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review

Effects of Oral Contraceptives on Blood Coagulation: A Review

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Introduction

Reports on the association between thromboembolic complications and the ingestion of oral contraceptives resulted in large numbers of studies concerning the effect of estrogens and progestagens on coagulation and the fibrinolytic enzyme system. The data simulated the physiologic increase of coagulation factors in pregnancy. It was therefore assumed that in both instances of human pregnancy and pill users, the estrogen was responsible for such an increase. In turn this would explain the higher incidence of thromboembolic complications during the ingestion of oral contraceptives. Mammen (114) recently pointed out that three problems are responsible for the confusion. This refers to the concept of a hypercoagulable state, postulated to be a prethrombotic or thrombophilic state, hypothetic at best since at present no test system can predict a thromboembolic event. Furthermore, coagulation changes *in vitro* were interpreted as being reflective of a thromboembolic event *in vivo*. Finally, investigators using retrospective and prospective epidemiologic data, claimed a cause:effect relationship without considering physiologic principles.

A review of the data in the literature revealed large variations of study design and results. Many coagulation tests were used and appear not to be very well standardized. Thus, methodical errors were frequently observed.

The physiologic changes of the coagulation system in pregnancy were recently reviewed (24). The present paper is concerned with a review of the world literature regarding changes of the coagulation and fibrinolytic enzyme system in patients taking oral contraceptives. Since the data of this as well as that of our previous review on the physiology of pregnancy are evaluated in a similar fashion results may be deemed comparable.

Parameter of Coagulation and Fibrinolysis during the normal cycle

The few studies on the coagulation and fibrinolytic enzyme system, performed during the normal ovulatory cycle revealed conflicting data. During menstruation the recalcification time was decreased in one study (41), other investigators found the results of this test to be normal. Older data failed to show changes of the prothrombin time. The plasma fibrinogen concentration was found to be unchanged (20); others found a peak increase during ovulation and 4 to 5 days before menstruation (172). Fibrinolysis was increased during menstruation but fibrinogen breakdown products remained unchanged. Beller et al. (21) found no change of fibrinolytic components in peripheral plasma during the menstrual cycle. Inhibitors, especially α_2-antiplasmin and α_2-macroglobulin revealed a tendency to somewhat increased values during the secretory phase, but this was not statistically significant (176).

The only significant change was which increased toward ovulation time and decreased during the secretory phase (64, 92, 141, 144). The peak increase of the platelet number predictable was to such a degree that it was used some 20 years ago for prediction of ovulation (130).

The unaltered system indicates that cycle-induced changes can be disregarded. Variables during the ingestion of sex steroids must therefore be attributed to the pill.

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The Effect of Estrogen and Progestogen on the Coagulation and Fibrinolytic Enzyme System

Clotting Tests

A number of studies indicated a shortened clotting time (thromboelastogram, recalcification time or similar methods). However, since the test systems were not standardized, none allow the conclusion of a hypercoagulable state.

Platelet Number and Vessel Wall Interaction during Oral Contraceptives

It was suggested in one study that women who had taken oral contraceptives synthesized more

Platelet aggregation was found to be less inhibited in females using the pill (26, 58, 75, 118, 125), but there were conflicting results (82, 151, 162). The same is true for platelet adhesion which some researchers found increased (7, 40, 58, 133), while others observed normal control values (13, 75, 108, 125, 171). An increase of platelet release reaction, especially of platelet factor IV, was noted.

With a few exceptions the platelet number was found unaltered by most authors (7, 12, 82, 98, 108, 133, 157, 162). An increase in the secretion profile together with an increased volume of platelet granules, reduced the number in mitochondria. A decreased volume and surface of the open canicular system and an increased surface of the dense tubular system were noted in morphologic studies of long-term pill users (1).

Activation phase. Only one study is available on the concentration of factor XI (53). Factor XII concentration seems to be unaltered and this is also true for the few studies regarding factor XIII (2, 17, 158).

Factor I (plasma fibrinogen concentration). A uniform reaction was noted regarding plasma fibrinogen. Increased concentration was found in nearly all studies (Table 1). This increase was clearly dose dependent (21, 107, 166). One study noted no change when a pill with 30 μg estriol was used while an increase of 11 per cent was noted in another study (121).

Intrinsic system. With just one exception (99) a slight increase in the concentration of plasma prothrombin, as determined by using one-phase or two-phase methods, was noted by the majority of authors (9, 21, 36, 50, 83, 107, 118, 121, 171). An increased thrombin formation was also noted (95). Most authors found an increase in factor VII (Table 2). Factor X, a factor closely related to factor VII, revealed as expected similar data (Table 3).

Factor V. In the very few studies available an increase was noted (50, 115, 118, 129) but most results indicated unchanged results even after ingestion of very high doses of the pill (7, 32, 82, 101, 133, 153, 157).

Table 1. Effect of Estrogen and Progestogen Containing Oral Contraceptives on Fibrinogen Concentration

Hormone	Effect (%)	Reference No.
Estrogen		
50 μg ethynylestradiol or 100 μg mestranol	9 ↑	2
50–100 μg estrogen	13 ↑	17
50 μg estrogen	13 ↑	171
2.5 mg piperazine estrone sulfate		107
		13
Estrogen + progestogen		
9.85 mg norethynodrel		
50 μg Ethynylestradiol + 4 mg Norethisterone acetate		
Ethynyl estradiol + Norethindrone acetate	Significant ↑	6
50 μg Ethynylestradiol	15	
30 μg Ethynylestradiol	11 ↑	121
50 μg Ethynylestradiol + 1 mg Norethisterone	11 ↑	
50 μg Ethynylestradiol + 3–4 mg Norethisterone	21 ↑	
50 μg Ethynylestradiol + 0.5 mg Ethynylacetate + 0.1 mg mestranol	20 ↑ 6 ↑	107 166
Mestranol + norethynodrel		115
100 μg mestranol + 5 mg megestrol acetate		9
75 μg estranol + 5 mg Norethynodrel		31
Estrogen + progestagen		14
Ethynylestradiol + Quingestranol acetate		98
50 μg Ethynylestradiol + 150 μg Levonorgestrel	Significant (1 week)	
50 μg Ethynylestradiol + 1 mg Norethindrone acetate	Significant	129
30 μg ethynylestradiol + 0.15 mg D-norgestrel		182
50 μg Ethynylestradiol + 1 mg Norethindrone		4
35 μg Ethynylestradiol + 400 μg norethindrone		
Progestogen		
5 mg norethynodrel		53

TABLE 2 Factor VII concentration

Hormone	Effect (%)		Reference No.
Estrogen			
2.5 mg piperazine estrone sulfate			107
50 μg ethynylestradiol	45	↑	
30 μg ethynylestradiol	16	↑	
Estrogen + Progestogen			
50 μg ethynylestradiol + 1 mg norethisterone			
50 μg ethynylestradiol + 3–4 mg norethisterone	66		
7.5 μg mestranol			157
5 mg norethynodrel			
50 μg ethynylestradiol 1 mg norethindrone	60	↑	107
Norethynodrel + mestranol	31–48	↑	115
100 μg mestranol	27	↑	83
150 μg mestranol 9.85 mg norethynodrel	8	↑	21
100 μg mestranol + norethisterone (2 mg)	10–15	↑	150
100 μg mestranol + 5 mg megestrol	Significant	↑	9
Ethynylestradiol + Norethindrone acetate	Significant	↑	6
0.25 mg D-Norgestrel + 50 μg Ethynylestradiol	Significant	↑	34
Progestogen			
Norethisterone	10	↑	153

TABLE 3 Factor X concentration

Hormones	Effect (%)		Reference No.
Estrogen			
2.5 mg piperazine estrone sulfate			
Estrogen + progestogen			
100 μg mestranol + 2 mg norethindrone	17	↑	83
50 μg estrogen + progestagen	42	↑	121
100 μg mestranol + 2 mg norethisterone	10–100	↑	
50 μg estrogen + 30 μg estrogen	26	↑	21
Ethynylestradiol + norethindrone acetate	Significant	↑	6
45 μg Ethynylestradiol + 0.5 mg norethindrone	Significant	↑	7
30 μg Ethynylestradiol 0.15 mg D-norgestrel		↑	180
Progestogen			
40 μg Megestrol acetate (implant)			108
Norethisterone		↓	153

Factor VIII. In one of the first papers regarding coagulation changes under the pill (53) an increase was noted. This was confirmed by some authors (7, 98, 108, 115, 133) but others found a decrease or normal concentration (48, 50, 82, 83, 99, 114). The problem of unstandardized methods was obvious in this regard. On the basis of newer studies it is assumed that factor VIII is, indeed, increased.

Fibrinolytic system. Most investigators observed an increase in the concentration of plasminogen (Table 4). However, it is not clear whether this indicates an increased production rate or decreased consumption. Looking at data of test systems for fibrinolytic activity a number of investigators observed an increased (13, 17, 31, 80, 98, 166), and others noted no changed activity (86, 124). The activator concentration in the vessel wall was unchanged (133), whereas urokinase was found to be increased (13).

Antiplasmin activity was found to be normal, decreased (129), or increased (6, 86). In one case an increase of inhibitors against urokinase was noted (133, 182), but in another instance a decrease (13, 17) was noted. Fibrinogen breakdown products were noted to be present in small quantities (13) which would mean an increase when compared to normal. In most studies there were no fibrin(ogen) breakdown products demonstrated in the circulation.

One author found an increase after termination of pregnancy. Mink et al. (129) stated that estrogens have a more distinct effect on the fibrinolytic effect than progestogens.

Antithrombin III (AT III) alpha one antithrombin (α_1 AT) and alpha 2 macroglobulin (α_2 MG). AT III activity decreases shortly after the ingestion of oral contraceptives (95). The effect was dose dependent and not observed after progestogen intake. The data are summarized in Table 4. Newer data using a dose of 30 μg of ethynyl estradiol revealed no significant change. There is agreement that α_1 AT increased as a result of estrogens (2, 11, 81, 98, 103). An increase of α_2 MG of the acute-phase protein α_1 AT was less significant described by the same authors.

Effects of Biphasic and Triphasic Oral Contraceptives

Most studies on the coagulation system were performed on patients taking the fixed combination of estrogens and progestogens. The sequential regimen was rarely examined, where estrogens for a period of 6 to 10 days were followed by a fixed dose of estrogens and progestogens (179). Only two stud-

TABLE 4 Plasminogen concentration

Hormone	Effect (%)		Reference No.
Estrogen			
Mestranol			171
Ethynylestradiol			
17-β-estradiol or ethynylestradiol		↑	13
50 μg estrogen	23	↑	171
50 μg ethynylestradiol or 100 μg mestranol	13	↑	2
2.5 mg piperazine estrone sulfate	5	↑	107
Estrogen + Progestogen			
150 μg mestranol + 9.85 mg norethinodrel	42	↑	21
100 μg mestranol + 5 mg megestrol	68	↑	82
Mestranol + megestrol	47	↑	103
60 μg mestranol + norethynodrel	20–60	↑	132
75 μg mestranol + 5 mg norethynodrel	31	↑	31
Estrogen + progestagen	40–60	↑	11
100 μg mestranol + 0.5 mg ethynodiol acetate	24–30	↑	166
Ethynylestradiol + norethindrone acetate	Significant	↑	6
Ethynylestradiol + quingestanol acetate		↑	
35 μg ethynylestradiol + 400 μg norethindrone		↑	136
50 μg estrogen + progestogen	33	↑	7, 176
Progestogen			
5 mg Norethynodrel bzw.		↑	142
5 mg norethisterone		↑	
1 mg Norethisterone acetate	Significant	↑	

TABLE 5 Antithrombin III

Hormone	Effect (%)		Reference No.
Estrogen			
50 μg ethynylestradiol	8	↓	121
30 μg ethynylestradiol	5		
50 μg ethynylestradiol or 100 μg mestranol	6.5	↓	2
80 μg mestranol or 1.25 mg Premarin	28	↓	95
50 μg Ethynylestradiol	8.5	↓	52
Mestranol or ethynylestradiol	12	↓	17
50 μg estrogen	11	↓	171
17-β-estradiol		↓	13
20–35 μg Ethynylestradiol or 50 μg mestranol	Significant	↓	116
2.5 mg Piperazine estrone sulfate			107
Estrogen + Progestogen			
Estrogen + progestogen		↓	86
Estrogen + progestogen	9 (activity) 0 (immunol.)	↓	14
50–100 μg mestranol + 1–2 mg norethindrone			80
30 μg ethynylestradiol + 0.15 mg D-norgestrel			182
50 μg Ethynylestradiol + 0.75 mg lynestrenol	28	↓	30
0.5 mg lynestrenol	31		
35 μg ethynylestradiol + 400 μg norethindrone			136

ies concerned the newer biphasic or triphasic oral month intake of contraceptives. Some differences were found when the factors II and X after a 6 the first, second and the sixth treatment were compared against the pretreatment cycle. It is difficult to explain why an increase of plasma fibrinogen concentration was noted under the triphasic formulation but found lacking under the biphasic pill. The coagulation factors most strongly affected were factor VIII, von Willebrand's factor and factor VIII reactive protein. However, it should be noted that even within the framework of statistical changes these occurred in the normal range (33, 179). In another study an increase was noted in plasma fibrinogen concentration, factor VII, factor VIII, and factor X. The intake of the biphasic preparation showed the highest in- gh (129). crease.

Long-Time Related Effects

After 9 months Ambrus et al. (4) found various changes in the coagulation system which were not present after 2 years. In one study there was a significant increase of plasma fibrinogen as well as of the factors II and X after intake of 50 μg of ethynyl estradiol and 1 mg of norethindrone. Plasma fibrinogen concentration remained high up to 24 months; factor X had, however, returned to normal values at 1 year (3). When 50 μg of mestranol was used combined with 1 mg of norethindrone concentrate there was an increase after a 3-month intake for factors I, II, and VII which persisted for 6 months (128). No change was found when 0.5 mg of chlormadinone acetate was used.

In another study using 30 μg of ethynyl estradiol and 0.15 mg of D-norgestrel during a 12-month period there was normalization of platelets, but the plasma thromboplastin time and the fibrinogen breakdown products remained

Estrogens in Menopause

The first study of the effect of estrogen in menopause was performed under administration of 30 μg of mestanol daily. There was an increase of plasma fibrinogen concentration and α_1 AT with a decrease of activated plasminogen and AT III at 1 year. Fibrinogen breakdown products were not increased (22). When 1.25 mg of Premarin was used, factor VII and X were increased (43) and AT III was decreased (167).

Nonsteroidal estrogen preparation did not induce changes in factors II, VII, VIII, X, AT III, and α_2 MG (99). There was only a slow decrease of AT III and an increase of α_1 AT and factor VII but no change of factors VIII and IX during the intake of estradiol valerate and estriol (66).

Largelius et al. (101) confirmed previous assump-

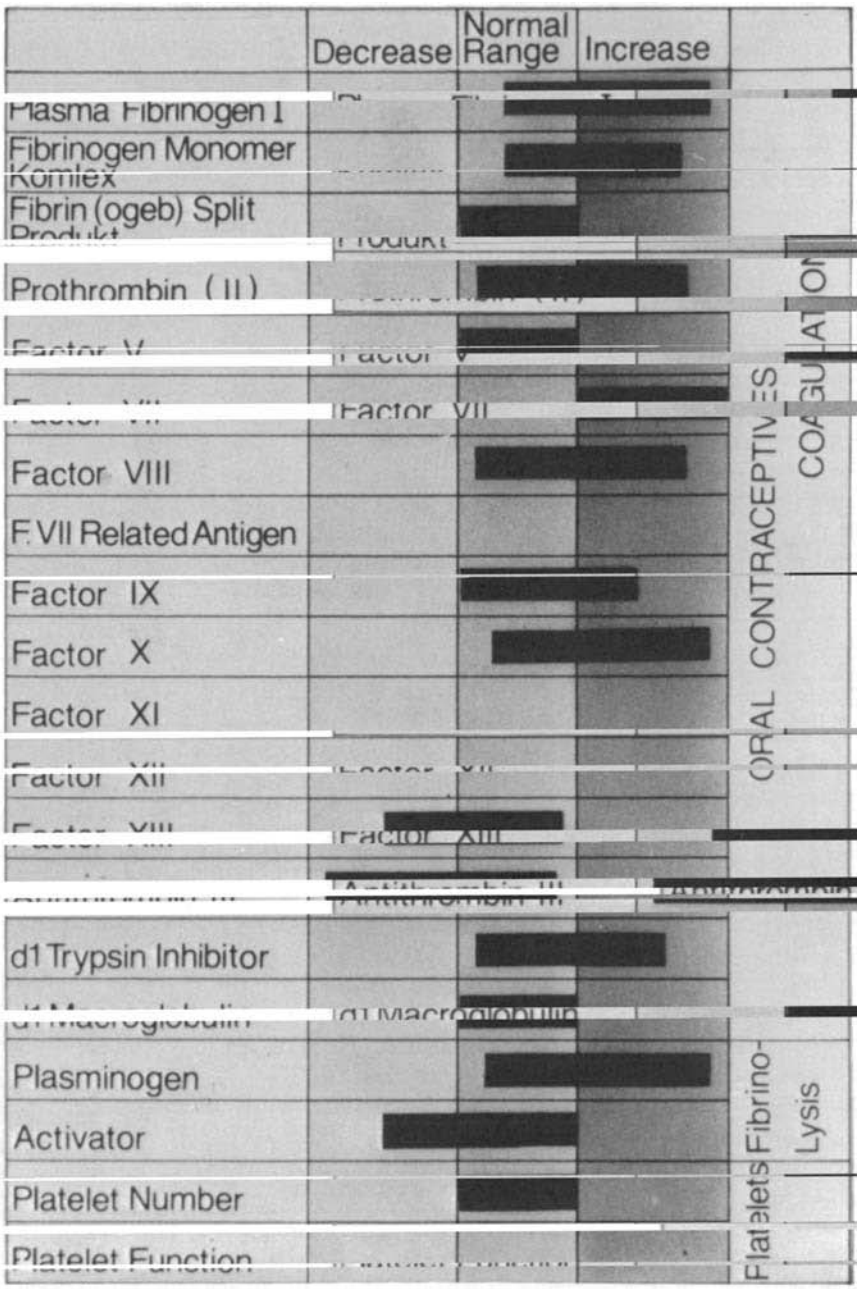

Fig. 1. Change of coagulation factors during pregnancy semischematic (used with permission from Ref. 1).

...tions that so-called natural estrogens produce... smaller effects than synthesized ones.

When Premarin (0.625 or 1.25 mg) was used together with medroxyprogesterone acetate there was no effect on coagulation system.

Some authors feel that postmenopausal women are less prone to thromboembolic complications than women in the reproductive age. But this assumption has to be clarified by studies with larger populations.

Estrogens above the dosage levels of 0.5 μg of ethinylestradiol induce effects in the coagulation and fibrinolytic enzyme system. Nearly all studies noted an increase in the plasma fibrinogen concentration, whereas factors II (prothrombin), VII, VIII, IX, X of the activation phase are not influenced. The same is true for platelet number, whereas platelet function is controversial. There is obviously a decreased ac-

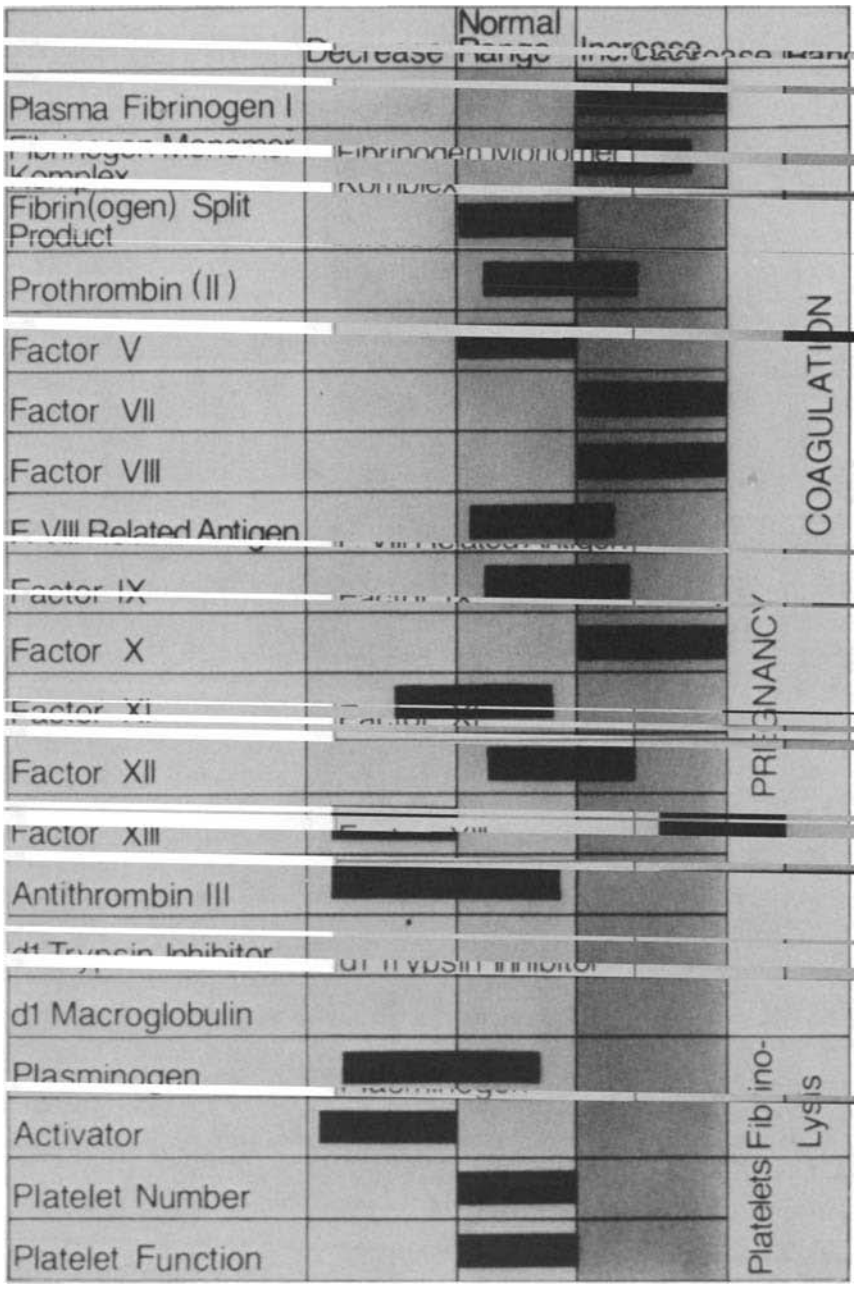

Fig. 2. Change of coagulation factors during ingestion of oral contraceptives.

tivity of the fibrinolytic enzyme system, predominantly related to activator activity. The effects are questionable in users of pills with an estrogen content of 0.3 μg of ethynylestradiol. There is little difference between monophasic, diaphasic, or triphasic preparations. There are no signs of induction of intravascular coagulation as the result of intake of the pill as judged by the lack of gamma-gamma dimers or free peptides a and b in the circulation. The existence of a hypercoagulable state is hypothetical at best. In this respect it is questionable as to whether the increase in concentration of coagulation factors can explain thromboembolic events associated with the use of oral contraception. Data to correlate the estrogen effect with smoking and age are lacking. If estrogens were such strong promoters of thromboembolic complications, many more women should be expected to become diseased since nearly all subjects demonstrated the effect with the higher doses. To explain thromboembolic events by the increase of coagulation factors is an unwarranted analogous conclusion.

Same data indicate that the increased coagulation factors return after months of normal use, although the individuals continue to take the pill. Data from estrogens alone, as well as from their use in the menopause, indicate that ethynylestradiol and mestranol are the steroids responsible for the coagulation effect. The so-called natural estrogens are effective only in high doses (1.25 mg), and nonsteroidal estrogens were inert. Presently the data available do not allow the conclusion that low dose progesterone has any effect on the coagulation system. This seems also to apply for the thromboembolic events. It should be considered therefore whether low dose progestogens can be used for patients with a history of thromboembolic disease.

In comparing the effects of oral contraception on coagulation and the fibrinolytic enzyme system with similar, physiological effects in pregnancy the concept was that in both instances the estrogens are responsible (Figs. 1 and 2). However, there are a number of obstacles against this concept. The increase in coagulation factors was not inducible in animals (138). When functional tests were used, i.e., activation of disseminated intravascular coagulation by endotoxin, disseminated intravascular coagulation was more pronounced in the gravid animal after a given dose than the nonpregnant animal prepared by estrogens and progestogen (23, 109). In humans thromboembolic complications in the puerperium are 10 times more frequent than in pregnancy. Therefore it occurs at a time when coagulation factors return or have already returned to normal (24). It remains to be seen to what extent thromboembolic complications will be reduced in users of pills containing 0.3 μg or less of ethynylestradiol.

The estrogen-induced change of coagulation factors is an interesting experimental model but its clinical significance is not yet clear.

Summary

A review of the data from studies of oral contraceptives on coagulation and the fibrinolytic enzyme systems reveal an increase of a variety of coagulation factors. This is dose dependent and related to estrogens and appreciable above a dose of 0.5 μg of ethynylestradiol. Smaller amounts are less effective or not at all active. The mechanism of this increase is unknown. The pathophysiological significance is not yet clear. There is no available data that associate the increase of coagulation factors with disseminated intravascular coagulation. Conclusive evidence that low dose progesterone has any effect on the coagulation system is lacking.

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