junctions, the adrenal medulla, and the brain. Nicotine administration by cigarette smoking (or by infusion) activates the sympathetic nervous system by stimulation of the adrenal medulla,[12] increasing cardiac output and blood pressure. There is cutaneous vasoconstriction which may be partly produced by release of vasopressin. Coronary blood flow and muscle perfusion are increased. Circulating levels of free fatty acids, glycerol, and lactate are increased.[13]

Paradoxically, nicotine does not increase coronary blood flow in coronary arteries affected by atherosclerosis; in fact, it may decrease it.[14] Spasm of the coronary arteries during smoking has been demonstrated by angiography.[15] These effects arise possibly from inhibited release of the endothelial-derived vasodilators, but also may be a result of supraphysiologic sympathomimetic activity. In addition, there are haemostatic effects of smoking. The blood of smokers coagulates more readily than does that of non-smokers,[16] and there is evidence that there may be increased platelet aggregation after exposure to nicotine.[17] It is feasible, therefore, to consider that cigarette smoke, by promoting platelet aggregation within a coronary artery already predisposed to thrombus formation by endothelial damage from atherosclerosis,

may result in thrombotic occlusion of coronary vessels.[18] The carbon monoxide in cigarette smoke is another factor contributing to vascular endothelial injury, further compounding the risk of thrombosis. With respect to the risk of myocardial infarction, this increased risk of thrombosis appears to be more significant than the direct vascular effects of smoking, because the association between smoking and angina pectoris is much weaker than the association between smoking and myocardial infarction.[19]

Additionally, it has been observed that the risk of myocardial infarction declines to baseline after cessation of smoking.[10,20]

ORAL CONTRACEPTION AS A RISK FACTOR FOR CARDIOVASCULAR DISEASE

The use of combined oral contraceptives increases the risk of venous thrombo-embolism. This risk is proportional to the dose of estrogen used, but is independent of the age of the woman.[21] The degree of risk associated with currently-used low-dose estrogen preparations is clearly less than the risk associated with preparations containing 50μg of ethinyl estradiol or greater. Recent data have suggested that the risk of non-fatal venous thrombo-embolism in women not on combined OC is in the range of five to 11 cases per 10,000 women per year. This figure is two to three times higher in women on low-dose combined OC.[22] It remains uncertain whether or not there is a higher risk of venous thrombo-embolism in women using preparations containing different progestins.[23] The increased risk of thrombo-embolism is associated only with current OC use, and does not persist after OC use is discontinued. The duration of the use of OC has no bearing on the incidence of venous disease. The mechanism for increasing the risk of thrombo-embolic disease is presumed to be the pro-coagulant effect of combined OC preparations.[24]

With respect to arterial disease, the Nurses' Health Study provides the largest cohort of subjects on which to base conclusions. In the 1990 analysis (119,061 participants followed for 8 years), there was no evidence of any age-related increase in the risk of major cardiovascular disease (defined as fatal and non-fatal stroke, death from coronary heart disease, and non-fatal myocardial infarction).[25] Further, this study showed no evidence of a trend to increased risk with increasing duration of OC use. For major coronary artery disease, the relative risk in past OC users was 0.8 in this study. A meta-analysis of 13 studies included in the same report gave a relative risk of 1.01. Women who were current users of OC had an age-adjusted relative risk of major coronary disease (non-fatal myocardial infarction and fatal coronary disease) of 2.5, although seven of the 10 cases in this category were current cigarette smokers. It is arguable that all of the observed risks to current users were a result of smoking. The reports on risks of stroke are too sparse and too conflicting to provide any meaningful estimate of risk.

These data, suggesting increased risk of cardiovascular disease only in current OC users, support the contention that it is thrombosis rather than atherosclerosis that underlies the increased risk of cardiovascular disease associated with oral contraception. Evidence from autopsy studies of women who have died from myocardial infarction serves to reinforce this contention.[26]

It has been recognized for three decades that combined oral contraceptive preparations can influence the levels of clotting factors.[27] The influence that different OC preparations have on coagulation appears to be proportional to the estrogen dose and independent of the progestin dose; this at least is the case with levels of fibrinogen and factor VIIc, levels of which are higher in women taking 50μg estrogen OC preparations than in women taking 30μg preparations.[28] As the levels of these factors are strongly predictive of ischaemic episodes in men, it seems reasonable to assume that this also may be the case in women. The effect of progestins in influencing cardiovascular events appears to be mediated through effects on blood pressure and lipid metabolism.[29]

Oral contraceptive preparations with high progestin activity may cause minor reductions in plasma high-density lipoprotein (HDL) cholesterol levels, theoretically increasing the risk of atherogenesis. These progestin-related effects of OC preparations on lipoprotein levels show some correlation with the androgenic or anti-estrogenic qualities of the individual progestin in the preparation. Thus, there has been an incentive to introduce progestins (desogestrel, norgestimate) which have reduced androgenic and anti-estrogenic properties.[30] However, Clarkson and colleagues showed that monkeys given high progestin-dose OC preparations that altered their lipid levels adversely nevertheless were protected against the development of coronary atheroma deposition.[31] These primate data suggest that OC preparations containing estrogen may have a direct anti-atherogenic

effect, even in the face of theoretically detrimental changes in plasma lipoprotein levels.

As with venous thrombo-embolism, it has not been demonstrated clinically that the use of different progestins in OC alters the risk of arterial disease.

ORAL CONTRACEPTIVE USE IN CIGARETTE SMOKERS

Cigarette smoking increases the risk of cardiovascular disease by direct vascular effects and probably by effects on haemostatic mechanisms. Combined oral contraceptives increase the risk of cardiovascular disease in current users by effects on haemostatic mechanisms, and possibly by metabolic effects in long-term users. Women who smoke and use oral contraception clearly will increase their risk of cardiovascular disease by a combination of effects, but it seems likely that the dominant combination is the effect of both OC preparations and smoking on the tendency for thrombosis.[32]

In a study of prostacyclin formation, women using OC who had smoked for more than five years had evidence of lower basal prostacyclin formation than did non-smokers or those women who had smoked for less than five years.[33] After inhalation of smoke, the OC users who smoked had a further reduction in prostacyclin formation, but the smokers who did not use OC showed no change in prostacyclin formation. This study suggested that the combination of smoking and OC use increased cardiovascular risk because of reduced potential for vasodilatation.

Smokers who took OC preparations containing 20 to 35μg of ethinyl estradiol showed increases in circulating levels of fibrinogen and fibrinopeptide A, but unlike non-smokers, they did not show an accompanying increase in antithrombin III activity.[34] These results suggest that oral contraceptive use in non-smokers is associated with a pro-coagulant trend, with a compensatory anti-coagulant effect. In smokers, however, the compensatory effect is absent, increasing the risk of thrombovascular disease.

The Royal College of General Practitioners' Study showed that the increase in the risk of cardiovascular disease in OC users who smoke is related to the number of cigarettes smoked daily and also to increased age.[35] The relative risk of myocardial infarction in current OC users who smoked less than 15 cigarettes daily was 3.5. In those who smoked more than this, the relative risk was 20.8. For women who had never used OC preparations, the respective relative risks were 2.0 and 3.3. Women over the age of 35 who smoked more than 15 cigarettes daily and used OC had a significantly higher risk of myocardial infarction than did smokers who did not use OC. The relative risk of smoking in past OC users was similar to the risk of never-users. Current OC users had no significant increase in the relative risk of myocardial infarction compared with non-users.

These results emphasize that the combination of OC use with heavy smoking (at least 15 cigarettes daily) produces a major increase in the risk of myocardial infarction. The risk of other cardiovascular disease which might be attributed to the combination is far from clear. Viewed separately, it appears that the cardiovascular risk of OC use is minimal in otherwise healthy women but the risk of smoking is substantial. Women over the age of 35 who do not wish to stop smoking may seek sterilization in order to maintain effective contraception, but they may not be prepared for such a permanent step. Non-smokers have the wider choice.

REFERENCES

1. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, Monson RR, Stason W, Hennekens CH. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1987;317:1303-9.
2. Fielding JE. Smoking: health effects and control. N Engl J Med 1985;313:491-8.
3. Baron JA. Smoking and estrogen-related disease. Am J Epidemiol 1984;119:9-22.
4. Proceed With Care: Final Report of the Royal Commission on New Reproductive Technologies. Ministry of Government Services Canada 1993, pp.235-48.
5. Ontario Tobacco Strategy. Summary of Two Research Projects for Development of a Communications Strategy Targeting Teens and Pre-Teens. Ministry of Health, Ontario. 1993, p.3.
6. Wack JT, Rodin J. Smoking and its effects on body weight and the systems of caloric regulation. Am J Clin Nutr 1982;35:366-80.
7. Boroditsky R, Fisher W, Sand M. The Canadian Contraceptive Study. J SOGC Special Supplement, July 1995, p.10.
8. Slone D, Shapiro S, Rosenberg L, Kaufman DW, Hartz SC, Rossi AC, Stolley PD, Miettinen OS. Relation of cigarette smoking to myocardial infarction in young women. N Engl J Med 1978;298:1273-6.

9. Rosenberg L, Shapiro S, Kaufman DW, Slone D, Miettinen OS, Stolley PD. Cigarette smoking in relation to the risk of myocardial infarction in young women: modifying influence of age and predisposing factors. Int J Epidemiol 1980;9:57-63.
10. Doll R, Gray R, Hafner B, Peto R. Mortality in relation to smoking: 22 years' observations on female British doctors. Br Med J 1980;1:967-71.
11. Khosla S, Laddu A, Ehrenpreis S, Somberg JC. Cardiovascular effects of nicotine: relation to deleterious effects of cigarette smoking. Am Heart J 1994;127:1669-72.
12. Benowitz NL. Clinical pharmacology of nicotine. Ann Rev Med 1986;37:21-32.
13. Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. N Engl J Med 1988;319:1318-30.
14. Winniford MD. Smoking and cardiovascular function. J Hypertens 1990;9:517-23.
15. Mauoad J, Fernandez F, Barillon A, Gerbaux A, Gay J. Diffuse or segmental narrowing (spasm) of the coronary arteries during smoking demonstrated on angiography. Am J Cardiol 1984;53:354-5.
16. Billimoria JD, Pozner H, Metselaar B, Best FW, James DC. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. Atherosclerosis 1975;21:61-76.
17. Saba SR, Mason RG. Some effects of nicotine on platelets. Thromb Res 1975;7:819-24.
18. Folts JD, Gering SA, Laibly SW, Bertha BG. Effects of cigarette smoke and nicotine on platelets and experimental coronary artery thrombosis. Adv Exp Med Biol 1990;273:339-58.
19. Rosenberg L, Kaufman DW, Helmrich SP, Miller DR, Stolley PD, Shapiro S. Myocardial infarction and cigarette smoking in women younger than 50 years of age. JAMA 1985;253:2965-9.
20. Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. Br Med J 1976;2:1525-36.
21. Gerstman BB, Piper JM, Tomita DK, Ferguson WJ, Stadel BV, Lundin FE. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. Am J Epidemiol 1991;133:32-7.
22. Farmer RDT, Preston TD. The risk of venous thromboembolism associated with low oestrogen oral contraceptives. Br J Obstet Gynaecol 1995;15:195-200.
23. Johannisson E, for the International Committee for Research in Reproduction. Safety of Modern Oral Contraceptives. Lancet 1996;347:258.
24. Stadel BV. Oral contraceptives and cardiovascular disease. N Engl J Med 1981;305:420-4.
25. Stampfer MJ, Willett WC, Colditz GA, Speizer FE, Hennekens CH. Past use of oral contraceptives and cardiovascular disease: a meta-analysis in the context of the Nurses' Health Study. Am J Obstet Gynecol 1990;163:285-91.
26. Engel HJ, Engel E, Lichtlen PR. Coronary atherosclerosis and myocardial infarction in young women—role of oral contraceptives. Eur Heart J 1983;4:1-6.
27. Poller L, Thompson JM. Clotting factors during oral contraception: further report. Br Med J 1966;2:23-5.
28. Meade TW, Haines AP, North WRS, Chakrabarti RR, Howarth DJ, Stirling Y. Haemostatic, lipid and blood pressure profiles of women on oral contraceptives containing 50μg or 30μg oestrogen. Lancet 1977;2:948-51.
29. Kelleher CC. Clinical aspects of the relationship between oral contraceptives and abnormalities of the hemostatic system: relation to the development of cardiovascular disease. Am J Obstet Gynecol 1990;163:392-5.
30. Godsland IF, Crook D, Wynn V. Clinical and metabolic considerations of long-term oral contraceptive use. Am J Obstet Gynecol 1990; 166:1955-63.
31. Adams MR, Clarkson TB, Koritnik DR, Nash HA. Contraceptive steroids and coronary artery atherosclerosis in cynomolgus macaques. Fertil Steril 1987;47:1010-18.
32. Stadel BV. Oral contraceptives and cardiovascular disease. N Engl J Med 1981;305:672-7.
33. Mileikowsky GN, Nadler JL, Huey F, Francis R, Roy S. Evidence that smoking alters prostacyclin formation and platelet aggregation in women who use oral contraceptives. Am J Obstet Gynecol 1988;159:1547-52.
34. Melis GB, Fruzzetti F, Nicoletti I, Ricci C, Lammers P, Atsma WJ, Fioretti P. A comparative study on the effects of a monophasic pill containing desogestrel plus 20 mcg ethinylestradiol, a triphasic combination containing levonorgestrel and a monophasic combination containing gestodene on coagulatory factors. Contraception 1991;43:23-31.
35. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' Oral Contraception Study. Br Med J 1989;298:165-8.