Smoking and use of oral contraceptives: Impact on thrombotic diseases

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OBJECTIVES: The study was intended to evaluate the effects of oral contraceptives and smoking on the risks of arterial and venous thromboembolic diseases among young women.

STUDY DESIGN: The study included a survey of data from published epidemiologic studies and evaluation of registry records of all Danish women discharged from the hospital from 1980 through 1993 after a first thromboembolic event. Questionnaires returned by survivors of such events and by control women during the period from 1994 through 1995 were analyzed.

RESULTS: In the 1980-1993 data the absolute risk of thrombotic diseases was seen to increase rapidly with age—exponentially for acute myocardial infarction or cerebral thromboembolic attack, linearly for venous thromboembolism—with risks of arterial diseases exceeding those of venous diseases. In the 1994-1995 data the relative risk of thrombotic diseases was seen to increase among users of oral contraceptives irrespective of age. Risk of venous thromboembolism (but not of acute myocardial infarction or cerebral thromboembolic attack) declined as duration of current oral contraceptive use lengthened, risk of acute myocardial infarction or cerebral thromboembolic attack was significantly decreased as ethinyl estradiol doses were reduced, and the relative risk (compared with nonusers of oral contraceptives) for arterial thromboembolic disease among users of desogestrel or gestodene (in conjunction with midrange or low doses of ethinyl estradiol) was lower than the relative risk among users of second-generation progestogens (in conjunction with midrange doses of ethinyl estradiol). The combination of smoking with oral contraceptive use may have a synergistic effect on risks of acute myocardial infarction and cerebral thromboembolic attack (but not of venous thromboembolism), particularly among users of high-dose (50 μg) ethinyl estradiol preparations.

CONCLUSION: Among the formulations currently marketed in Denmark, where only the progestins desogestrel and gestodene are available with low-dose (20 μg) ethinyl estradiol (and only desogestrel was available in that form at the time of our studies), we prefer these third-generation oral contraceptives for smokers. We might also consider such oral contraceptives for women >35 years old as long as they had no other risk factors for thrombotic arterial diseases. (Am J Obstet Gynecol 1999;180:S357-63.)

Key words: Acute myocardial infarction, cerebral thromboembolic attack, oral contraceptives, smoking, venous thromboembolism

To assess the concomitant impacts of cigarette smoking and oral contraceptive (OC) use on the risk of thrombotic disease among women in their reproductive years, it is necessary to (1) evaluate the prevalence of thrombotic diseases in this population, (2) determine the influence of OCs on the risks of these diseases, and (3) compare the prevalence of thrombotic diseases among smoking and nonsmoking users of OCs. When analyzing the results of such studies, we must also differentiate between arterial and venous thrombotic diseases, because each entity has its own epidemiology of morbidity and mortality. In addition, pregnant women should be excluded from these studies—not only because they are obviously not current users of OCs but also because pregnancy itself is associated with a significant risk of venous circulatory problems.

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Thrombotic diseases in young women: Danish registry data 1980 through 1993

The major venous disorder affecting women in their reproductive years is venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism. The major arterial diseases in this young population are acute myocardial infarction and cerebral thromboembolic attacks, with the latter including thrombotic strokes and transient ischemic attacks.

To assess the incidence of these conditions we analyzed the 1980 through 1993 records of the Danish National Patient Registry of women 15 to 44 years old discharged from the hospital after being treated for acute myocardial infarction, cerebral thromboembolic attack, or venous thromboembolism. Pregnant women were excluded and adjustments were made for readmissions within the same year. Data were reported as cases per

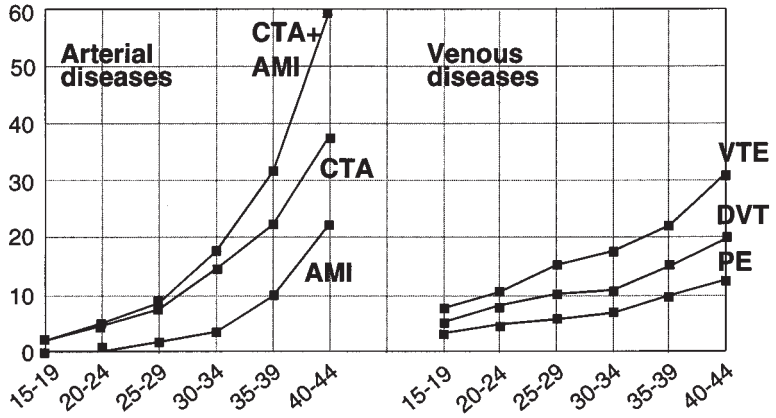

Fig 1. Incidences of arterial and venous diseases per 100,000 nonpregnant, nonpuerperal women per year in Denmark between 1980 and 1993. The cerebral thromboembolic attack and acute myocardial infarction (*AMI + CTA*) graph illustrates the total incidence of arterial diseases. The venous thromboembolism *(VTE)* graph includes the incidence of deep vein thrombosis *(DVT)* and pulmonary embolism *(PE)*. Adapted from Lidegaard Ø. Thrombotic diseases in young women and the influence of oral contraceptives: expert meeting in Montreal, September 13, 1997. Am J Obstet Gynecol 1998;179:S362-7. Used with permission.

100,000 women per year of specific 5-year age groups. Results were as follows.[1]

The occurrence of these thrombotic diseases—irrespective of OC use or smoking habits—was strongly age related (Fig 1). Incidence rose rapidly with advancing age, particularly after 29 years. Overall, arterial diseases were more common and caused more short- and long-term mortality and morbidity than venous diseases. During the 1980-1993 study period, the rates of acute myocardial infarction and cerebral thromboembolic attack increased almost exponentially with increasing age, whereas the rise in venous thromboembolism was more linear. Likewise, the overall incidence of arterial diseases was significantly higher than that of venous thromboembolism.

The annual mortality rate for arterial diseases was 18 deaths/million women (15 deaths from acute myocardial infarction and 3 from cerebral thromboembolic attack), compared with only 2.3/million women for venous disease, an 8-fold difference. The case fatality rates for acute myocardial infarction and cerebral thromboembolic attack were 25% and 2.3%, respectively, versus 1.3% for venous thromboembolism. In addition, life expectancy was significantly shortened among women surviving acute myocardial infarction, decreased somewhat among those surviving cerebral thromboembolic attack, but essentially unchanged among women initially surviving venous thromboembolism.

Significant morbidities caused by acute myocardial infarction in surviving young women included significant chest pains at rest or during exercise, impaired physical activity, and functional dyspnea. Cerebral thromboembolic attack caused significant paresis of the extremities, visual disturbances, disturbed coordination, and impaired concentration. Venous thromboembolism resulted in pain in the legs at rest or during exercise, impaired physical activity, and functional dyspnea. Generally, the rate of morbidities resulting from either arterial or venous disease was very low among women 15 to 29 years old, among whom venous complications exceeded arterial complications. Women 30 to 44 years old had more morbidities, with arterial complications exceeding venous complications.

Despite the increase of thrombotic diseases with age, it is noteworthy in this context that the use of OCs has been shown to decrease with age. During the years 1983, 1990, and 1995, between 30% and 50% of Danish women 15 to 19 years old used OCs, compared with only 10% of those 40 to 44 years old.[2] A similar pattern has been reported among American women.[3] Any consideration of the health impact of OCs and smoking therefore should clearly be age specific. Recommendations for young women do not necessary apply to women >35 years old.

Thrombotic diseases in users of oral contraceptives: Three ongoing Danish case-control studies

Case-control studies were conducted in all Danish hospitals from 1994 through 1998. Their objective was first to assess the effect of OCs on the risk of acute myocardial infarction, cerebral thromboembolic attack, and venous thromboembolism among users versus nonusers of OCs and then to evaluate these risks in smoking versus nonsmoking users and nonusers. Preliminary results for the first 2 years (1994-1995) of these ongoing case-control studies are discussed here.[4,5]

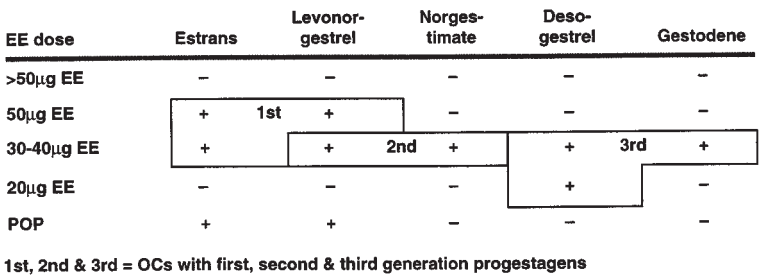

Fig 2. Categories of OCs according to estrogen dose and progestogen type used in our studies. A *plus sign* indicates that the formulation was available in Denmark and a *minus sign* indicates that it was not. *EE,* Ethinyl estradiol; *Estrans,* first-generation progestogens (eg, norethindrone [norethisterone in Europe]); *POP,* progestogen-only OC. Reprinted from *Contraception,* Lidegaard Ø, Edström B, Kreiner S. Oral contraceptives and venous thromboembolism: a case-control study. Contraception 57:291-301. Copyright 1998, with permission from Elsevier Science.

Material and methods

Study sample and procedure. Questionnaires were sent to all women 15 to 44 years old who had been hospitalized for a first-time acute myocardial infarction, cerebral thromboembolic attack (including thrombotic stroke or transient ischemic attack), or venous thromboembolism (including deep vein thrombosis or pulmonary embolism) during the study years. Questionnaires were also sent to 1200 randomly selected, community-based, age-matched female control subjects. The age bands analyzed were identical to those of our 1980-1993 registry study. Those with previous thrombotic disease or current pregnancy were excluded. Multivariate analyses for potential confounders included body mass index; length of OC use (<1 year, 1-5 years, or >5 years); family history of acute myocardial infarction, stroke, or venous thromboembolism; coagulopathies; diabetes; certainty of diagnosis; previous delivery; treated hypertension during any pregnancy; years of schooling; and smoking habits.

Classification of oral contraceptives. We categorized OCs according to their estrogen dose and progestogen generation (Fig 2). This enabled comparison with studies conducted in other countries, although it on occasion underscored the difficulty of making a valid comparison. For example, the preparations taken by two thirds of Danish users of OCs contain a third-generation progestogen (gestodene or desogestrel), with the remaining third containing a second-generation agent (levonorgestrel or norgestimate; although it is chronologically a third-generation progestogen, we consider norgestimate to be a second-generation progestogen because it metabolizes primarily into levonorgestrel before becoming active). In contrast, the great majority of OCs used in the United States contain a first-generation progestogen (usually norethindrone). In Denmark at the time of our studies, gestodene was combined only with 30 μg ethinyl estradiol and desogestrel with either 30 or 20 μg ethinyl estradiol; 20 μg ethinyl estradiol was not available in combination with either first- or second-generation progestogens during the period being analyzed. In the United States, gestodene is not available, desogestrel is available only with 30 μg ethinyl estradiol, and 20 μg ethinyl estradiol is available in combination with either norethindrone or levonorgestrel. Because OCs containing estrans (eg, norethindrone) are hardly used in Denmark and are certainly not available in combination with 20 μg ethinyl estradiol, our studies included estrans combined with either 50 or 30 to 40 μg ethinyl estradiol. To facilitate comparison with results of the Transnational Research Group on Oral Contraceptives and the Health of Young Women[6] and the World Health Organization (WHO) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception[7]—both of which classified second-generation OCs as containing 30 to 40 μg ethinyl estradiol and other than a third-generation progestogen—we categorized second-generation OCs in a comparable manner.

Results

Thrombotic diseases in users of oral contraceptives

Oral contraceptives and acute myocardial infarction. Among the 113 women who had been hospitalized for a first-time acute myocardial infarction during the study years and 1200 control subjects who received questionnaires, 103 case patients (91%) and 1074 control subjects (90%) responded. Of these, 94 case patients and 1041 control subjects were eligible for analysis.

Multivariate analysis after confounder control showed that the odds ratios (compared with nonusers of OCs) for acute myocardial infarction among current users of OCs with 50, 30 to 40, and 20 μg ethinyl estradiol were 7.3 (2.7-20.0), 1.4 (0.7-2.6), and 2.1 (0.5-10.0), respectively (P trend = .002). Compared with nonusers, the odds ratio for acute myocardial infarction among current users of first-generation progestogens (estrans) and high-dose (50 μg) ethinyl estradiol was 4.8 (2.1-11.0). That among users of second-generation progestogens (levonorgestrel or norgestimate) and low to midrange doses (30-40 μg) of ethinyl estradiol was 1.8 (0.8 to 4.3). That among users of third-generation progestogens (deso-

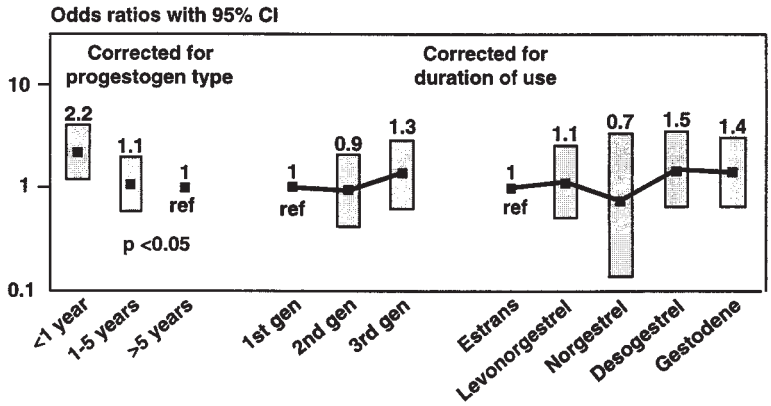

Fig 3. Ongoing study (Denmark, 1994-1995). Risk of venous thromboembolism corrected for progestogen type (left) and for duration of use (shown by generation and by type). The odds ratio of venous thromboembolism was statistically significant only in association with duration of use (left): the longer the use, the lower the risk. *ref,* Reference (baseline) risk; *gen,* generation; *Estrans,* first-generation progestogens (eg, norethindrone [norethisterone in Europe]). Based on data from Lidegaard Ø, Edström B, Kreiner S. Oral contraceptives and venous thromboembolism: a case-control study. Contraception; 57:291-301. Copyright 1998, with permission from Elsevier Science.

gestrel or gestodene) with low-dose (20-30 μg) ethinyl estradiol was 1.1 (0.5-2.5). The ratio between the odds ratios for acute myocardial infarction among users of OCs containing second- and third-generation progestogens was 1.6 (0.5-5.1), but this difference was not statistically significant.

Duration of OC use had no effect on the risk of acute myocardial infarction, and the odds ratio of current users was constant across all age bands studied. Compared with women who never used OCs, the odds ratio for acute myocardial infarction among former users was 0.7 (0.4-1.2).

These preliminary results suggest that compared with nonusers of OCs the risk of acute myocardial infarction is significantly higher among women who used OCs containing high to midrange doses of ethinyl estradiol and first- or second-generation progestogens. They also imply that the third-generation progestogens in conjunction with ≤30 μg ethinyl estradiol do not increase this risk.

Our results confirm the conclusions of most other studies[8-12] that OCs have less of an effect on the risk of acute myocardial infarction than on the risk of cerebral thromboembolic attack and that the effects on either arterial event are directly associated with the ethinyl estradiol dose. Among these studies, only the Transnational investigators[10] found a significantly lower risk for acute myocardial infarction among users of OCs containing a third- rather than second-generation progestogen; in other studies,[11, 12] the difference was not significant.

Oral contraceptives and cerebral thromboembolic attack. Questionnaires were sent to 309 women hospitalized for cerebral thromboembolic attack and to 1200 control subjects; 271 (87.7%) case patients and 1041 (89.5%) control subjects responded. Of these, 219 case patients and all 1041 control subjects were eligible for analysis.[4]

Multivariate analysis, including confounder control, revealed that the odds ratios for cerebral thromboembolic attack among current users of OCs compared with nonusers were as follows: 1.9 (0.9-3.9) among users of first-generation progestogens, 2.4 (1.4-4.2) among users of second-generation progestogens, and 1.3 (0.8-2.2) among users of third-generation progestogens. Odds ratios for the specific progestogen types were as follows: 1.4 (0.6-3.1) among current users of estrans, 2.4 (1.4-4.2) among current users of levonorgestrel, 7.1 (1.9-26.0) among current users of norgestimate, 1.6 (0.7-3.6) among current users of desogestrel, and 1.2 (0.7-2.3) among current users of gestodene. When analyzed by ethinyl estradiol dose, the odds ratios for cerebral thromboembolic attack among current users were as follows: 2.7 (1.1-6.3) for 50 μg, 1.6 (1.1-2.4) for 30 to 40 μg, and 1.6 (0.6-4.6) for 20 μg.

Duration of OC use had no significant effect on the risk of cerebral thromboembolic attack, and the odds ratios among current users were constant across all age bands studied. Compared with women who never used OCs, the odds ratio among former users was 0.95 (0.7-1.5).

These preliminary results suggest that the risk for cerebral thromboembolic attack among current Danish users of OCs decreases as the dose of ethinyl estradiol is reduced and that OCs with third-generation progestogens (in conjunction with 30 or 20 μg ethinyl estradiol) may confer less risk of cerebral thromboembolic attack than those containing second-generation progestogens (in combination with 30-40 μg ethinyl estradiol). In terms of the overall influence of OCs and the decreased risk with decreasing estrogen dose, our results for 1994-1995 are similar to those we reported from Denmark for 1985-1990,[13] as well as those reported from France by Tzourio et al[14] for 1990-1993, from the United States by Petitti et al[15] for 1991-1994, and from several developed and developing countries by the WHO for 1989-1993.[7] Con-

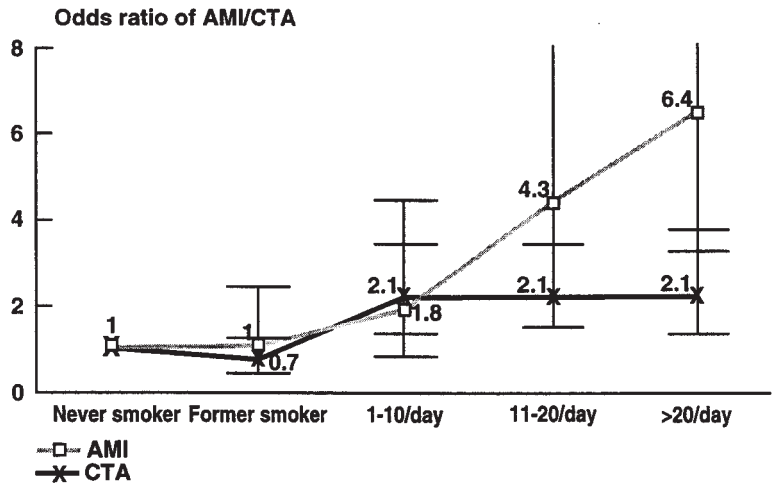

Fig 4. Ongoing study (Denmark, 1994-1995). Risk of arterial thrombotic diseases according to smoking status in 15- to 44-year-old women. *AMI,* Acute myocardial infarction; *CTA,* cerebral thromboembolic attacks, including thrombotic strokes and transient ischemic attacks. Based in part on data from Lidegaard Ø, Kreiner S. Cerebral thrombosis and oral contraceptives: a case-control study. Contraception 57:303-14. Copyright 1998, with permission from Elsevier Science. Data on acute myocardial infarction and smoking have not previously been published.

cerning the influence of different progestogen types, the results differed. No difference was found between second- and third-generation OCs in the WHO[7] and Transnational studies,[6] whereas the Danish study found significant differences. In the WHO study only a few women were taking third-generation OCs; the statistical power thus was low.

Oral contraceptives and venous thromboembolism. Questionnaires were mailed to 586 women who had been hospitalized for venous thromboembolism; 523 (89.2%) responded and 375 questionnaires were eligible for analysis. Of 1200 control subjects mailed questionnaires, 1074 (89.5%) responded and 1041 questionnaires were eligible.

Preliminary results indicate that, unlike the risks of acute myocardial infarction and cerebral thromboembolic attack, the risk of venous thromboembolism among current users of OCs compared with nonusers was influenced primarily by duration of OC use: the shorter the use, the higher the risk. Compared with nonusers, the odds ratios for venous thromboembolism were 5.1 (3.1-8.5) after <1 year of OC use, 2.5 (1.6-4.1) after 1 to 5 years, and 2.1 (1.5-3.1) after >5 years,. The trend toward reduced risk with use time remained significant after adjustment for progestogen types. A plausible explanation is that susceptible women (eg, those with the factor V Leiden mutation) had venous thromboembolism develop during the first year and therefore discontinued OC use. Estrogen dose had no effect on the odds ratio for venous thromboembolism.

The question arises whether the higher risk for venous thromboembolism among women with short-term OC use was due to the fact that the OCs used by most Danish women contained desogestrel or gestodene or whether the higher risks for venous thromboembolism reported among women from other countries who used OCs containing third-generation progestogens were due to the fact that these women also had short-term use. To answer that question, we adjusted our results for (1) progestogen type and (2) duration of use. Without adjustment for duration of use, the odds ratio among current users of OCs with second-generation progestogens was 1.8 (1.1-2.9) and that among users of third-generation progestogens was 3.2 (2.3-4.4). After adjustment for duration of use, however, there was no significant difference in the risks for venous thromboembolism associated with the different types of progestogens. As can be seen in Fig 3, even when corrected for progestogen type, the odds ratio for venous thromboembolism during the first year of OC use was 2.2 higher than after >5 years ($P < .05$). The odds ratio for venous thromboembolism among the users of third-generation OCs was 1.3 higher than that among users of first-generation OCs and 1.4 times higher than that among users of second-generation OCs. These differences, however, were not statistically significant.

Thrombotic diseases in smoking and nonsmoking users of oral contraceptives. In the early 1990s the percentages of users of OCs were similar in Denmark[2] and in the United States,[3] but the rate of smoking was twice as high among Danish women. The preliminary results of our ongoing case-control studies of Danish users of OCs who smoke are described here.

Smoking. Compared with women who never smoked, the odds ratio for acute myocardial infarction increased from 2.1, to 4.3, to 6.4 for women currently smoking 1 to 10, 11 to 20, or >20 cigarettes/d (Fig 4). The odds ratio for cerebral thromboembolic attack (including throm-

Table I. Relative versus absolute risks for cerebral thromboembolic attack: Effects of OCs, smoking, and age

Risk of cerebral thromboembolic attack	*Relative*	*Absolute*	*Etiologic fraction (%)*
Indicates	Risk versus unexposed	Risk versus 100,000 women/y	Preventable fraction
No use of OCs			
Age 20 y*	1	2	0
Age 40 y	10	20	90
Use of OCs containing low-dose (≤30) μg ethinyl estradiol			
Age 20 y	1.8	3.6	29
Age 40 y	1.8	36	4
Smoking but no use of OCs			
Age 20 y	1.5	3	20
Age 40 y	1.5	30	20

Based on data from Lidegaard Ø. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. BMJ 1993;306:956-63.
*Baseline risk case.

botic strokes and transient ischemic attacks) among women who currently smoked any number of cigarettes was 2.1. These risks remained constant across all analyzed age bands.

Our preliminary results are similar to those of previous studies, which reported that young female smokers increased their risk of acute myocardial infarction by about 2 to 5 times if they smoked <10 cigarettes/d and by about 5 to 10 times if they smoked >10 cigarettes/d.[12, 16] Their risk for cerebral thromboembolic attack rose 1.2 to 4.5 times.[7, 8, 13]

Our study also determined that the longer Danish women had gone to school, the lower was the impact of cigarette smoking on their risk for cerebral thromboembolic attack. The odds ratio for cerebral thromboembolic attack among smoking women with 7 to 9 school years was 3.4, versus 1.0 in nonsmoking women; ratios were 1.7 and 0.8 for 10 school years, and 1.2 and 0.6 for 11 to 12 school years.[4]

Epidemiologic studies suggest that the risk for arterial disease in young (but not older) men and women gradually decreases within 5 to 10 years of smoking cessation. It may return to the risk level of nonsmokers. Our preliminary results confirmed that smoking has little effect on the risk of venous thromboembolism (including deep vein thrombosis and pulmonary embolism) in young women.

Smoking and oral contraceptive use and the risk of acute myocardial infarction. In the 1997 WHO comparison[12] with nonusers who were nonsmokers, the odds ratios for acute myocardial infarction among European nonusers currently smoking <10 and ≥10 cigarettes/d were 4.7 and 11.1, respectively. However, among heavily smoking users of OCs, most of whom used OCs with second-generation progestogens, the odds ratio was synergistically and dramatically increased: from 4.0 among users of OCs who were nonsmokers and 5.0 among users of OCs who smoked <10 cigarettes/d to 87.0 among users of OCs who smoked ≥10 cigarettes/d.

In a 1997 Transnational study,[17] the odds ratio for acute myocardial infarction was 9.7 among European nonusers of OCs who were smokers, 2.3 among users of OCs who were nonsmokers, and 22.3 among users of OCs who were smokers. Among users of OCs with third-generation progestogens, smoking increased the risk 3.75 times. Among those who used OCs with a second-generation progestogen, it increased the risk 9.5 times.

In the Danish study, current users of OCs with second-generation progestogens (n = 63) had odds ratios (compared with nonsmoking nonusers) for acute myocardial infarction of 3.3, 7.8, and 11.5 with increasing number of cigarettes smoked. The corresponding figures among users of OCs with third-generation progestogens (n = 125) were 2.0, 4.8, and 7.0.

Our preliminary analysis thus suggests that cigarette smoking and the use of low-dose OCs act as independent risk factors for acute myocardial infarction and cerebral thromboembolic attack. Older, high-dose preparations may act synergistically in combination with smoking. The extent of the risk of acute myocardial infarction depends on the type of OC used and the daily number of cigarettes smoked, whereas the risk for cerebral thromboembolic attack depends primarily on the type of OC used. We calculated that if all Danish women 15 to 44 years old were to stop smoking, 63% of acute myocardial infarction cases and 20% of cerebral thromboembolic attack cases could be prevented.

Smoking and oral contraceptive use and the risk of cerebral thromboembolic attack. Smoking and OCs not only are independent risk factors for cerebral thromboembolic attack but may act synergistically. The Royal College of General Practitioners (1968-1987) in England[8] reported that compared with the risk of cerebral thromboembolic attack in nonusers of OCs who were nonsmokers the relative risks were 1.7 among nonusers smoking <15 cigarettes/d and 4.3 among nonusers smoking >15 cigarettes/d. The relative risk among users of OCs who were nonsmokers was 1.8; this increased to 3.5 among users of OCs who smoked <15 cigarettes/d but escalated to 20.8 among users of OCs who smoked >15 cigarettes/d.

In the international WHO study (1996),[7] the relative risk for cerebral thromboembolic attack among nonusers of OCs who smoked was 1.2; that among users of OCs who were nonsmokers was 2.1, but that among users of OCs who smoked was 7.2. Similarly, our preliminary results show that compared with nonusers of OCs who are nonsmokers the relative risks for cerebral thromboembolic attack were 1.6 among users of OCs who were non-

smokers and 2.1 among nonusers of OCs who smoked; in contrast, the odds ratio rose to 3.4 among users of OCs who smoked, indicating independence between smoking and OC use.

Analysis of our own results and of the Royal College of General Practitioners[8] and WHO[7] studies suggests that the risk of cerebral thromboembolic attack among users of OCs who smoke depends on the type of OC taken and the daily number of cigarettes smoked. Compared with nonsmoking nonusers, the relative risk for cerebral thromboembolic attack in smokers who used OCs containing low-dose-ethinyl estradiol ranged from 2.5 to 7.0, falling within the lower end of the range when the OC contained a third-generation progestogen and within the upper range when it contained a second-generation agent.

In translating these results to clinical practice, we must also be cognizant of the difference between relative and absolute risks. Table I lists the risks for cerebral thromboembolic attack of 20- and 40-year-old women who (1) did not use OCs, (2) used OCs containing low-dose (≤30 μg) ethinyl estradiol, or (3) smoked but did not use OCs. The absolute risks of the older nonusers who were nonsmokers were 10-fold higher than the risks of the younger nonusers who were nonsmokers (20 versus 2). Although the relative risks of the older and younger populations listed in the last 2 comparisons in Table I are identical (1.8 for users of OCs and 1.5 for smokers), the absolute risk increase of the older women would be 10-fold higher were they to use OCs (36 vs 3.6) or smoke (30 vs 3). Because the proportion of women who use OCs declines with increasing age, we calculated that if all 40-year-olds were to discontinue OC use, cerebral thromboembolic attack would be prevented in only 4%, compared with 29% of the 20-year-old women. In contrast, if all 20- and 40-year-old women were to stop smoking, the incidence of cerebral thromboembolic attack in either population would be reduced by 20%.

Comment

The combination of OCs and smoking may increase the risk for thrombotic arterial diseases several times (smoking per se does not affect venous diseases). Because the absolute risks for acute myocardial infarction and cerebral thromboembolic attack are very low among young women, however, we believe that the increased risk caused by this combination is acceptable in this population.

Among the formulations currently available in Denmark, we usually choose OCs containing low-dose ethinyl estradiol and desogestrel or gestodene for young women who wish to use OCs but refuse to or cannot stop smoking. We might also consider such an OC for a woman >35 years old who smoked, provided she had no other risk factors for thrombotic arterial disease (eg, hypertension, diabetes mellitus, family history of acute myocardial infarction).

We usually test for coagulation abnormalities, including the factor V Leiden mutation, in young women specifically predisposed toward venous thrombotic diseases (eg, those with a family history of venous thromboembolism). If OCs are prescribed for women at increased risk for venous complications (whether they smoke or not), a low-dose OC with a second-generation progestogen would be a natural first choice in Denmark.

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