Coagulation effects of oral contraception

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In Europe and North America, estrogen/progestogen oral contraception has been associated with an increase in venous thromboembolism, myocardial infarction, and stroke. These hazards are found mainly in smokers and in women over the age of 35. Venous thromboembolism appears to correlate with the estrogen dosage, and the arterial complications with both the estrogen and progestogen components. Blood coagulation and vascular thrombosis are intimately related. Estrogen/progestogen oral contraception affects blood clotting by increasing plasma fibrinogen and the activity of coagulation factors, especially factors VII and X; antithrombin III, the inhibitor of coagulation, is usually decreased. Platelet activity is also enhanced with acceleration of aggregation. These changes create a state of hypercoagulability that, to a large extent, appears to be counterbalanced by increased fibrinolytic activity. Studies of the oral contraceptives in current use show that the coagulation effects depend on the dosage of estrogen and the type of progestogen used in combination. Current research is aimed at finding the estrogen/progestogen formulations that induce the least changes in the coagulation system and other physiologic processes. In this respect, the new low-dose formulations are a major step forward and should reduce the risk of vascular thrombotic complications. (Am J Obstet Gynecol 1987;157:1042-8.)

Key words: Estrogen/progestogen contraceptives, thromboembolism, myocardial infarction, stroke, dosage of estrogen, type of progestogen

After 25 years of extensive use of oral contraceptives (OCs), the most important concern about the effects of these substances on women's health is the increased risk of cardiovascular disease, specifically, venous thromboembolic disease, myocardial infarction, and stroke.[1,2] These hazards increase especially in older patients and with smoking. The information on the vascular effects of OCs is derived almost entirely from the epidemiologic research carried out in Europe and in the United States and is based on preparations that contain one of several progestogens in combination with 50 μg of mestranol or ethinyl estradiol. These findings therefore relate to countries in which the incidence of cardiovascular disease is high; thus they may not be relevant to countries in which the incidence of these diseases is low. In this context, it should also be noted that important differences in coagulation and hemostatic tests have been shown in healthy women from different ethnic groups and geographic locations,[3] and that epidemiologic studies from certain countries do not demonstrate an increased incidence of vascular disease in association with oral contraception.[4]

Since 1974, important information on the effects of OCs on morbidity and mortality has come from three cohort studies that involved more than 80,000 women, half of whom were using OCs (The Royal College of General Practitioners Oral Contraception Study, the Oxford/F.P.A. Contraceptive Study, and the Walnut Creek Contraceptive Drug Study[2]). The Royal College of General Practitioners data suggest that the morbidity from vascular complications was increased fourfold; most deaths were caused by ischemic heart disease or subarachnoid hemorrhage and were concentrated in women over the age of 35 or older and in smokers (Table I). In general, among women of reproductive age the risk of death from a vascular complication attributable to OCs was 22 to 24 deaths per 100,000 women per year in both current and past users.

The effect of oral contraception on the incidence of venous thromboembolic disease is shown in Table II. Oral contraceptive use was considered to be responsible for 19 cases of overt venous thromboembolic disease per 10,000 current users per year; just over half of these cases were superficial leg vein thrombosis. The relative risk of idiopathic deep vein thrombosis and pulmonary embolism was approximately fourfold, and the relative risk of postoperative venous thrombosis was twofold.

Pathogenesis of vascular complications

The pathogenesis of venous thromboembolism in OC users may relate to increases of blood coagulability (including changes in the levels of coagulation factors and inhibitors and altered fibrinolytic and platelet activity) and to changes in the structure of veins and arteries (such as endothelial proliferation and changes in the

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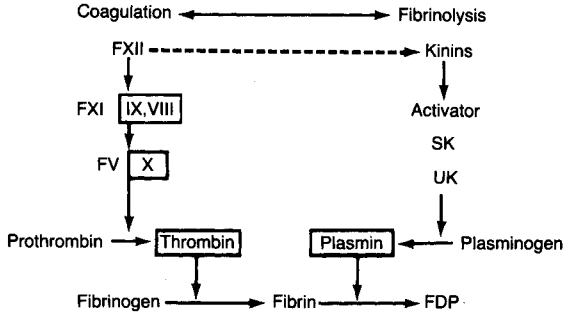

Fig. 1. Normal dynamic equilibrium between coagulation and fibrinolysis. *FXII,* Factor XII; *FXI,* factor XI; *FV,* factor V; *FDP,* fibrin degradation products; *SK,* streptokinase; *UK,* urokinase.

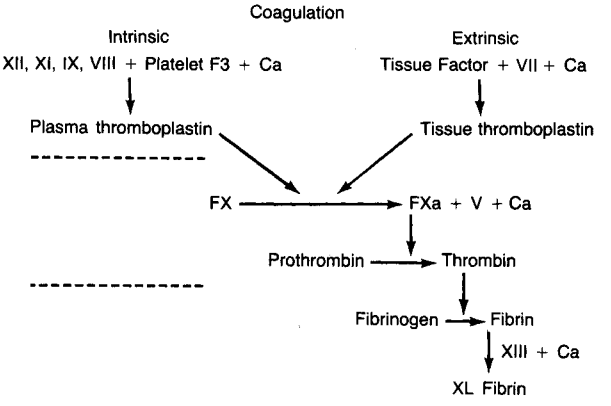

Fig. 2. Intrinsic and extrinsic coagulation pathways.

Table I. Royal College of General Practitioners data on mortality from vascular complications in OC users

Deaths			*Relative risk*		*Attributable risk*	
Current user	*Past user*	*Never user*	*Current versus never*	*Past versus never*	*Current versus never*	*Past versus never*
29	31	7	4	4	22	24

Number of deaths and attributable risk are per 100,000 per year.

Table II. Venous thromboembolic disease

Type	*Incidence (cases/10,000 women/yr)*		*Relative risk*	*Attributable risk (cases/10,000 women/yr)*
	Current users	*Nonusers*		
Superficial leg vein thrombosis	19	8	2	11
Deep vein thrombosis or pulmonary embolism	11	3	4	8
Postoperative venous thrombosis	61	30	2	31

rate of venous flow). The risk of overt venous thromboembolism appears to be related primarily to the estrogen component of OCs and is confined to the time of current usage.

The pathogenesis of arterial vascular complications—myocardial infarction and stroke—associated with OC use appears to be much more complex than that responsible for venous complications and relates to both increased platelet activity and fibrin deposition and to other factors that contribute to accelerated atherogenesis. These factors include increased arterial blood pressure and changes in glucose tolerance and lipoprotein and cholesterol metabolism. Once an atherogenic lesion develops, the process is difficult to reverse because of built-in self-maintaining or autoregulating mechanisms that are involved in this arterial lesion. The progestogen component, which was formerly regarded as the "innocent" party of the combined OC, is now considered to be an important factor with respect to arterial vascular disorders.

Blood coagulation and thrombosis

Blood coagulation and thrombosis are not identical processes, but they are intimately related. Vascular thrombosis can be regarded as hemostasis involving platelets and blood clotting occurring in the wrong place and involving an intact blood vessel. When new types of OCs or estrogen-containing drugs are introduced, it is important to investigate their effects on the physiologic processes involved in hemostasis.

The blood coagulation and fibrinolytic systems are normally in a dynamic equilibrium that controls the formation and removal of fibrin. Both systems are dependent on proteolytic enzymes, which are produced from inactive precursors: With blood coagulation, thrombin is derived from prothrombin, and in the fi-

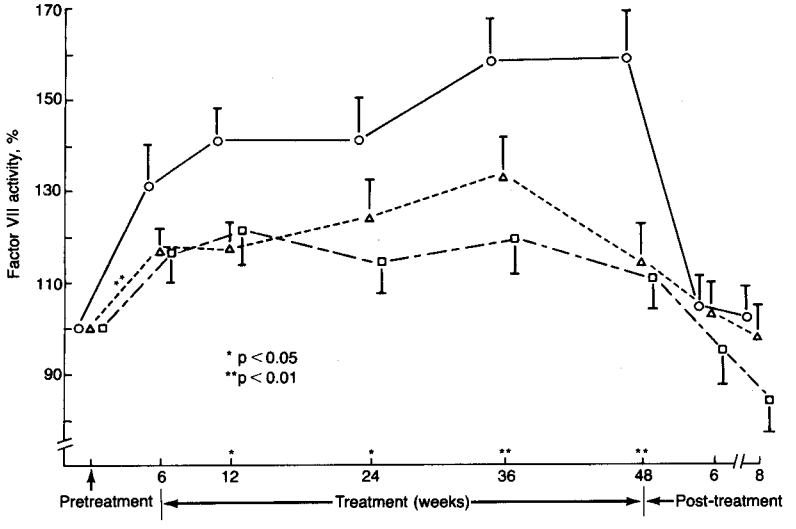

Fig. 3. Effects of oral contraceptives containing 50 and 30 μg estrogen on coagulation factor VII. Norethindrone acetate plus 50 μg estrogen, o——o; norethindrone acetate plus 30 μg estrogen, △ - - - - △; levonorgestrel plus 30 μg estrogen, □ — - — - □.

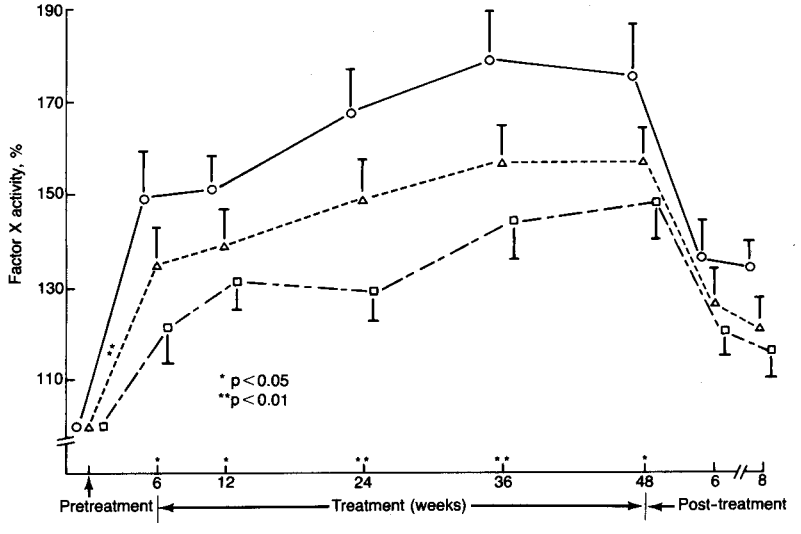

Fig. 4. Effect of oral contraceptives containing 50 and 30 μg estrogen on coagulation factor X. Norethindrone acetate plus 50 μg estrogen, o——o; norethindrone acetate plus 30 μg estrogen, △ - - - - △; levonorgestrel plus 30 μg estrogen, □ — - — - □.

Table III. Effect of 50 and 30 μg estrogen OCs on the hemostatic system

Formulation	*No. of patients*
Norethindrone acetate: 1.0 mg norethindrone acetate and 50 μg mestranol	31
Norethindrone acetate: 1.5 mg norethindrone acetate and 30 μg ethinyl estradiol	27
Levonorgestrel: 150 μg levonorgestrel and 30 μg ethinyl estradiol	28

brinolytic system plasmin is derived from plasminogen (Fig. 1).

Blood coagulation and fibrinolysis also share a common activation from factor XII. The coagulation system is designed as a biochemical amplifier, and the initial trigger may emanate from within the blood itself (the intrinsic system) or from outside the blood vessel from the tissues (the extrinsic system). The interaction of coagulation factors leads to the formation of either plasma thromboplastin or tissue thromboplastin, which

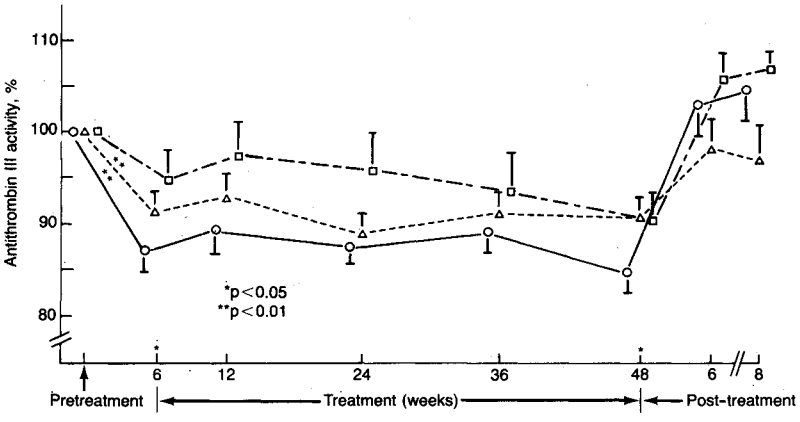

Fig. 5. Effect of oral contraceptives containing 50 and 30 μg estrogen on antithrombin III. Norethindrone acetate plus 50 μg estrogen, o——o; norethindrone acetate plus 30 μg estrogen, Δ - - - - Δ; levonorgestrel plus 30 μg estrogen, □ – – – – □.

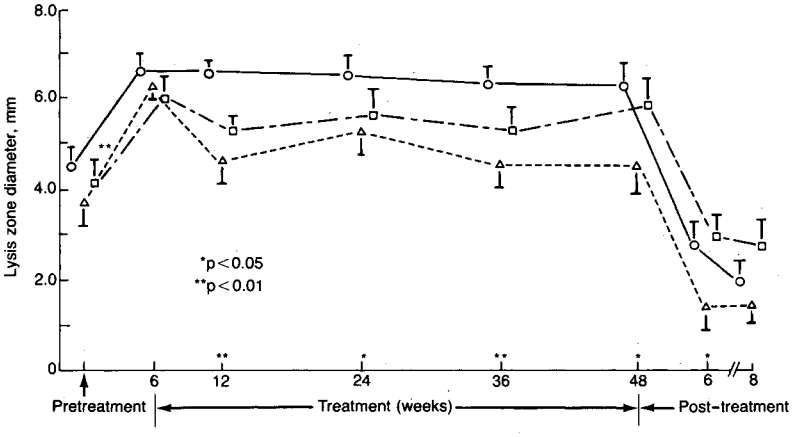

Fig. 6. Effect of oral contraceptives containing 50 and 30 μg estrogen on the fibrinolytic system (fibrin plate assay [resting]). Norethindrone acetate plus 50 μg estrogen, o——o; norethindrone acetate plus 30 μg estrogen, Δ - - - - Δ; levonorgestrel plus 30 μg estrogen, □ – – – – □.

converts factor X to its activated form. The complex of activated factor X, with factor V and calcium converts prothrombin to thrombin. Thrombin converts soluble fibrinogen into fibrin, which in the presence of factor XIII and calcium forms cross-linked fibrin (Fig. 2).

Estrogen therapy is known to influence the clotting mechanism by increasing the levels of factors II, VII, VIII, IX, and X, fibrinogen, and soluble fibrin. Estrogen also decreases the levels of antithrombin III and vessel wall fibrinolytic activator. The effects of OCs on blood coagulation have been recently reviewed by Beller and Ebert[5] and Notelovitz.[6]

Comparative studies of OCs

The comparative effects of different low-dose estrogen/progestogen contraceptives on the hemostatic system are best investigated by serial studies in healthy women. We have carried out two major studies, with the following objectives: (1) to compare the effects of 50 and 30 μg estrogen OCs on blood coagulation, fibrinolysis, and platelets; (2) to compare the effects of 30 μg ethinyl estradiol combined with different progestogens.

Comparison of 50 μg versus 30 μg estrogen. Participants in this study received either 50 μg of mestranol combined with 1.0 mg norethindrone acetate, 30 μg of ethinyl estradiol in combination with 1.5 mg of norethindrone acetate, or 30 μg of ethinyl estradiol combined with 150 μg of levonorgestrel[7] (Table III). Blood samples were taken for laboratory assay during a pretreatment cycle, after 6, 12, 24, 36, and 48 weeks of treatment, and at 6 and 8 weeks after cessation of treatment.

Factor VII levels increased sharply with both estro-

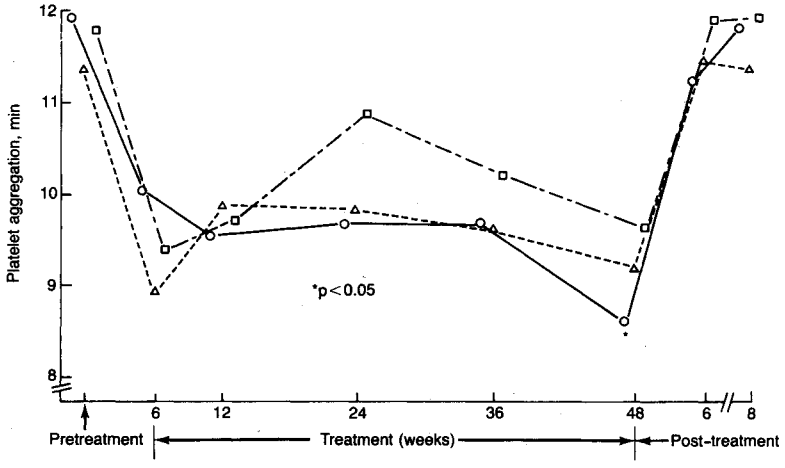

Fig. 7. Effect of oral contraceptives containing 50 and 30 μg estrogen on platelet aggregation (Chandler's tube method). Norethindrone acetate plus 50 μg estrogen, o——o; norethindrone acetate plus 30 μg estrogen, △ - - - △; levonorgestrel plus 30 μg estrogen, □ — — — □.

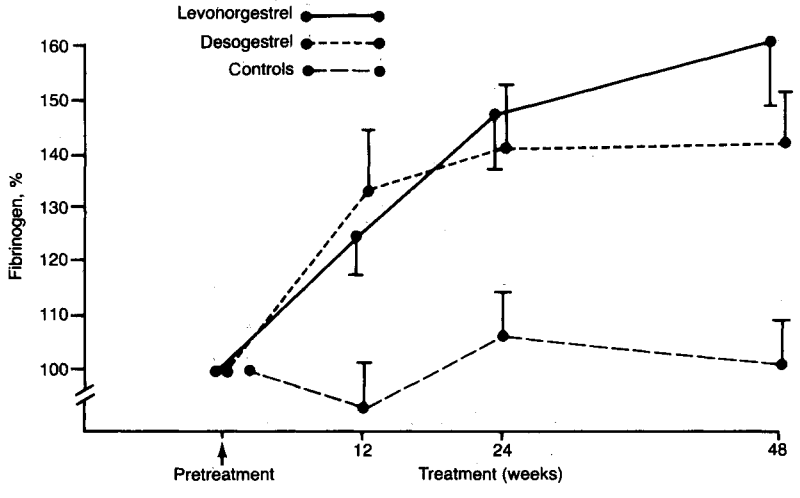

Fig. 8. Effects of levonorgestrel triphasic and desogestrel monophasic on fibrinogen.

Table IV. Comparative study of triphasic levonorgestrel and monophasic desogestrel

Formulation	*No. of patients*	*1 yr*
Levonorgestrel: 50-125 μg levonorgestrel combined with 30-40 μg ethinyl estradiol (triphasic formulation)	30	20
Desogestrel: 150 μg desogestrel and 30 μg ethinyl estradiol	36	13

gen dosages, but the increase with the 50 μg OC was significantly higher than that occurring with the two 30 μg preparations (Fig. 3). Similar results were noted with factor X. The least increase in factor X activity occurred with the levonorgestrel combination (Fig. 4). Levels of the coagulation inhibitor antithrombin III decreased significantly in patients who received 50 μg OCs and to a lesser extent with the 30 μg OCs that contained norethindrone acetate. In the group who received the 30 μg OC that contained levonorgestrel, antithrombin III levels did not significantly decrease until the forty-eighth week (Fig. 5).

The resting plasma fibrinolytic activity was significantly increased with 50 and 30 μg preparations, and the greatest increase was found with the 50 μg OC (Fig. 6). Fibrinolytic activity after venous occlusion also increased significantly with all three preparations.

Spontaneous platelet aggregation with the Chandler tube method showed that both the 50 and 30 μg formulations produced significant shortening of the ag-

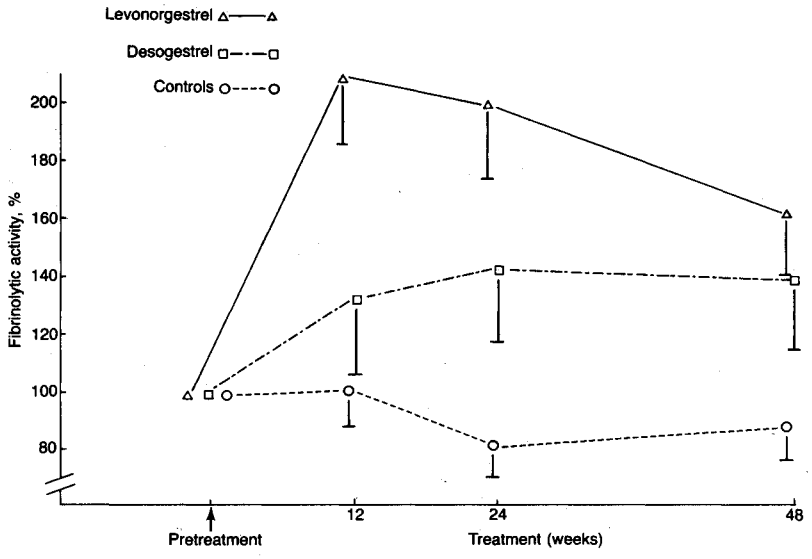

Fig. 9. Effects of levonorgestrel triphasic and desogestrel monophasic on fibrinolytic activity.

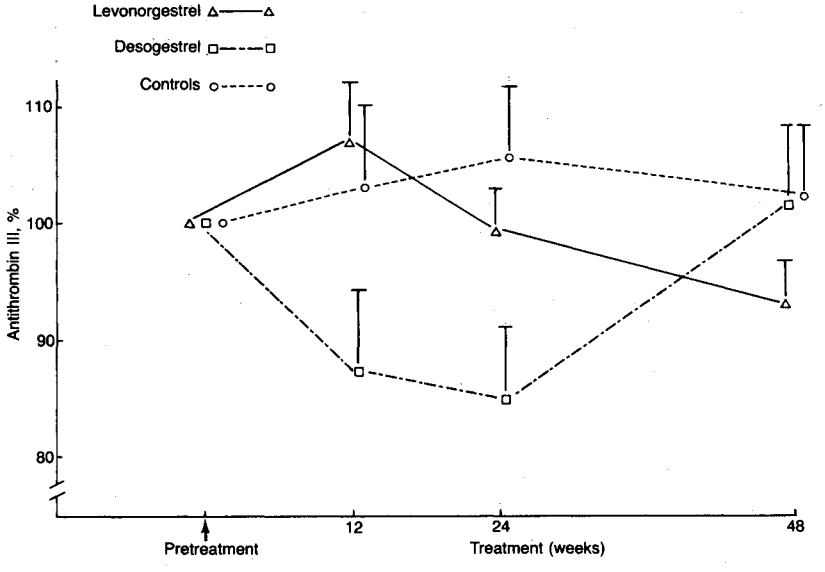

Fig. 10. Effects of levonorgestrel triphasic and desogestrel monophasic on antithrombin III (immunologic method).

gregation time, indicating enhanced platelet activity (Fig. 7).

These studies show that: (1) The effects of ethinyl estradiol on coagulation, fibrinolysis, and platelet function are related to dose, with 50 μg producing significantly greater changes than 30 μg; (2) the effects of 30 μg of ethinyl estradiol are modified by the progestogen that is used in combination.

Effects of different progestogens. Recently, we have compared the effects of triphasic levonorgestrel with monophasic desogestrel (Table IV). The effects of both combinations on fibrinogen are shown in Fig. 8. Fibrinolytic activity increased less with desogestrel than with triphasic levonorgestrel (Fig. 9). We also found that antithrombin III levels remained unchanged with triphasic levonorgestrel and decreased with desogestrel at 12 and 24 weeks on treatment but not at 48 weeks (Fig. 10).

In summary, these studies, which have compared 50 μg estrogen contraceptives with 30 μg estrogen contraceptives and different progestogens, show clearly that the changes in coagulation activity and fibrinolysis are related to the dose of estrogen and progestogen. The progestogen that is used in combination with low-

dose estrogen may potentiate or reduce the estrogen effects. The low-dose OC formulations in current use produce significantly less change in the hemostatic system than do preparations that contain 50 μg of estrogen. The estrogen/progestogen combinations also increase fibrinolytic activity, which most probably balances the increase in coagulation activity, thus preserving the dynamic equilibrium between coagulation and fibrinolysis.

Current research is aimed at finding low-dose formulations of estrogen/progestogen that will produce the least change in the hemostatic system and in other metabolic processes. This appears to be the most logical way of minimizing the risk of vascular complications and thus increasing the safety of oral contraception for the millions of women who use this method of fertility control.

I would like to thank Dr. Ali Sabra, Leisha Daly, and Eilis Carroll for their excellent teamwork in these research studies.

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Progestogen potency in oral contraceptive pills

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The most important target organs for combined oral contraceptive preparations are the anterior pituitary gland and the uterus. The long-term unopposed administration of estrogen produces endometrial hyperplasia and amenorrhea, which are unacceptable to most women and their medical advisors. Cyclic administration of progestogens in combination with the estrogen, however, produces predictable endometrial shedding and achieves a regular and acceptable bleeding pattern in most women. This was the main reason that the "delay of menses" test was adopted as the earliest clinical means of comparing the relative potencies of progestogens that were administered orally. Recently attempts have been made to compare the potency of progestogens on the other organ systems by the extrapolation of data derived from studies on the endometrium. This is inappropriate, inasmuch as the effects of progestogens and estrogens independently and in combination differ greatly depending on the target organ. In this article, the literature on this controversial subject is reviewed. (Am J Obstet Gynecol 1987;157:1048-52.)

Key words: Oral contraceptives, progestogen potency, delay of menses test, lipid metabolism

To appreciate fully the confusion that currently surrounds the concept of the potency of progestogen, it is necessary to know the early history of the combined oral contraceptive (OC).

History of the combination pill

The first 19-norprogestogen, norethisterone, was synthesized in October 1952, and the U.S. patent for the drug was filed a month later by Carl Djerassi on behalf of Syntex. In August 1953, nearly a year later, Frank B. Colton of Searle filed the patent for norethynodrel. Although it was known that norethynodrel was converted to norethisterone by weak acids and that this conversion almost certainly occurred in the stomach after ingestion, commercial reasons led to the choice of norethynodrel as the preparation that was used in the first studies of the OC pill. According to Vaughan,[1] the reason given for this decision was that norethisterone had been shown to produce testicular enlargement in rats, and it was feared that this compound might have masculinizing effects. However, Pincus, who played a

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