

# Oral Contraception and Coagulation

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Within a few years of the introduction of oral contraception, clinical case reports linked their usage to thrombogenic cardiovascular events. Retrospective population studies in the United Kingdom<sup>1</sup> and in the United States<sup>2</sup> confirmed this relationship, although dissenting opinions based on similar retrospective<sup>3</sup> plus some prospective<sup>4</sup> studies have also been published. The literature on the subject is complicated by reference to older studies, which on review yield conflicting conclusions. For example, a report issued by the Royal College of General Practitioners in 1977 stated: "... in general, it would be wise for all contraceptive users over 35 years of age to reconsider their method of contraception. . . ."<sup>5</sup> Yet 4 years later a report from the same group concluded, when referring to mortality rates in women between the ages of 35 and 44, "... these estimates permit a more flexible approach to

women who are between 35 and 45 years of age. It is now apparent that the major risk occurs in smokers."<sup>6</sup>

The hemostatic mechanism is very intricately balanced between factors which promote coagulability and those which ensure the fluidity of blood within the vascular tree. The three sets of circumstances that are necessary for clot formation—damage to the intima, impaired blood flow, and hypercoagulability—are influenced in different ways by a number of factors such as life-style (e.g., exercise), personal habits (e.g., smoking), and medications (e.g., oral contraceptives). In order to understand the potential thrombogenic effect of oral contraceptives, one must consider all of the above factors, plus the differential effect the various constituents of the contraceptives themselves have on the coagulation/fibrinolytic mechanism. Further, it is important to differentiate their effect on arterial and that on venous thrombosis.

In order to fully appreciate the real cause-and-effect relationship between oral contraceptive use and thromboembolic disease, we need to consider a few points relative to

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the coagulation cascade. There are many reports that show an increase in a number of coagulation factors associated with a "hypercoagulable" state. At this time, there are, in fact, no tests, single or in combination, that can measure hypercoagulability or be used in predicting in whom a blood clot will develop.<sup>7</sup> Further, there are no studies that have shown a cause-and-effect relationship between a procoagulant alteration in a coagulation profile and the development of a thrombus. Finally, cognizance needs to be taken of the overall effect: an elevation in factor X, for example, may be "balanced" by an increase in the fibrinolytic activity of the vascular intima or plasmin.

A thrombus will form when alterations in blood flow and an enhancement of the coagulation cascade are superimposed on an area of intimal damage, in the absence of normal anticoagulant and fibrinolytic activity. The factors that result in venous thrombosis probably differ from those of an arterial blood clot. The former may indeed be related to the estrogen component of the oral contraceptive, because studies have shown a definite decrease in the incidence of venous thromboembolic disease—but not arterial thrombosis—as the dosage of estrogen in the oral contraceptive is lowered.<sup>8</sup>

### **Intimal Damage**

A thrombus is unlikely to develop in a vessel as long as the endothelial lining remains intact. When it is damaged, certain elements (especially collagen) become exposed and stimulate thrombogenic activity. Data that suggest endogenous and exogenous estrogen as common denominators in the formation of intrinsic vascular lesions<sup>9</sup> have been discounted by the observation of intimal proliferation occurring in a number of other clinical conditions unassociated with excess estrogen.<sup>10</sup> Nevertheless, it is possible that intimal proliferation is one of the factors responsible for the reduction of

the lumen of the vessel and/or the alteration of the hemodynamics of blood flow in a susceptible individual taking oral contraceptives.

Persons who have defective fibrinolytic activity in the vessel wall may also be more susceptible to vascular accidents. Studies performed with women who had experienced recurrent thrombosis while taking oral contraceptives revealed a defect in the endothelial fibrinolytic system and a normal blood coagulation profile.<sup>11</sup> This has been confirmed in two other studies,<sup>12,13</sup> suggesting that it may not be the oral contraceptive *per se*, but a "sensitivity" in a particular individual, that predisposes her to clot formation.

A defective vascular fibrinolytic system has been noted in as many as 30–50% of persons with proven idiopathic venous thrombosis.<sup>13</sup> The results to date indicate that defective endothelial fibrinolysins, if present, predispose individuals to venous, rather than arterial thrombosis. It is the estrogen component of the oral contraceptive that is thought to have a dampening effect on the fibrinolytic activity on vein walls, because the same observation has been made in postmenopausal women treated with ethinyl estradiol.<sup>14</sup> Although there are no practical and consistent ways of documenting this deficiency, there is one practical preventive application, namely, exercise. Exercise has been shown to increase the fibrinolytic response in healthy adults,<sup>15</sup> and is one of the important associated factors alluded to earlier that needs to be considered when deciding on the relative risks and safety of oral contraceptive usage for a particular individual.

Blood flow *per se* has also been associated with decreased spontaneous fibrinolytic activity and an impaired defense against fibrin deposition. This is consistent with the clinical association between deep vein thrombosis and venous stasis. Oral contraceptives influence blood flow and venous distensibility, according to their overall hormonal effect. Progestin-dominant oral

contraceptives (d-norgestrel, 0.125 mg, and ethinyl estradiol, 0.03 mg) were found to significantly increase venous capacitance when compared with a low-progestin preparation (megestrol, 1 mg; ethinyl estradiol, 0.1 mg) and control values during the follicular phase of the menstrual cycle.<sup>16</sup>

The overall effect was one of venous stasis, unlike another progesterone-dominant situation—pregnancy—in which secondary vasodilatation is associated with a compensatory increase in blood flow.

A most important mediator of the vascular wall tone is the homeostasis between prostacyclin—which is produced by the endothelial lining and which results in vasodilatation—and thromboxane  $A_2$ —which is synthesized by the platelet membrane and is a potent vasoconstrictor. Animal experiments have shown that progesterone seems to have a protective effect, in that prostacyclin production is either unchanged or increased.<sup>17</sup> Estrogen on its own has a tendency to decrease endothelial prostacyclin synthesis.<sup>18</sup> In women, oral contraceptives appear to produce the opposite effect, because platelet aggregation is less inhibited by endothelial cells<sup>19</sup> (less prostacyclin), and/or there is a greater synthesis of thromboxane  $A_2$ .<sup>20</sup> This issue is far from clearly established, but it is the balance between the stimulators or inhibitors of the vasodilating and anti-platelet aggregator prostacyclin, and its platelet antagonist thromboxane  $A_2$ , which will determine the overall effect. The interaction between these two metabolic products of prostaglandin synthesis is also influenced by other drugs (e.g., aspirin). Depending on the dosage used, the intermittent use of a low-dose aspirin regimen (e.g., 30 mg every second or third day) has been shown to alter the balance in favor of greater prostacyclin activity. Thus, once again, factors related to but not directly associated with the pharmacologic effect of the oral contraceptive per se may influence the eventual acceptability and safety of this method of contraception.

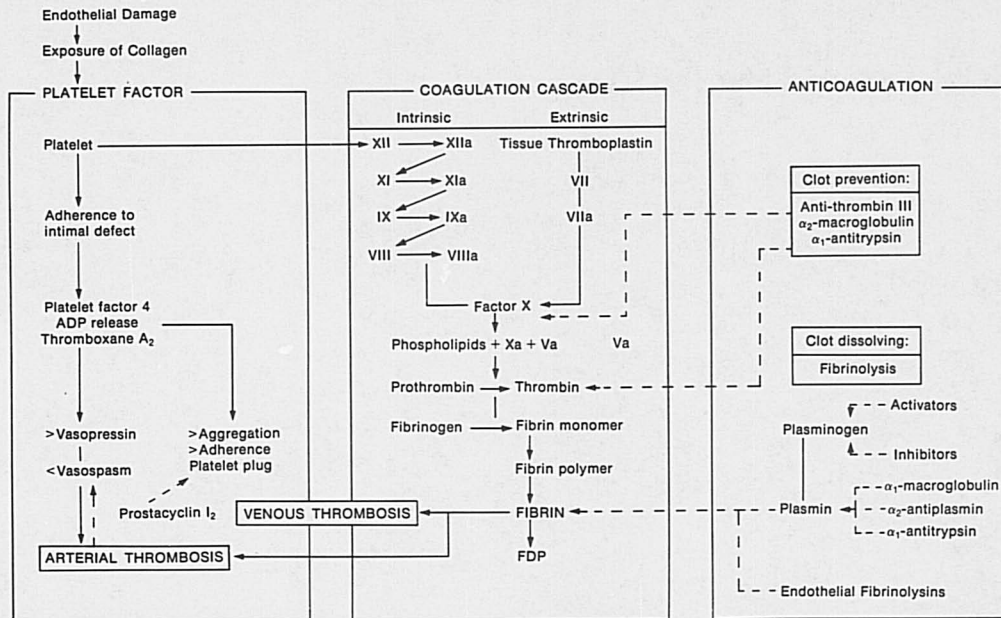
## Platelet Activity

Platelet function is a vital aspect of coagulation, because platelet activity determines three separate yet interrelated pathways: the synthesis of thromboxane  $A_2$ , which, apart from its influence on the vessel wall, increases the ability of platelets to aggregate; adhesion of the platelets to the intimal defect, especially in arterial thrombus formation; and the stimulation of the coagulation cascade by the activation of factor XII.

Data on the effect of oral contraceptives on platelet function are contradictory because of the technical difficulty of the various tests of platelet function and their relatively poor reproducibility.

A fairly consistent feature has been an increase in the platelet count. Because this is true also for postmenopausal women receiving estrogen replacement therapy, it may be an estrogen-related effect.<sup>21</sup> The clinical significance of this change is not apparent, especially because the values still appear to be within the range of normal for a given laboratory. Zuck et al.<sup>22</sup> and others<sup>23</sup> have shown that platelet adhesiveness is not significantly increased in *asymptomatic* women taking oral contraceptives. Other researchers<sup>24,25</sup> have obtained different results, but this may be due to differences in methodology. Platelet adhesiveness is increased in women who develop a thrombus while taking oral contraceptives,<sup>22</sup> but this may reflect a blood change due to the thrombotic incident, rather than a preexisting thrombotic tendency.

Platelet aggregation is increased after long-term oral contraceptive use,<sup>23,26</sup> and in individuals taking estrogen alone, but is normal when only progesterone is used. The correlation between in-vitro platelet function and in-vivo platelet behavior must be interpreted cautiously, because the tests are highly artificial, and the results may bear little relation to the vascular event. As an example, platelet adhesiveness has not been useful in detecting thrombosis after surgery.



**FIG. 1.** Integrated relationship between platelet activity, coagulation, and fibrinolysis. -----, inhibitory; ———, stimulatory. (Modified from Notelovitz M, Ware M. Coagulation risks with menopausal estrogen therapy. In: Studd J, ed. Progress in obstetrics and gynecology. Vol 2. Edinburgh: Churchill-Livingstone, 1982:228.)

or as cofactors to other enzymes, and are of themselves "inactive" until a suitable clot-promoting surface has been provided; and all of the clotting factors circulate in plasma far in excess of that actually required for clot formation. For example, although the level of factor VIII is present in a wide range—60-200% in a healthy population—only 25% of this activity is actually needed for homeostasis. Conversely, individuals will only bleed after their measured clotting factors have fallen to below 30-40% of normal levels.<sup>31</sup> Finally, the tests that measure the various factors do not differentiate between the proenzyme and activated forms, nor is there any evidence that the infusion of clotting factors in their proenzyme state will precipitate a thrombogenic event. A parallel can be drawn from estrogen and hepatic renin-substrate synthesis and the relatively infrequent occurrence of a directly related elevation in blood pressure.

The effect on the various clotting factors referred to above appears to be estrogen-mediated, because the use of progesterone alone—for as long as 2 years—has not been associated with a rise in the clotting factors.<sup>29</sup> In another study, elevated levels of factors VII and X, following combination oral contraceptive use, fell to normal values when progestogen oral contraceptive preparations were substituted.<sup>33</sup>

### Anticoagulation

The fluidity of blood is maintained by potent natural anticoagulants, of which anti-thrombin III appears to be the most important. Antithrombin III accounts for at least 50% of the anticoagulant activity. It is catalyzed by heparin, and in its complexed form neutralizes thrombin instantly. Antithrombin III, together with some of the other less potent thrombin inhibitors such as  $\alpha_1$ -antitrypsin and  $\alpha_2$ -macroglobulin, can be measured immunologically or by their biologic activity. These coagulation in-

hibitors can be regarded as clot "preventers."

A deficiency of antithrombin III is associated with an increased liability of thrombosis. This has been clearly established in families with congenital antithrombin III deficiency. These families have plasma values ranging between 40% and 50% of normal.<sup>34</sup> As summarized elsewhere,<sup>28</sup> a number of studies have shown a statistically significant decrease in antithrombin III antigen and activity in women taking combination oral contraceptives. This seems to be dose-related, because the lower dose oral contraceptives (those containing 30-35  $\mu$ g of ethinyl estradiol) are associated either with no significant change<sup>30,35</sup> or a much reduced effect when compared with higher dose oral preparations (50  $\mu$ g of ethinyl estradiol or more).<sup>32,36</sup>

The level at which antithrombin III deficiency would cause thrombus formation is not known, but it would probably have to be reduced to about 50% of its normal activity. When interpreting the clinical significance of depressed antithrombin III levels, two points need to be considered: the level of its activity and whether it was measured in plasma or serum. Antithrombin III assayed in serum is a measurement of the amount of antithrombin left after clotting, and not that consumed during clotting. This accounts for many of the reports that showed significant lowering of antithrombin III activity in oral contraceptive users,<sup>37,38</sup> and, as with the coagulation factors, has no real bearing on the actual risk of inappropriate thrombus formation.

Antithrombin III inhibits many of the other enzymes in the coagulation cascade, such as factors Xa. In addition, the "minor" anticoagulants (e.g.,  $\alpha_2$ -macroglobulin) also demonstrate some activity, but it is not known whether this enzyme can compensate for decreases in antithrombin III activity. Levels of  $\alpha_2$ -macroglobulin have been reported as being increased<sup>30,35</sup> or normal.<sup>39</sup>

## Fibrinolysis

Fibrinolysis involves the enzymatic degradation of fibrin and fibrinogen. The endothelium has fibrinolysin activators that are continuously liberated into the bloodstream and counteract thrombosis by removing fibrin deposits. In addition, there is a plasma fibrinolytic system that has five distinct components: plasminogen, plasmin, plasminogen activators, plasminogen activator inhibitors, and plasmin inhibitors.

Clot lysis is activated by the conversion of plasminogen to plasmin, the active fibrinolytic principle. Plasmin digests both fibrinogen and fibrin but has a relative substrate specificity for the latter. Plasminogen is a  $\beta$ -globulin synthesized in the liver and, as such, is highly responsive to sex steroids. Plasminogen activators also include stress, exercise, surgery or other trauma, and thrombin.

There are two main plasminogen-plasmin inhibitors in human serum—plasminogen activator inhibitors and plasmin inhibitors. The main antiplasmins are  $\alpha_2$ -plasmin inhibitor,  $\alpha_2$ -macroglobulin, which reacts quickly as a competitive plasmin inhibitor, and  $\alpha_1$ -antitrypsin, which reacts more slowly but more firmly. The latter two proteases also inhibit thrombin activity, and so have conflicting functions—they inhibit clot formation by antagonizing thrombin, and they encourage fibrin and fibrinogen integrity by inhibiting plasmin. Their overall effect on thrombogenesis has not been ascertained. Antiplasmin ( $\alpha_2$ -plasmin inhibitor) is said to inhibit 35% of the plasmin generated from plasminogen, and thus has a most important biologic role in hemostasis. It acts through two pathways: it inactivates plasmin directly by forming a stable complex with the enzyme; and it interferes with the absorption of plasminogen to fibrin, thereby preventing the plasminogen from lysing the fibrin clot.

Overall lytic activity is measured by the

euglobulin lysis time. Quantitation of plasmin is hampered by the fact that it rarely exists in the free state and is rapidly neutralized by the inhibitory mechanism. Its precursor, plasminogen, can be measured both in amount and activity. Elevated plasminogen levels may result from reduced turnover, increased production, or reduced consumption. As with so many of the other hematologic factors discussed, the clinical significance of elevated plasminogen is not known. There are quantitative and functional methods of assessing plasmin inhibitor and the other fibrinolytic proteases.<sup>40</sup>

From clinical practice it is known that an increase in activators—and therefore plasmin formation—or a decrease in  $\alpha_2$ -plasmin inhibitor can lead to a dangerous bleeding diathesis,<sup>41</sup> but the level at which this occurs is not known. Results of the euglobulin lysis time have been variable; the majority has shown no change, although a few report an increase in lysis time.<sup>28</sup> Similarly, plasminogen activity and decreased antiplasmin activity have been reported to be increased<sup>42,43</sup> or unaffected.<sup>44</sup>

## Fibrin Degradation Products

Cleavage of fibrin and fibrinogen produces a variety of fragments known as fibrin or fibrinogen degradation products (FDP). FDP have potent anticoagulant properties and may interfere with platelet activity as well. There have been few reports in the literature regarding the effect of oral contraceptives on FDP formation. In one longitudinal study, no alterations were noted.<sup>30</sup>

After thrombin converts the fibrinogen molecule to a fibrin monomer, some of these fractions polymerize into complexes that have a higher molecular weight than the native fibrinogen, and can be detected in plasma and quantitated by a sophisticated chromatography technique. This test correlates well with subclinical fibrin deposi-

tion in blood vessels detected by the <sup>125</sup>I-fibrinogen test. Many, but not all, of the patients taking oral contraceptives have high levels of these fibrinogen complexes in plasma. In one study,<sup>45</sup> the fibrinogen complex increased fourfold after the initiation of oral contraceptives—a figure which closely parallels the reported epidemiologic increase in contraceptive-related thromboembolic disease.

### **Lifestyle Habits: The Individual**

Smoking and exercise serve as two diametrically opposed social activities that will, respectively, enhance and decrease the potential thrombogenic risk of oral contraceptives. Smoking and oral contraceptive use appear to act synergistically to increase the risk of myocardial infarction.<sup>46,47</sup> This is especially true for women who are at higher risk because of their age. Thus, in one study,<sup>6</sup> for women aged 35 to 44 the excess annual death rate was 1:6700 in nonsmokers, and 1:2000 in smokers; at 45 years and above, the risks were 1:2500 and 1:500. One of the possible mechanisms is the recent finding linking the inhalation of nicotine-containing tobacco smoke with a reduction in vascular prostacyclin production.<sup>48</sup>

Exercise has an anticoagulant effect and has even been shown to act with certain oral contraceptives to increase fibrinolytic activity—as measured by plasminogen activator—over and above that induced by the oral contraceptive itself.<sup>49,50</sup> A similar positive effect of exercise has been reported in other studies involving women using oral contraceptives as measured by a decrease in  $\alpha_2$ -plasmin inhibitor<sup>51</sup> and an increase in fibrinolytic activity when expressed as 100/dilute clot lysis time.<sup>52</sup>

Oral contraceptives have been used very successfully and safely by millions of women. Yet there is that significant minority of women in whom a venous or arterial thrombosis will develop—occasionally fatal. At present there are no reliable

markers that will allow the physician to predict who will behave idiosyncratically. Just as one has to consider both the pro- and anticoagulant properties of a specific oral contraceptive when assessing its thrombogenic potential, one must consider factors which will increase (e.g., smoking) or decrease (e.g., exercise) the risk of oral-contraceptive-induced thrombosis. Individual assessment and close monitoring of measurable adverse signs (e.g., hypertension) should allow the majority of healthy women below the age of 35 (and, perhaps, women up to the age of 45) to use oral contraceptives safely and relatively free from the risk of thrombosis. This has been particularly true since the introduction of the low-dose oral contraceptives and the newly released bi- and tri-phasic preparations.

### **The Size of the Problem: What to Tell Your Patient**

It must be very confusing, and at times frightening, for a patient, having just read the package insert listing the probable complications, to feel confident about the safety of taking oral contraceptives. Explain the facts: there does appear to be an increase in certain thrombogenic and other cardiovascular events, but the numbers are small. For example, the hospital admission rate for nonfatal myocardial infarction is 2.1:100,000 in married women aged 30 to 39 years who do not use oral contraceptives and 5.6:100,000 among those who do. Most women are *not* affected. These data are based on the higher dose oral contraceptives, which are now no longer prescribed. As a result of the lowering of the estrogen/progestogen dosage of many of the oral contraceptives<sup>8,53</sup> and the avoidance of prescribing oral contraceptives to those women really at risk, the relative risk of venous thromboembolic disease and myocardial infarction has been dramatically reduced.<sup>8,53,54</sup> A reduction of the estrogen content to approximately 50% leads to a reduction in the complication rate



to 30%.<sup>8</sup> By withholding oral contraceptives from women with major risk factors, the overall risk for these women has been reduced to 1.4:1, less than the 2.2:1 for women without risk factors.<sup>54</sup>

Contrary to earlier opinions, there does not appear to be an increased risk of death due to vascular disease with increasing duration of pill use.<sup>6</sup> An exception to this is the association between the progestin component of the oral contraceptive and its lowering effect on the protective high-density lipoprotein<sup>55</sup> and the concomitant increase in blood pressure<sup>53</sup> leading to potential arterial complications such as stroke. These events do not involve the hemostatic mechanism and can be easily monitored by regular measurement of the blood pressure and by biannual assessment of the patient's plasma high-density lipoprotein.

Finally, the real adverse effect of smoking on cardiovascular disease should be emphasized. Where appropriate, patients should be encouraged to give up smoking and not the pill.

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