Comparative studies of 30 μg ethinyl estradiol combined with gestodene and desogestrel on blood coagulation, fibrinolysis, and platelets

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An association between an increase in the incidence of thromboembolic disease and the use of combined oral contraceptives has been shown by several epidemiologic studies. Evidence of the vascular complications of oral contraceptives suggests that venous thromboembolism correlates with estrogen dosage and arterial complications with both estrogen and progestogen components. In 60 healthy, randomly allocated women, the effects of ethinyl estradiol, 30 μg, combined with gestodene, 75 μg, and desogestrel, 150 μg, on blood coagulation, fibrinolysis, and platelet function were compared. Subjects were studied before oral contraceptive use, at 12, 24, 36, and 48 weeks of treatment, and at 6 and 12 weeks after treatment. Both oral contraceptives affected the hemostatic system, but our results indicate that the ethinyl estradiol/gestodene combination causes changes in the hemostatic system similar to those in the ethinyl estradiol/desogestrel combination. Factors VII and X activity were slightly higher with the ethinyl estradiol/desogestrel combination than with the ethinyl estradiol/gestodene combination, possibly reflecting a greater estrogenic effect. (AM J OBSTET GYNECOL 1990;163:430-7.)

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Since the introduction of oral contraceptives in the early 1960s, several epidemiologic studies have reported an association between their use and an increased risk of vascular disease. The main vascular complications are venous thromboembolic disease, myocardial infarction, and hemorrhagic and thrombotic strokes. This risk appears to have decreased in parallel with a reduction in the estrogen content. The progestogen component of the pill modifies the estrogen effects on blood coagulation and may contribute to the increased risk of stroke and ischemic heart disease. New formulations of oral contraceptives have recently been introduced containing low doses of estrogen in combination with new progestogens. This study is designed to examine the effects of two new combined oral contraceptives on blood coagulation, fibrinolysis, and platelet function. These pills contain 30 μg of ethinyl estradiol, in combination with gestodene or desogestrel, in monophasic formulations.

Material and methods

Subjects. Sixty healthy women who were between the ages of 18 and 34 years with no contraindications to estrogen/progestogen therapy took part in the study. Women who smoked 15 cigarettes or more per day were excluded. Subjects were randomly allocated to two groups: (1) group 1: 30 women taking Femodene, containing 30 μg of ethinyl estradiol + 75 μg of gestodene, 21 tablets per cycle, and (2) group 2: 30 women taking Marvelon, containing 30 μg of ethinyl estradiol + 150 μg of desogestrel, 21 tablets per cycle.

Method and timing of blood collection. Venous blood specimens were taken between 10:00 AM and noon each morning in the control cycle and thereafter at 12, 24, 36, and 48 weeks of treatment and at 6 and 12 weeks after hormone treatment. In the pretreatment cycle, blood samples were taken between days 21 and 24 of the cycle. In the treatment cycles blood samples were taken between days 21 and 24 of the cycle. In the treatment cycles blood samples were taken between days 15 and 21 of tablet administration.

Laboratory methodology. Prothrombin time, activated thromboplastin time, factor VII activity, and fibrinogen were assayed by standard laboratory techniques. Specific chromogenic substrates were used to assay plasminogen, antithrombin III, factor X, anti-Xa, and antiplasmin. Plasminogen activator was measured by means of the euglobulin precipitate and the fibrin plate technique. The Chandler tube method was used to measure thrombin-induced platelet aggregation, and platelets were counted with a Thrombocounter. Prothrombin clotting time, factor VII, activated thromboplastin time, platelet aggregation, platelet count, and fibrin plate assay were car-
ried out within 1 hour of venipuncture. Factor X, anti-Xa, antiplasmin, plasminogen, antithrombin III, and fibrinogen were assayed on fresh-frozen plasma stored at −20°C.

**Statistical analysis.** The null hypothesis was that both oral contraceptives were equal with respect to the hemostatic parameters that were measured. The alternative hypothesis was that with a sample size of 30 women in each treatment group, a type I error of α = 0.05, and a test power of 1 − β = 0.90, a t test would detect a difference of Δ = 0.8*σ. The maximal increase or minimal decrease in the treatment phase was analyzed with an analysis of covariance (covariate = prevalue as covariate at α = 0.05). Similarly, the values of 12 weeks after treatment were analyzed with an analysis of covariance with the prevales as covariate at α = 0.05. Descriptive statistics (average, minimum, maximum, percentage averages, and box plots) (Fig. 1) were computed for all variables. Student t tests were used to determine the level of significance of the observed changes within the groups.

**Results**

**Coagulation system**

*Prothrombin time.* There was no observable difference between treatments in the treatment and posttreatment phases (p > 0.05). The maximal increase has a positive slope β = 0.05; Fig. 2 shows a stable progression of the average time curve.

*Activated partial thromboplastin time.* There were no observable differences between treatments in the treatment and posttreatment phases (p > 0.05). The maximal increase over the treatment phase has a negative slope β = −0.17; Fig. 3 shows a slight decrease in the average time curve.

*Factor VII.* Factor VII clotting time was decreased at 12, 24, 36, and 48 weeks in women taking either the desogestrel or the gestodene combination, which indicated an increase in factor VII activity (p < 0.001); the decrease was slightly greater in those women taking the desogestrel combination. There was no observable difference between treatments in the treatment and posttreatment phases (p > 0.05). The maximal increase over the treatment phase has a positive slope β = 0.34 (p < 0.05), but Fig. 4 shows a decrease in the average time curve.

*Factor X.* Factor X was increased at 12, 24, 36, and 48 weeks in women taking either the desogestrel or the gestodene combination, which indicated an increase in factor VII activity (p < 0.001); the increase was slightly greater in the desogestrel group. Factor X activity 6 weeks after treatment was decreased from that at 48 weeks while receiving treatment. There was no observable difference between treatments in the treatment phase (p > 0.05), but 12 weeks after treatment there was a difference between the two treatment groups (p < 0.05). The level of factor X for the desogestrel group was higher than that for the gestodene group. The maximal increase over the treatment phase has a positive slope β = 0.14; Fig. 5 shows a slight increase in the average time curve.

*Antithrombin III.* Antithrombin III levels were decreased at 36 weeks in women taking either combination (p < 0.01). At 6 weeks after treatment, the antithrombin III levels of both groups had returned to within the normal range. There were no observable differences in antithrombin III levels between treatments in the treatment and posttreatment phases (p > 0.05). The minimal decrease over the treatment phase has a positive slope β = 0.38; Fig. 6 shows a stable progression of the average time curve.

*Anti-Xa.* There was no observable difference between treatments in the treatment and posttreatment phases (p > 0.05). The minimum decrease over the treatment phase has a negative slope β = −0.11; Fig. 7 shows a slight decrease in the average time curve.

**Fibrinolytic system**

*Plasminogen.* Plasminogen levels at 12, 24, 36, and 48 weeks in women taking either the desogestrel or the gestodene combination were assayed on fresh-frozen plasma stored at −20°C.

**Explanation of the box-plots**

- Case reports: extreme values further than one box length from Q 75
- Maximum within 3 box lengths
- 75% quartile
- Mean value
- 50% quartile = median
- 25% quartile
- Minimum within 3 box lengths
- ≥ 25% quartile − 1 box length
- Case reports: extreme values at least one box length below Q 25

Fig. 1. Description of box plots.
Fig. 2. Effects of gestodene and desogestrel on prothrombin time.

Fig. 3. Effects of gestodene and desogestrel on activated partial thromboplastin time.

Fig. 4. Effects of gestodene and desogestrel on factor VII.
Fig. 5. Effects of gestodene and desogestrel on factor X.

Fig. 6. Effects of gestodene and desogestrel on antithrombin III.

Fig. 7. Effects of gestodene and desogestrel on anti-Xa.
weeks were increased by both pills ($p < 0.001$). There was a difference between treatments in the treatment phase ($p < 0.05$), and there was no difference between treatments 12 weeks after treatment ($p > 0.05$). The plasminogen level was higher in the gestodene group than in the desogestrel group. The maximal increase over the treatment phase has a positive slope $\beta = 0.08$; Fig. 8 shows a slight increase in the average time curve.

Antiplasmin. There was no observable difference between treatments in the treatment phase ($p > 0.05$), but there was a difference between the two treatment groups 12 weeks after treatment ($p < 0.05$). The antiplasmin level was higher in the desogestrel group than in the gestodene group. The maximal increase over the treatment phase has a negative slope $\beta = -0.33$; Fig. 9 shows a slight decrease in the average time curve.

**Fibrinogen.** Fibrinogen levels increased with both pills ($p < 0.01$) and returned to pretreatment levels after treatment. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase over the treatment phase has a positive slope $\beta = 0.24$; Fig. 10 shows a slight increase in the average time curve.

**Fibrinolytic activity.** Fibrinolytic activity increased from 12 weeks on treatment in both groups ($p < 0.001$). During treatment increased fibrinolytic activity was sustained and rapidly returned to pretreatment levels 6 weeks after the pill was stopped. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase over the treatment phase has a positive slope
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Fig. 10. Effects of gestodene and desogestrel on fibrinogen.

Fig. 11. Effects of gestodene and desogestrel on fibrinolytic activity.

\[ \beta = 0.22; \text{ Fig. 11 shows a slight increase in the average time curve.} \]

**Platelets aggregation.** Platelet aggregation was decreased in both groups and the decrease was greater in the desogestrel group \((p < 0.001)\) than in the gestodene group \((p < 0.01)\). There was no observable difference between treatments in the treatment and posttreatment phases \((p > 0.05)\). The minimal decrease over the treatment phase has a slope \( \beta = 0.20 \), but Fig. 12 shows a slight decrease in the average time curve.

**Platelet count.** There was no observable difference between treatments in the treatment and posttreatment phases \((p > 0.05)\). The maximal increase over the treatment phase has a slope \( \beta = 0.00 \); Fig. 13 shows a stable progression in the average time curve.

**Comment**

The new low-dose estrogen/progestogen oral contraceptives induce major changes in the coagulation and fibrinolytic systems and in platelet function. The prothrombin time and activated partial thromboplastin time, which measure the overall activity of the extrinsic and intrinsic coagulation pathways, respectively, showed no significant changes with both oral contraceptive formulations. This indicates that the overall effects of the new pills are less than what occurs with the 50 \( \mu \)g pills that induce significant changes in these tests. Likewise, changes in the coagulation system with respect to factor X, antithrombin III, and platelet aggregation are not as marked with the new low-dose monophasic oral contraceptives as with those previously studied that contained 50 \( \mu \)g of estrogen.
gen/progestogen pills increased significantly the activity or factors VII and X, and the greater increase with the desogestrel pill suggests this combination has a greater estrogenic effect. Plasminogen and fibrinolytic activity were markedly increased by both hormonal preparations, and this enhancement of fibrinolysis is likely to counteract the increase in fibrinogen and coagulation activity that protects the dynamic balance between coagulation and fibrinolysis. Platelet aggregation was decreased by both pills and more so by the desogestrel combination. This would seem to be an undesirable effect.

The low-dose oral contraceptives with the new progestogens studied induce marked changes in the hemostatic system, in particular, enhanced activity of factors VII and X and acceleration of platelet aggregation. These changes in the physiology of hemostasis suggest that these new pills will also carry a thrombogenic hazard in susceptible women. The effects on hemostasis arise from the overall estrogenic activity, which is determined by the progestogen used in combination with the estrogen. More research is required to find whether effective combinations can be obtained that will induce fewer changes in the hemostatic system and other physiologic processes. Meantime, it would be unwise for any claims to be made that oral contraceptives with the new progestogens, gestodene and desogestrel, will be free of vascular complications.

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REFERENCES