Review Article

Medical Progress

Oral Contraceptives and the Risk of Venous Thrombosis

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In the early 1960s, shortly after the introduction of oral contraceptives, the first case reports appeared describing venous thrombosis and pulmonary emboli in women using this method of birth control. Later, myocardial infarction and stroke were also found to be associated with the use of oral contraceptives. These observations led to numerous epidemiologic and clinical studies of oral-contraceptive pills and thrombosis and subsequently to the development of new oral contraceptives with a lower estrogen content. These lower-estrogen contraceptives were considered safer: changes in hemostatic factors remained small, inconsistent in direction, and mostly within the normal range.[1-4]

Recent studies have challenged the concept that reducing the dose of estrogen in oral contraceptives eliminates the risk of venous thrombosis. These studies have included epidemiologic data suggesting that certain progestins may increase the risk of thrombosis associated with low-estrogen preparations, new findings regarding individual genetic susceptibilities to the thrombogenic effect of oral contraceptives, and new insights into the hemostatic changes that predispose women to thrombosis. These advances have consequences with respect to the development of new contraceptives and tailoring of the prescription of currently available preparations.

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Arterial thrombosis is also a complication of oral-contraceptive therapy, but the risk factors for this condition differ from those for venous thrombosis. For example, smoking increases the risk of myocardial infarction associated with the use of oral contraceptives,[5,6] but it has no material effect on the risk of venous thrombosis in users of oral contraceptives.[7,8] In contrast, several prothrombotic genetic defects are strong risk factors for venous thrombosis and increase the risk associated with the use of oral contraceptives, but most are likely to be only weak risk factors for myocardial infarction or stroke. This review will focus on recent developments in our understanding of venous thrombosis as a side effect of oral-contraceptive use.

Risks Associated with Low-Dose Oral Contraceptives

In 1981, Stadel estimated that the risk of venous thrombosis was increased by a factor of four in users of oral contraceptives.[9] This estimate reflected the use of the oral contraceptives available in the 1970s, which were predominantly "high-dose" (estrogen content, 50 μg or more of ethinylestradiol). At that time, little was known about the effect of lowering the dose of ethinylestradiol below 50 μg.

Primarily on the basis of studies involving the use of "low-dose" oral contraceptives (30 to 40 μg of ethinylestradiol), an expert committee of the World Health Organization concluded in 1998 that current users of oral contraceptives have a risk of venous thrombosis that is three to six times that of nonusers.[10] The highest risk occurred during the first year of use, and an increased risk persisted until, but not beyond, the discontinuation of the contraceptives. A recent review of studies involving healthy young women without risk factors[11] also reported that the risk of venous thrombosis increased by a factor of 3 to 6; one study estimated an increase in risk by a factor of 11 (Table 1).[12-16] The absolute risk, however, remains low. A base-line risk of less than 1 per 10,000 person-years is increased to 3 to 4 per 10,000 person-years during the time when oral contraceptives are being used.[6,8,11]

One issue of concern regarding the methods used in studies of the risk of venous thrombosis with oral contraceptives is the possibility of diagnostic-suspicion and referral bias. In other words, the awareness by the physician that a patient with calf pain or swelling is taking oral contraceptives might increase the likelihood that the patient will be evaluated for deep-vein thrombosis[17] and might lead to an overestimation of the risk posed by oral contraceptives. The finding in early studies that the risks associated with oral con-

TABLE 1. CURRENT BEST EVIDENCE OF THE RISK OF VENOUS THROMBOSIS AMONG APPARENTLY HEALTHY USERS OF AVAILABLE LOW-DOSE COMBINED ORAL CONTRACEPTIVES.*

STUDY	YEARS INCLUDED	AGE RANGE	STUDY DESIGN	EVENTS	NO. IN WHOM VENOUS THROMBOSIS DEVELOPED	RELATIVE RISK (95% CI)
		yr				
Helmrich et al.[12]	1976–1983	18–49	Case–control	Nonfatal deep venous thromboembolism and pulmonary embolism	5	11.0 (3.7–32.0)
Vessey et al.[13]	1968–1985	25–56	Cohort	Fatal and nonfatal superficial venous thrombophlebitis, deep venous thromboembolism, and pulmonary embolism	3	3.3 (0.9–11.4)
World Health Organization[14]	1989–1993	15–49	Case–control	Nonfatal deep venous thromboembolism and pulmonary embolism	132 from Europe, <35 yr old 42 from Europe, ≥35 yr old 93 from developing country, <35 yr old 28 from developing country, ≥35 yr old	4.3 (2.9–6.5) 3.9 (2.3–6.6) 3.2 (2.3–4.5) 2.5 (1.5–4.3)
Jick et al.[15]	1991–1994	<40	Cohort	Nonfatal deep venous thromboembolism and pulmonary embolism	75	6.1 (2.5–15.1)
Lewis et al.[16]	1993–1995	16–44	Case–control	Fatal and nonfatal deep venous thromboembolism and pulmonary embolism	334	4.4 (3.4–5.8)

*Adapted from Hannaford and Owen-Smith.[11] CI denotes confidence interval.

traceptives were similar regardless of whether the diagnosis of venous thrombosis was certain or uncertain suggested that such a bias was not the explanation for the observed risks.[18,19]

More recently, two studies addressed this issue by focusing on women who were referred to testing facilities for clinically suspected deep-vein thrombosis.[20,21] A case was defined as an objectively confirmed diagnosis of venous thrombosis, and controls were women with similar cause for clinical suspicion who proved not to have venous thrombosis. Information about the use of oral contraceptives was obtained before diagnostic testing was conducted. The relative risk of confirmed venous thrombosis associated with oral contraceptives was 6.4 (95 percent confidence interval, 1.2 to 34.3) in the smaller study[20] and 3.9 (95 percent confidence interval, 2.6 to 5.7) in the larger study.[21] These results confirm the existence of an increased risk associated with the use of modern oral contraceptives that cannot be explained by surveillance bias.

THE EFFECT OF PROGESTINS IN COMBINED PREPARATIONS

Before 1995, the progestin component of oral contraceptives was not generally thought to contribute to the risk of thrombosis. However, more recent data showing a higher risk of venous thrombosis with third-generation progestins (desogestrel and gestodene) than with second-generation progestins (e.g., levonorgestrel and norgestrel) have challenged this view.[15,22–24] Whereas the beneficial effects of third-generation progestins on the levels of high-density lipoprotein cholesterol had suggested that they might lower the risk of arterial thrombosis, studies demonstrated a relative risk of venous thrombosis in users of these oral contraceptives that was six to nine times that in nonusers.[22–24]

Of 16 original studies addressing the risk of third-generation as compared with second-generation oral contraceptives, 3 found no difference between the two types of contraceptives[25–27] and all the others found higher risks associated with the use of third-generation preparations, with estimates of risk ranging from 1.4 to 4 times as high as that associated with second-generation preparations.[15,21–24,28–35] In a prospective study involving a pharmacy data base in the Netherlands, the absolute risk associated with third-generation contraceptives approached 1 per 1000 new users per year during the first year of use.[32] This finding is consistent with those of earlier studies that also found higher risks among first-time users.[15,22,23,36]

Findings of an increased risk with third-generation contraceptives led to a protracted debate about possible bias and confounding.[6,16,37–47] Some suggested that oral contraceptives were being differentially prescribed on the basis of the patient's underlying risk factors,[41] but the appropriate stratification for risk factors such as obesity and age did not eliminate the difference in risk between third-generation and second-generation contraceptives.[6,46] The possibility that the findings were due to selective "attrition of susceptibles"[16,41] was addressed by the confirmation of the findings in a separate analysis of the first year of use.[6,36,46] Reanalyses according to the duration of use were suggested,[41–43] but they failed to reverse the findings convincingly.[6,40,46] Taking into account these and other methodologic considerations, independent ex-

perts who were not involved in the original studies concluded that bias and confounding could not explain the consistent epidemiologic findings of an increased risk.[10,44-48] Recent package inserts for third-generation oral contraceptives used in the United States and the United Kingdom explain that they are associated with a higher risk of venous thrombosis than are other oral contraceptives.

The epidemiologic evidence that some oral contraceptives are more thrombogenic than others led to the elucidation of the hemostatic mechanisms that may underlie the association between oral contraceptives and venous thrombosis.

SUSCEPTIBILITY TO PROTHROMBOTIC STATES

Hereditary Resistance to Activated Protein C and the Factor V Leiden Mutation

In 1993, Dahlbäck et al. described a newly recognized hereditary prothrombotic condition[49]: the diminished anticoagulant response, or resistance, to activated protein C. The activated protein C system is one of the hemostatic checks and balances that inhibit coagulation. Dahlbäck et al. described persons from families with multiple episodes of venous thrombosis who had normal levels of protein C, but in whom activated protein C did not have its expected anticoagulant effect. One year later, the molecular basis was identified as a mutation in coagulation factor V (the substitution of adenine for guanine at nucleotide 1691) at one of the sites where activated protein C exerts its inactivating effect by cleaving factor V.[50] The mutant factor is commonly referred to as factor V Leiden. Its prevalence is about 5 percent in white persons, with some geographic variation, but it is virtually absent in Asian and African populations.[51,52] The presence of factor V Leiden increases the risk of venous thrombosis by a factor of 4 to 10 in heterozygotes and by a factor of 50 to 100 in homozygotes.[53]

It is now recognized that factor V Leiden greatly increases the risk of venous thrombosis associated with oral-contraceptive use (Fig. 1).[8] As compared with the base-line risk for women who do not use oral contraceptives and do not carry factor V Leiden, the risk is increased by a factor of 4 in those who use oral contraceptives but do not carry factor V Leiden, by a factor of 7 in carriers of the factor V mutation who do not use oral contraceptives, and by a factor of 35 in women who carry the mutation and also use oral contraceptives. This susceptibility has been confirmed in other studies[29,54] and is even higher in the few women who are homozygous for this mutation.[53]

Other Hereditary Prothrombotic Defects

The prevalence of previously recognized prothrombotic defects — deficiencies of protein C, protein S, and antithrombin — is much lower than that of factor V Leiden; their combined prevalence is less than 1 to 2 percent.[55,56] Their rarity makes it difficult to conduct extensive studies of the interaction between these defects and the use of oral contraceptives. Nevertheless, multiple case reports and studies in large families indicate that the risk is particularly high in young women with these defects who begin to use oral contraceptives.[57-59] Another recently identified genetic defect, a mutation in the prothrombin gene (the substitution of adenine for guanine at nucleotide 20210), is a moderate risk factor for thrombosis; its prevalence among white persons is approximately 2 to 4 percent,[60,61] and it has also been shown to increase the risk of venous thrombosis associated with the use of oral contraceptives.[27]

Women who have a prothrombotic defect have oral-contraceptive–associated venous thrombosis not only more often, but also sooner: their risk of venous thrombosis in the first year of use is more than 10 times that in later years.[62] Thus, the development of venous thrombosis in the first year of use may be a warning that a woman has a hereditary risk factor for venous thrombosis.[62]

Prothrombotic Conditions of Uncertain Heredity

High levels of factor VIII are linked to blood groups other than O,[63,64] which accounts in part for the observation that having a blood group other than O increases the risk of venous thrombosis by a factor of about 1.6 in general, and by a factor of 3.3 among users of oral contraceptives.[65] However, some data have suggested that the effects of high levels of factor VIII and the use of oral contraceptives are merely additive.[66]

A recent study of carriers of factor V Leiden demonstrated that women with blood groups other than O were four times as likely to have venous thrombosis than those with blood group O. This increased risk was greater than previous general estimates derived from studies in unselected patients and points to a possible interaction.[67]

MECHANISMS OF VENOUS THROMBOSIS INDUCED BY ORAL CONTRACEPTIVES

Until recently, it was uncertain whether the use of low-dose oral contraceptives disturbed the hemostatic balance.[1-4] Potential prothrombotic effects included increases in the levels of coagulant factors and decreases in the levels of the anticoagulant proteins antithrombin and protein S. However, these changes were believed to be at least partially counterbalanced by such antithrombotic effects as increases in the levels of other anticoagulant proteins and increased fibrinolysis. Furthermore, the levels of coagulation factors typically remained within the normal range during oral-contraceptive use.[1-4]

New studies of the effects of second-generation and third-generation oral contraceptives on the pro-

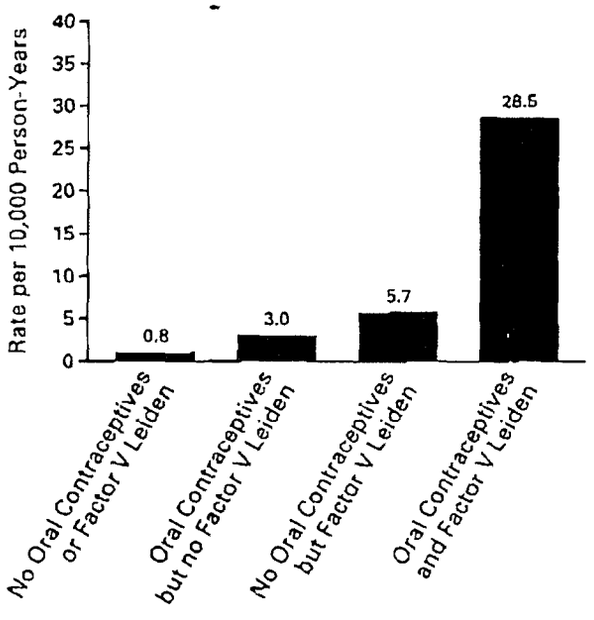

Figure 1. Cases of Deep-Vein Thrombosis per 10,000 Person-Years, According to the Use of Oral Contraceptives and the Presence of Factor V Leiden.

coagulant, anticoagulant, and fibrinolytic pathways, in contrast, indicate that oral contraceptives have a net prothrombotic effect. Quantitatively, the effect is greater with preparations that confer a higher risk of thrombosis. The hemostatic factors involved in this process are shown in Figure 2.[68]

Procoagulant Effects

A recent randomized, crossover study[69] confirmed that there are increases in the levels of prothrombin, factor VII, factor VIII, factor X, fibrinogen, and prothrombin fragment 1+2 and decreases in the levels of factor V during the use of oral contraceptives. The increase in prothrombin and factor VII and the decrease in factor V were significantly more pronounced with the use of third-generation oral contraceptives (those containing desogestrel) than with the use of second-generation oral contraceptives containing levonorgestrel. It is now recognized that moderately increased levels of prothrombin[60] and factor VIII[63,64] are associated with an increased risk of venous thrombosis. Since factor V may exhibit anticoagulant activity because of its ability to act as a cofactor in the inactivation of activated factor VIII that is mediated by activated protein C,[70,71] a decrease in the level of factor V may contribute to the thrombotic side effects of oral contraceptives.

Anticoagulant Effects

Oral contraceptives have profound effects on the anticoagulant system. Between 1994 and 1997 there were several reports that acquired resistance to activated protein C develops in women who use oral contraceptives. Like carriers of factor V Leiden (who have hereditary resistance to activated protein C), these women become less sensitive to the anticoagulant action of activated protein C.[72-76] Furthermore, third-generation oral contraceptives cause more pronounced resistance than do second-generation oral contraceptives.[76-78] The clinical relevance of acquired resistance to activated protein C during the use of oral contraceptives is evidenced by the observation that the levels of resistance reported among users of oral contraceptives, carriers of factor V Leiden, and heterozygous carriers of factor V Leiden who use oral contraceptives correlate with the relative risks of venous thrombosis that have been found in epidemiologic studies to be associated with these conditions.[76,79] Since resistance to activated protein C, even in the absence of factor V Leiden, is an independent risk factor for venous thrombosis,[80,81] these observations support the theory that acquired resistance to activated protein C contributes to the increased risk of thrombosis in users of oral contraceptives. The molecular basis of acquired resistance to activated protein C during the use of oral contraceptives is unknown. Decreased levels of plasma protein S, the cofactor of activated protein C (the levels of which were significantly lower in users of desogestrel[82]), only partially explain the resistance to activated protein C found in users of oral contraceptives.

Fibrinolytic Effects

Changes in fibrinolytic variables (plasminogen, tissue plasminogen activator, plasminogen-activator inhibitor type 1, and plasmin–antiplasmin complexes) with the use of oral contraceptives suggest that fibrinolytic activity is increased.[1-4,83] It is not known whether enhanced fibrinolytic activity during oral-contraceptive use has clinical implications, since changes in the fibrinolytic system have not been demonstrated to affect the risk of venous thrombosis. One antifibrinolytic mechanism involves thrombin-activatable fibrinolysis inhibitor (TAFI), which, when activated, inhibits fibrinolysis by removing from fibrin the lysine residues that are essential for the binding and activation of plasminogen.[84,85] Elevated levels of TAFI are a risk factor for venous thrombosis.[86] An assay for clot lysis that probes the activity of both the fibrinolytic system and the TAFI-dependent antifibrinolytic pathway demonstrated that the overall clot-lysis time remained unchanged during oral-contraceptive use.[83] This finding suggests that in the users of oral contraceptives an enhanced down-regulation of fibrinolysis by the TAFI system compensates for the increased fibrinolytic potential. Levels of TAFI are higher in women taking contraceptives containing desogestrel than in those taking contraceptives containing levonorgestrel, indicating a stronger down-regulation of

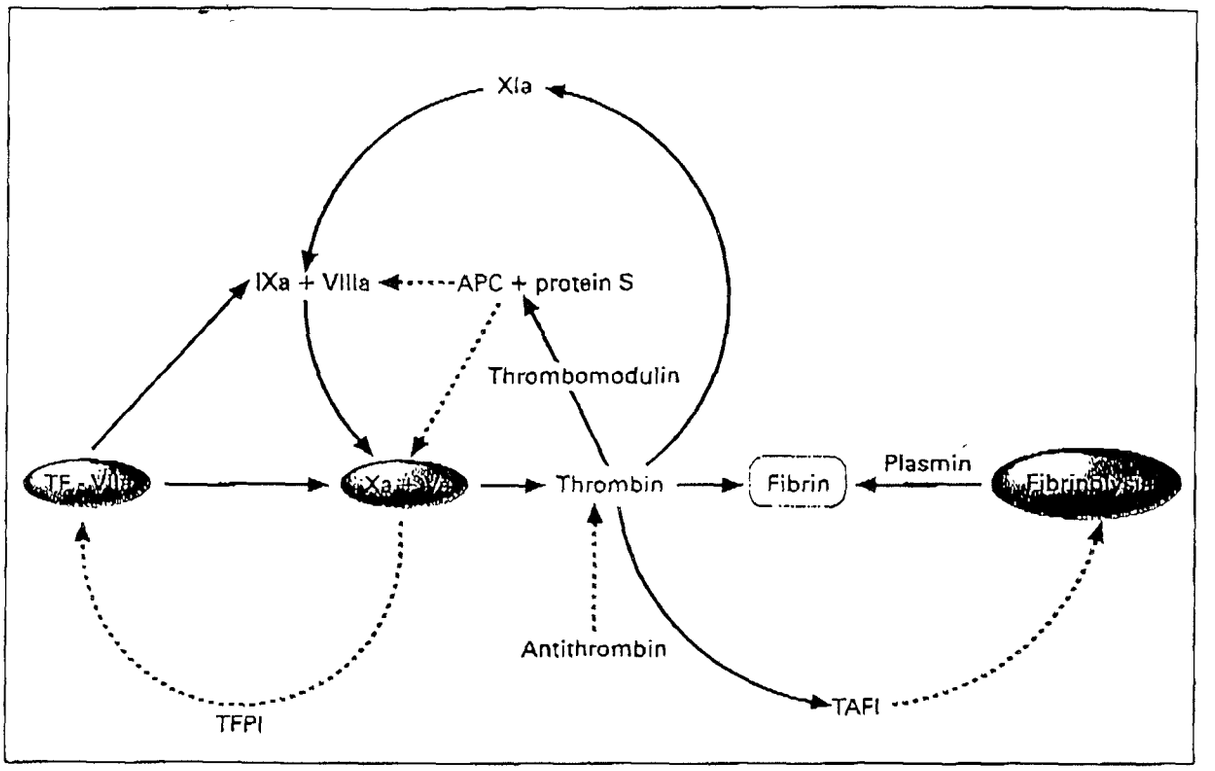

Figure 2. Regulation of Blood Coagulation and Fibrinolysis.

Coagulation is initiated by a tissue factor (TF)–factor VIIa complex that can activate factor IX or factor X. At high tissue factor concentrations, factor X is activated primarily by the TF-VIIa complex, whereas at low tissue factor concentrations the contribution of the factor IXa–factor VIIIa complex to the activation of factor X becomes more pronounced. Tissue factor–dependent coagulation is rapidly inhibited by tissue factor–pathway inhibitor (TFPI). Coagulation is maintained through the activation by thrombin of factor XI. Through the intrinsic tenase complex (factors IXa and VIIIa) and the prothrombinase complex (factors Xa and Va), the additional thrombin required to down-regulate fibrinolysis is generated by the activation of thrombin-activatable fibrinolysis inhibitor (TAFI). Activated TAFI down-regulates fibrinolysis by removing from partially degraded fibrin C-terminal lysine residues that are involved in the binding and activation of plasminogen. The coagulation system is regulated by the protein C pathway. Thrombin activates protein C in the presence of thrombomodulin. Together with protein S, activated protein C (APC) is capable of inactivating factors Va and VIIIa, which results in a down-regulation of thrombin generation and consequently in an up-regulation of the fibrinolytic system. The activity of thrombin is controlled by the inhibitor antithrombin. The solid arrows indicate activation and the broken arrows inhibition. To improve the clarity of the figure, most zymogens and procoagulant surfaces are not depicted. Modified from Bouma et al.[80] with the permission of the publisher.

fibrinolysis with the former type of contraceptive.[83] The increased TAFI-dependent inhibition of fibrinolysis most likely results from both elevated levels of TAFI and enhanced formation of thrombin (the activator of TAFI).

Overall Hemostatic Effect

The increase in procoagulant effects, the decrease in anticoagulant effects, and the equivocal effects on fibrinolysis (with increases in the activity of the antifibrinolytic system) indicate that oral contraceptives have a net prothrombotic effect. Significant differences between users of oral contraceptives that contain levonorgestrel and users of those that contain desogestrel in the plasma levels of prothrombin, factor V, factor VII, and protein S and in susceptibility to the anticoagulant action of activated protein C may explain the higher risk of venous thrombosis observed in users of third-generation oral contraceptives. The more pronounced hemostatic changes associated with third-generation oral contraceptives might be related to their increased estrogenic profile, which might also cause the moderate increase in the level of high-density lipoprotein cholesterol that has been observed in women using these contraceptives.[87]

CONCLUSIONS

Hormonal contraception is used by more than 100 million women worldwide.[10] The number of excess deaths from cardiovascular disease (venous and

arterial combined) among young, low-risk users — nonsmoking women between 20 and 24 years of age — ranges from 2 to 6 per million per year worldwide,[88] depending on the region of the world, the underlying cardiovascular risk, and the extent of the screening for risk factors that is performed before the contraceptives are prescribed. Whereas the risk of venous thrombosis is more important for younger users, the risk of arterial thrombosis becomes more important at older ages. Among older smokers who use oral contraceptives, the number of excess deaths is estimated to vary from 100 to slightly more than 200 per million per year.[88]

The reduction of the dose of estrogen has had a limited effect on reducing the risk of venous thrombosis. Third-generation progestins in combination preparations increase the extent of adverse hemostatic changes and the associated risk of thrombosis and thus should not be the first choice for new users.[34,39,40,47] The ability to prescribe prudently by withholding oral contraceptives from women with known risk factors is limited by the absence, in the majority of cases, of clinically recognizable risk factors for venous thrombosis. An investigation in New Zealand of a series of deaths due to pulmonary emboli suggested that in most cases physicians could not have foreseen the risk.[89]

In contrast, prudent prescribing can help prevent arterial thrombosis, almost all women who have a myocardial infarction during the use of oral contraceptives are older and either smoke or have other risk factors for arterial disease — in particular, hypertension.[5] The avoidance of the use of oral contraceptives by such women may underlie the reduction in the rates of arterial thrombosis reported in recent studies in industrialized countries.[5,6,88] The beneficial effect that third-generation contraceptives theoretically have on the lipid profile has not translated into a lower incidence of stroke or myocardial infarction in large case–control studies.[90,91]

To prevent venous thrombosis when prescribing oral contraceptives, physicians generally consider a personal history of venous thrombosis to be an absolute contraindication, although little is known about the risk of recurrence during the use of oral contraceptives. The only existing evidence is indirect; venous thrombotic disease that occurred during the use of oral contraceptives was less likely to recur when the contraceptives were stopped.[92] Contraceptives containing low doses of progestin alone (first-generation or second-generation) are associated with a lower risk of venous thrombosis than are combined preparations[33,93]; however, the risk among women with a history of thrombosis is unknown.

Gross obesity is a recognized risk factor for venous thrombosis, but it is unknown whether it increases the risk associated with the use of oral contraceptives, and thrombosis is rare even among obese users. Obesity is therefore not considered a contraindication to the use of oral contraceptives. Superficial varicose veins that are not the consequence of a previous venous thrombosis are not, by themselves, risk factors for deep venous thrombosis.[94] A family history of venous thrombosis may cause concern, although the sensitivity of a family history as a marker for identifying persons at high risk remains unclear. A personal history of superficial thrombophlebitis might also suggest a hereditary risk factor, especially if it is coupled with a family history of the disorder.

The susceptibility to venous thrombosis conferred by factor V Leiden and other prothrombotic mutations has led to questions about the value of screening for these mutations before oral contraceptives are prescribed. In the absence of a clear family history of venous thrombosis, there is little justification to screen for prothrombotic mutations. More than half a million women would need to be screened for factor V Leiden to avoid a single death from pulmonary embolus, since only 5 percent of women are carriers and the mortality associated with venous thrombosis in young women is low.[95] If all the costs associated with the treatment of all occurrences of venous thrombosis — including the post-thrombotic syndrome that occurs in up to one third of patients[96] — were considered, and if the cost of screening became very low (less than about $9), screening might be rationalized on economic grounds.[97] Such cost–benefit calculations, however, might be too general to be of use, since the risk of carrying the factor V Leiden mutation varies according to the presence or absence of a family history of thrombosis — presumably because of concomitant genetic or environmental risk factors.[98] Also, denying oral contraceptives to women who test positive for factor V Leiden would leave at least 5 percent of young women without access to the most efficacious form of contraception. Moreover, the implications of a prothrombotic genetic defect in a woman without a history of thrombosis are unclear, and awareness of the presence of the defect has daunting psychosocial, medical, and legal consequences (in terms of insurance, in particular). Finally, the absence of a recognized biochemical or genetic defect does not eliminate the possibility of thrombosis. Even in the absence of one of the defects that are currently known to be relevant, a strong family history of venous thrombosis warrants caution about the use of oral contraceptives, purely on clinical grounds. In the absence of decisive data regarding the risks and benefits of genetic screening before prescribing oral contraceptives, either in the general population or in high-risk families, decisions regarding screening and prescribing should be based on clinical judgment that takes into account each woman's family history and risk factors.[95]

The past five years have yielded key advances in understanding the epidemiology and the hemostatic

mechanisms of the risk of venous thrombosis associated with the use of oral contraceptives. An increased understanding of individual susceptibility to the hemostatic changes induced by oral contraceptives and of markers of the risk of thrombosis should lead to the development of preparations that are even safer.

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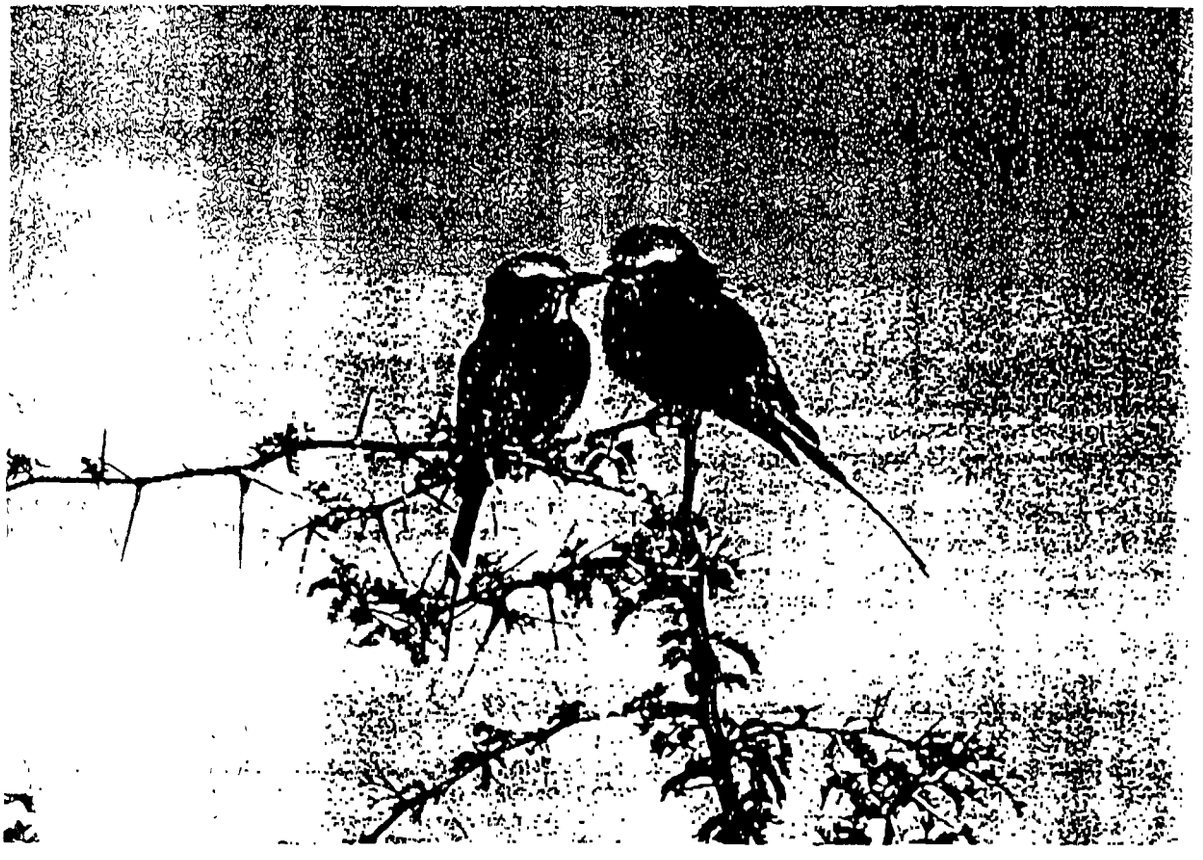

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