ter understanding of the natural history of specific acute illnessess and of the effectiveness of specific intensive interventions. Our findings emphasize the importance of clinical uncertainty in determining resource expenditures for the critically ill; when the outcome is least expected, the expenditures are greatest. This uncertainty warrants greater consideration in future studies of expenditures for the care of the catastrophically ill.

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MEDICAL PROGRESS

ORAL CONTRACEPTIVES AND CARDIOVASCULAR DISEASE

(Second of Two Parts)

BRUCE V. STADEL, M.D.

Myocardial Infarction and Stroke

It is now established that in addition to increasing the risk of venous thromboembolic disease, oral contraceptives increase the risks of myocardial infarction, thrombotic stroke, and hemorrhagic stroke.[11] (Some recent data suggest that oral contraceptives may also increase the risk of other forms of cardiovascular disease,[17] but the findings are inconclusive and are therefore not considered in this review.) Vital statistics and epidemiologic studies in Great Britain and the United States show that among nonpregnant women of reproductive age who are not using oral contraceptives, the risks of myocardial infarction and stroke (of both categories) increase substantially with age and are increased by the presence of such risk factors as cigarette smoking or hypertension.[2,67-75] In general, oral contraceptives have been found to multiply the effects of age and other risk factors for myocardial infarction and stroke rather than add to them.[67,69-76] Therefore, the risk of myocardial infarction and stroke that is attributable to oral contraceptives is primarily concentrated among older women and women with other risk factors.

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Current Use, Past Use, and Duration of Use

Numerous epidemiologic studies have found that the risk of myocardial infarction is increased among current users, diminishes after use has been discontinued for one month or more, and — among current users — appears to be unrelated to the duration of use.[67,69-73] However, only one study of oral contraceptives and myocardial infarction has been large enough to examine in detail the effects of past use and the duration of use on the risk of myocardial infarction. In this case-control study of 556 women hospitalized with first episodes of myocardial infarction in the northeastern United States between 1976 and 1979 (and 2036 controls), three main findings have emerged: First of all, the risk of myocardial infarction among current users 25 to 49 years of age is about three to four times greater than that among comparable women who have never used oral contraceptives, and it does not appear to be related to the duration of use. Secondly, the risk of myocardial infarction among short-term past users (those who used the agents for less than five years) is not increased. These two findings are in agreement with those of previous smaller studies. Thirdly, however, the risk of myocardial infarction among long-term (five years or more) past users 40 to 49 years old appears to be about two times greater than that among comparable women who have never used oral contraceptives; furthermore, this

increased risk appears to persist for up to 10 years after the drugs have been discontinued.[77]

The risk of thrombotic stroke has consistently been found to be increased among current users of oral contraceptives but has not been observed to be increased among past users.[7,9,10,76,78] In contrast, two studies have found the risk of subarachnoid hemorrhage (the most common type of hemorrhagic stroke among women of reproductive age) to be increased among both current and past users,[17,75] and one of these studies has suggested that the risk of subarachnoid hemorrhage among users may increase with duration of use.[75] However, these findings are based on a total of only 31 cases of subarachnoid hemorrhage, and all but three of these occurred in women 35 or older.[17,75] In a larger study involving 134 cases of subarachnoid hemorrhage among women 15 to 44 years of age, 50 per cent of whom were less than 35 years old, only borderline evidence of an increased risk among current or past users was found.[79] Thus, although both current and past use probably increase the risk of subarachnoid hemorrhage, this increased risk appears to be largely confined to women about 35 or older.

Magnitude of Risk Attributable to Oral Contraceptives

Estimates of the incidence of myocardial infarction and stroke (thrombotic and hemorrhagic combined) among current users of oral contraceptives and nonusers, and estimates of the relative and attributable risks, are presented in Table 2. The estimates for myocardial infarction are derived from British case-control studies of nonfatal[67] and fatal[69,70] myocardial infarction, whereas those for stroke are from the two British cohort studies that were begun in 1968.[13,17,18,21] Investigations carried out in the United States have yielded generally similar results,[71-76,78] but they provide less information concerning attributable risk.

Because of sampling variation and other methodologic problems, the figures are only approximate, but they do serve to illustrate two major findings: In the first place, the relative risk of myocardial infarction among women 30 to 39 years old is similar to that among women 40 to 44 (relative risk, 3 to 4). However, the incidence of myocardial infarction among women not using oral contraceptives increases from about four cases per 100,000 women per year among women 30 to 39 to around 22 cases per 100,000 per year among women 40 to 44.[67,69,70] Therefore, oral contraceptives multiply the effects of age, so that the risk of myocardial infarction that is attributable to oral contraceptives increases from only about seven cases per 100,000 current users per year among women 30 to 39 to around 67 cases per 100,000 current users per year among women 40 to 44. About half these myocardial infarctions were fatal.[67,69,70]

Secondly, among women of reproductive age in general, the risk of thrombotic or hemorrhagic stroke that is attributable to oral contraceptives is around 37 cases per 100,000 current users per year.[13,18] About 5 to 10 per cent of these strokes were fatal, and most of these fatalities were due to subarachnoid hemorrhage.[17,21] Direct estimates of the attributable risk in women of different ages are not available. However, because the incidence of stroke (of both categories) among women in Great Britain and the United States increases markedly between the ages of 25 and 34 and 35 and 44 (ref. 2), and because the relative risk associated with current oral-contraceptive use does not appear to decrease,[76] the risk of thrombotic or hemorrhagic stroke that is attributable to oral contraceptives is undoubtedly much lower than 37 cases per 100,000 current users per year among women less than 35 years of age, and correspondingly higher among women 35 or older — a pattern basically similar to that seen for myocardial infarction.

Estimates of the overall risk (fatal and nonfatal) of myocardial infarction and stroke that is attributable to past use of oral contraceptives are not available. However, the larger of the two British cohort studies has provided a pertinent comparison of death rates for all circulatory disease among current users, past users, and never-users.[17] These data are presented in Table 3. It appears that among women of reproductive age in general, the risk of death from any circulatory disease attributable to oral contraceptives is in the range of 22 to 24 deaths per 100,000 women per

Table 2. Oral-Contraceptive Use and Risk of Myocardial Infarction and Stroke.*

Category of Disease	Incidence		Relative Risk	Attributable Risk	Source of Data
	Current user	Nonuser			
	no. of cases/ 100,000 women/yr			*no. of cases/ 100,000 current users/yr*	
Myocardial infarction †					
At 30–39 yr	11	4	3	7	Refs. 67, 69, 70
At 40–44 yr	89	22	4	67	
Stroke, thrombotic and hemorrhagic combined, all ages combined ‡	47	10	5	37	Refs. 13, 18

*All figures have been rounded to the nearest integer.

†The figures presented are combined from the references cited (fatal plus nonfatal myocardial infarction). About half the infarctions were fatal. The risk was concentrated in smokers and women with predisposing medical disorders.

‡The figures presented are averages from the references cited. About 5 to 10 per cent of the strokes were fatal, primarily because of subarachnoid hemorrhage. The risk was concentrated in women about 35 or older, smokers, and women with predisposing medical conditions.

Table 3. Oral-Contraceptive Use and Mortality from All Circulatory Diseases.*

Fatalities			Relative Risk		Attributable Risk	
Current User	Past User	Never Used	Current vs. Never	Past vs. Never	Current vs. Never	Past vs. Never
no./100,000 women/yr					*no. of deaths/ 100,000 women/yr*	
29	31	7	4	4	22	24

*All figures have been rounded to the nearest integer. Data are taken from the Royal College of General Practitioners[17] and refer to all ages combined. Most of the deaths were from ischemic heart disease or subarachnoid hemorrhage. The risk was concentrated in women about 35 or older and in smokers.

year in both current and past users.[17] However, 37 of the 65 deaths on which this figure is based (and the majority of the excess deaths among current and past users) were due to ischemic heart disease or subarachnoid hemorrhage.[17] Furthermore, the deaths were concentrated among women 35 or older (54 of the 65), and the deaths among oral-contraceptive users were concentrated among women who smoked cigarettes.[17]

Estrogen and Progestogen Content of Oral Contraceptives

Among current users, the risk of myocardial infarction and stroke (most data pertain to thrombotic stroke) appears to be directly related to both the estrogen content and the progestogen content of the oral contraceptives being used, although information on this subject is fragmentary and difficult to interpret.[40,41] If one ignores the progestogen content of oral contraceptives and combines older (1970) and more recent (1980) data, one sees that a decrease in the estrogen content of oral contraceptives from 100 or 150 μg (of either ethinyl estradiol or mestranol) to 30 μg is accompanied by a decrease in the risk of myocardial infarction or stroke among current users; the decrease may be as large as 80 per cent.[40,41] However, some of this decrease could be due to changes in the progestogen content of oral contraceptives. Recently, it was observed that the risk of myocardial infarction or stroke appears to be about 1.5 to two times greater among women using oral contraceptives containing 3 to 4 mg of norethindrone acetate and 50 μg of ethinyl estradiol than among women using otherwise similar oral contraceptives that contain only 1 to 2 mg of norethindrone acetate; a generally similar dose-response relation was also observed for norgestrel (comparable data are not available for other progestogens).[41] The effect of the estrogen and progestogen content of oral contraceptives on the risks of myocardial infarction and subarachnoid hemorrhage among past users has not been investigated.

Relation between Oral Contraceptives and Other Risk Factors

Other than age, the major factors that have been found to increase the risk of myocardial infarction and stroke among women of reproductive age in Great Britain and the United States who are not using oral contraceptives are as follows: for myocardial infarction, cigarette smoking (especially 15 or more cigarettes per day), a history of preeclamptic toxemia or hypertension, Type II hyperlipoproteinemia, and diabetes mellitus[67,68,71-73,80]; for thrombotic stroke, hypertension[74]; and for hemorrhagic stroke, cigarette smoking and hypertension.[74,75] In general, epidemiologic data indicate that oral contraceptives multiply the effects of these other factors on the risks of myocardial infarction and stroke[67,71-75] in the same way that they have been found to multiply the effects of age (Table 2). Therefore, the risk of myocardial infarction and stroke that is attributable to oral contraceptives is concentrated among women with other risk factors, in addition to being concentrated among women about 35 or older. However, cigarette smoking is far more prevalent among women of reproductive age in Britain and the United States than are other risk factors for myocardial infarction and stroke[67,72,74,80]: one recent study has found that about 40 per cent of women 20 to 49 years old admitted to hospitals in the northeastern United States between 1976 and 1978 for reasons other than cardiovascular disease smoked 15 or more cigarettes per day, whereas fewer than 15 per cent had a history of preeclamptic toxemia (5 per cent), hypertension (13 per cent), hyperlipoproteinemia (4 per cent), or diabetes mellitus (2 per cent).[72,80] Because of this factor, the increased risk of myocardial infarction and stroke that is attributable to oral contraceptives among women with other risk factors is predominantly an increased risk among women who smoke cigarettes.

The data in Table 2 aggregate the risk of myocardial infarction and stroke that is attributable to oral contraceptives among women who do and do not smoke cigarettes. In Table 4, the risk of myocardial infarction that is attributable to current use of oral contraceptives among women who smoke cigarettes heavily (≥15 per day) is separated from the risk

Table 4. Oral-Contraceptive Use, Cigarette Smoking, and Risk of Myocardial Infarction.*

Age	No. of Cigarettes Smoked Daily	Incidence		Relative Risk	Attributable Risk
		Current User	Nonuser		
yr		*no. of cases/ 100,000 women/yr*			*no. of cases/ 100,000 current users/yr*
30–39	0–14	6	2	3	4
	≥15	30	11	3	19
40–44	0–14	47	12	4	35
	≥15	246	61	4	185

*These estimates are derived from the data of Mann et al.[67,69,70] with the formula:

$$I_{total} = [I_{0-14}][P_{0-14}] + RR_{\geq 15 \text{ vs. } 0-14}\,[I_{0-14}][1 - P_{0-14}]$$

where I_{total} denotes the incidence in users or nonusers (from Table 3, I_{0-14} the incidence among smokers of 0 to 14 cigarettes per day, P_{0-14} the proportion of controls who smoke 0 to 14 cigarettes per day, and $RR_{\geq 15 \text{ vs. } 0-14}$ the relative risk in smokers of ≥15 cigarettes per day as compared with smokers of 0 to 14. All figures have been rounded to the nearest integer.

among nonsmokers or light smokers (≤15 per day). (The data are from the same source as those in Table 2.) It can be seen that although the relative risk of myocardial infarction for current users (as compared with nonusers) is similar among younger and older women and among women who do and do not smoke cigarettes heavily, the risk of myocardial infarction that is attributable to oral contraceptives increases from only about four cases per 100,000 current users per year among women 30 to 39 years old who do not smoke cigarettes heavily to around 185 cases per 100,000 current users per year among women 40 to 44 who smoke heavily.[67,69,70] Although the available data do not permit estimation of the risk of hemorrhagic stroke that is attributable to oral contraceptives among women of different ages who do and do not smoke heavily, it is probable that the pattern of risk is similar to that seen for myocardial infarction in Table 4. No reliable information is available on the risk of myocardial infarction and subarachnoid hemorrhage that is attributable to past use of oral contraceptives among women with and without other risk factors.

Pathogenesis of Myocardial Infarction and Stroke Attributable to Oral Contraceptives

The epidemiologic data discussed above suggest that the pathogenesis of myocardial infarction that is attributable to oral contraceptives involves two components: the effects of current use that are unrelated to the duration of use and that disappear when oral contraceptives are discontinued, and the effects of past use that are directly related to the duration of use and that persist when oral contraceptives are discontinued.

Post-mortem examinations in women who have died while using oral contraceptives suggest that myocardial infarction attributable to current oral-contraceptive use is more likely to be thrombotic than atheromatous in origin.[69] The effects of current use that seem most likely to increase the risk of coronary thrombosis are of two types. In the first place, platelet hyperactivity is believed to be central to the pathogenesis of coronary (and other arterial) thrombosis,[51] and oral contraceptives appear to accelerate platelet aggregation[49,81] and to increase platelet prothrombin-converting (factor III) activity.[49,82] Secondly, fibrin deposition is necessary for platelet aggregation to become irreversible,[51] and the effects of oral contraceptives on antithrombin III activity[32,52] and on the plasminogen-activator content of endothelium[50,65] (described in Part I) are believed to enhance the formation and accumulation of fibrin. The estrogenic component of oral contraceptives appears to be primarily responsible for accelerating platelet aggregation[49] and for decreasing antithrombin III activity[58,59] and the plasminogen-activator content of endothelium[50,65]; information about the separate effects of estrogens and progestogens on platelet prothrombin-converting activity is not available. It is probable that these effects of oral contraceptives are all acute effects of current use, that they are unrelated to duration of use, and disappear when use is discontinued. However, this pattern has been described only for decreased antithrombin III activity.[32] How these effects of current use may multiply the effects of age, cigarette smoking, and other risk factors for myocardial infarction has not been established. One possibility is that age, cigarette smoking, and other risk factors increase the occurrence of subclinical thrombosis in coronary arteries, and that the effects of current oral-contraceptive use increase the probability that subclinical coronary thrombosis will progress to coronary occlusion.

The pathogenesis of myocardial infarctions attributable to the long-term past use of oral contraceptives has not been investigated. However, the most likely source of increased risk that is directly related to the duration of use is accelerated atherogenesis, and oral contraceptives have been observed to have effects on each of the three major factors that are believed to influence the occurrence of atherosclerotic cardiovascular disease: blood pressure (an increase in which appears to accelerate atherogenesis), glucose tolerance (a decrease appears to accelerate atherogenesis), and serum high-density-lipoprotein cholesterol concentration (a decrease appears to accelerate atherogenesis).[13,15,24,83-89] Although these effects of oral contraceptives appear to be effects of current use that generally disappear when the drugs are discontinued, any cumulative effect (i.e., an effect related to the duration of use) that they have on atherosclerosis seems likely to persist after discontinuation.

Blood Pressure

Oral contraceptives elevate blood pressure in most women.[84,85] On the average, this elevation is small (1 to 2 mm Hg diastolic, 5 mm Hg systolic),[84,85] but it does apparently lead to a threefold to sixfold increase in the risk of overt hypertension.[13,85] The risk of hypertension that is attributable to oral contraceptives has been observed to increase with age (becoming substantial only in women about 35 or older),[85] with increasing duration of oral-contraceptive use,[13] and in direct relation to the amount of norethindrone acetate in oral contraceptives containing this progestogen.[15] It seems plausible that such factors as a family history of hypertension or a history of renal disease may also increase the risk of hypertension that is attributable to oral-contraceptive use, but this has not been established.

Glucose Tolerance

Oral contraceptives have been found to decrease glucose tolerance in most women.[86,87] On average, this effect is small (an increase of 11 mg per deciliter [0.61 mmol per liter] in one-hour serum glucose), that it is unrelated to the duration of oral-contraceptive use, and is only additive to the effects of age, obesity, and family history of diabetes, all of which decrease glucose tolerance.[86] However, the decrease does ap-

parently represent a shift in levels of glucose tolerance among current oral-contraceptive users to those of nonusers who are about seven or eight years older.[86] Decreased glucose tolerance among current users appears to be directly related to the estrogen content of oral contraceptives[87,88]: oral contraceptives very low in estrogen (35 μg of ethinyl estradiol) have been observed to have little if any effect on glucose tolerance.[88] However, estrogen given alone does not appear to decrease glucose tolerance, and the effects of oral contraceptives on glucose tolerance therefore seem to represent a complex interplay between their estrogenic and progestogenic components.[87]

Serum High-Density-Lipoprotein Cholesterol Concentration

The progestogenic component of oral contraceptives has been found to decrease high-density-lipoprotein cholesterol, whereas the estrogenic component has been found to increase it.[24,89] Thus, the net effect of different oral contraceptives on high-density-lipoprotein cholesterol appears to depend entirely on their specific composition. The cohort study that was initiated in the United States in 1968 has examined the effects of 13 different oral contraceptives on high-density-lipoprotein cholesterol.[24] Of these, five were combined oral contraceptives containing 50 μg of either mestranol or ethinyl estradiol (the type that has been extensively used in Great Britain and the United States since the late 1960s[2,14,18]). Two of these five were found to decrease high-density-lipoprotein cholesterol (a mean decrease of about 10 mg per deciliter [0.26 mmol per liter], or 16 per cent), whereas the other three were found to have no effect.[24] Of the two oral contraceptives that decreased high-density-lipoprotein cholesterol, one contained norethindrone acetate (2.5 mg) and the other contained norgestrel (0.5 mg); these progestogens are believed to have strong antiestrogenic effects and thus may overpower the tendency of the estrogenic component of oral contraceptives to increase high-density-lipoprotein cholesterol.[24]

As previously discussed, epidemiologic data[7,9,10,76,78] suggest that the pathogenesis of thrombotic stroke that is attributable to oral contraceptives involves primarily the effects of current use that are unrelated to the duration of use (e.g., accelerated platelet aggregation), and that for subarachnoid hemorrhage the effects of past use (e.g., sustained elevation of blood pressure) may also have a role in determining the level of risk that is attributable to oral contraceptives.[17,75] However, the distinction that has been made here between the effects of current and past use on the risk of myocardial infarction and stroke is somewhat artificial. The effects of current use on blood pressure, glucose tolerance, and high-density-lipoprotein cholesterol probably increases the risk of arterial thrombosis in addition to possibly accelerating atherogenesis; evidence that the risk of myocardial infarction and stroke among current users is directly related to the amount of norethindrone acetate or norgestrel in oral contraceptives containing these progestogens suggests that this is so.[41] Finally, mechanisms other than those considered in this review may be involved in the pathogenesis of thromboembolic disease that is attributable to oral-contraceptive use; one interesting new theory is that in some instances the formation of antibodies to ethinyl estradiol may be involved.[90]

Conclusion

This brief review of current information indicates that although oral contraceptives appear to cause a generally similar relative increase in the risk of cardiovascular disease among women of different ages and among smokers and nonsmokers, most of the risk of serious, potentially fatal cardiovascular disease that is attributable to oral contraceptives is concentrated among women about 35 or older and among smokers.[2,67,69-76] When this is taken into account, and when estimates of mortality associated with oral contraceptives in countries such as Great Britain and the United States are compared with estimates of mortality associated with complications of pregnancy among women using no method of contraception and with estimates of mortality associated with other methods (such as the intrauterine device or diaphragm), the following picture emerges[28] (these figures are based on numerous assumptions and should therefore be regarded as illustrative rather than precise):

(1) Among women who do not smoke cigarettes, the annual risk of death associated with current use of oral contraceptives increases from about one per 100,000 among women 15 to 19 years old to about three per 100,000 among those 30 to 34 and to around 18 per 100,000 among those 40 to 44. In women under 35, these figures are one fourth or less of the risk of death associated with complications of pregnancy among women using no method of contraception, and they are similar to the risk of death associated with current use of other methods of contraception. However, as age increases beyond 35, the risk of death associated with current use among nonsmokers begins to approach the risk of death associated with complications of pregnancy among women using no method of contraception (in women 35 years of age or older, this figure is about 21 deaths per 100,000 women per year), and it is considerably greater than the risk of death associated with current use of other methods of contraception (in women 35 or older, this figure is about two to five deaths per 100,000 users per year, regardless of smoking habit).[28]

(2) Among women who smoke cigarettes, the annual risk of death associated with current use of oral contraceptives increases from about two per 100,000 among women 15 to 19 years old to about 12 per 100,000 among women 30 to 34 and around 61 per 100,000 among women 40 to 44. In women younger than 35, these figures are only somewhat lower than the risk of death associated with complications of pregnancy among women using no method of contraception, and they are considerably greater than the risk of death associated with current use of other

methods (in women younger than 35, this risk is about one to three deaths per 100,000 users per year). Furthermore, as age increases beyond 35 years, the risk of death associated with current use among smokers increasingly exceeds the risk of death associated with complications of pregnancy among women using no method of contraception (about 21 deaths per 100,000 women per year) and dramatically exceeds the risk of death associated with other methods (about two to five deaths per 100,000 users per year).[28]

Although the oral contraceptives that have been widely used in Great Britain, the United States, and similar countries over the past two decades do appear to cause a substantial increase in the risk of cardiovascular disease among certain groups of women, it is probable that this risk can be reduced while the benefits of oral contraceptives can be retained. In the first place, it seems clear that the risk of cardiovascular disease among current users is directly related to both the estrogen and progestogen content (at least for some progestogens) of the oral contraceptives being used.[16,37,40,41] Thus, the increasing use of "very-low-dose" oral contraceptives (e.g., 0.5 mg of norethindrone with 35 μg of ethinyl estradiol) that has occurred since the mid-1970s[2] may have already begun to reduce the risk of cardiovascular disease that is attributable to oral contraceptives. Secondly, there is now some evidence suggesting that the effects of different oral-contraceptive formulations on the risk of cardiovascular disease can be at least partially predicted by their effects on physiologic indicators of the risk of cardiovascular disease (such as antithrombin III activity,[32,52] blood pressure,[13,15,84,85] and high-density-lipoprotein cholesterol[24,89]) and that it may be feasible to monitor these variables to identify individual users who seem more likely than others to develop cardiovascular disease as a consequence of oral-contraceptive use, and to identify specific oral-contraceptive formulations that seem less likely than others to increase the risk of cardiovascular disease.

Evidence that the risk of cardiovascular disease among users varies according to the progestogen and estrogen content of the oral contraceptives being used[16,37,40,41] also suggests another intriguing possibility for future research aimed at reducing the risk of cardiovascular disease or other adverse effects among users: evaluation of the extent to which women vary in the absorption, distribution, and elimination of contraceptive steroids. If such variation is substantial — a possibility that is suggested by two recent studies[91-93] — an oral-contraceptive formulation that is appropriate for some women may be inappropriate for others, and it may therefore be desirable to develop procedures for titrating the steroid dosage to achieve similar plasma levels in women with different patterns of absorption, distribution, or elimination.

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