

**Perspective**

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# Visualization of The Procoagulant Effects of Combined Oral Contraceptives (COCs)



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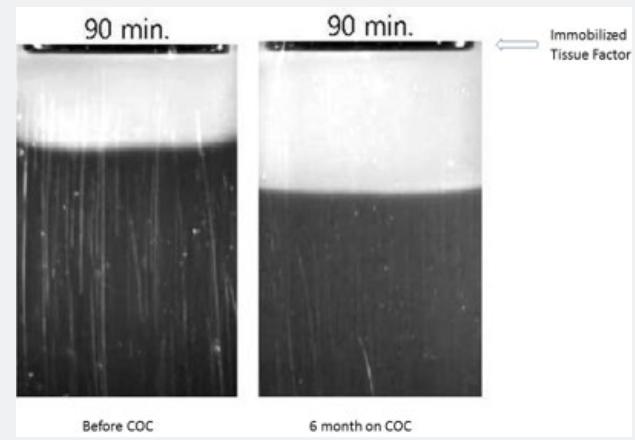
**Abbreviations:** COC: Combined Oral Contraceptives; VTE: Venous Thrombotic Embolism; APC: Activated Protein C

## Introduction

It is well established that the use of oral contraceptives increases the risk of venous thromboembolism. Attempts to understand the underlying mechanisms have resulted in documentation of changes in many specific haemostatic factors. The changes related to the thrombosis risk have not been established and prevented validated evaluation of new COCs for thrombosis risk before exposing large groups of women and evaluating clinical effects, i.e. venous thrombotic embolism (VTE) [1].

An obvious approach of laboratory analysis would have been to use global haemostatic assays. It has been documented that the global clotting assay APTT becomes shorter compatible with an increased potency of the system to clot, and thereby disclose an increased coagulation activating potential. However, this variable is not robust, and changes are small [2]. Another global coagulation test for the inhibitory potential of coagulation inhibition, the APC-resistance test, was more successfully applied and showed a reduced inhibition potential during COC-use [3]. APC-resistance, therefore has been considered one of the beacons in evaluation of VTE risk of COCs. A test for thrombin formation showed between 18 and 31% increases [4-6]; this test reveals thrombin formation during the presence of the clot.

Recently, a new pharmacodynamic method for coagulation activation potential has been developed. Unlike previous global clotting tests, this test evaluated the increase (volume) of the fibrin clot. This was a lacuna in *in-vitro* analysis of humans, while frequently employed in experimental thrombosis models in animals.



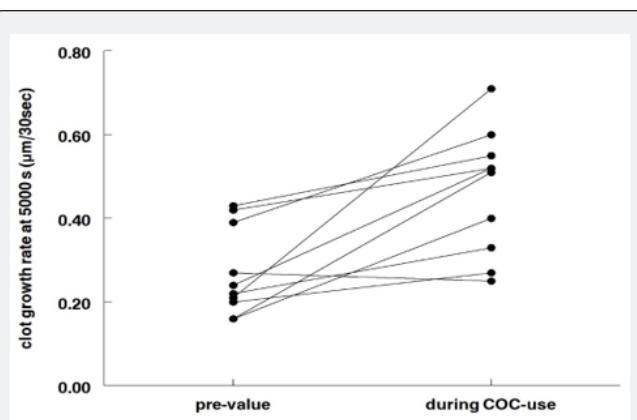
**Figure 1:** Clot view. The clot after 90 minutes in the thrombodynamics analyzer (Hemacore ®) is shown for a volunteer before use of COCs and after 6 month use. In this system the clot is growing from a surface with immobilized Tissue Factor (top of the cuvette) into the cuvette with plasma.

In Figure 1, it can be clearly seen that after a fixed period the clot during COC-use is larger.

## Results

We tested the growth in 10 apparently healthy young women (age 18-35y) with the same regimen of 6 month use of a third generation COC of 30 µg Ethinyloestradiol/150 µg Desogestrel, from a larger study [7]. The size of the clot after 5000 seconds was on average (median) 27% (range 14-46%) larger during COC-

use. The growth rate at 5000 seconds, showed for the individuals in Figure 2, was more clearly increased with a median of 71% (range 59-143%). Next to the increases a substantial range in effect can be seen. The values of clot size and growth rate during COC-use were for 5 of the 10 cases above the highest pretreatment value of the small study sample.



**Figure 2:** Individual changes in clot growth rate at time point 5000 secs (in  $\mu\text{m}/30\text{sec}$ ) for 10 women from before the start and to after 6 months of COC-use.

## Conclusion

This method to assess coagulation activity potential, expressed in clot size and growth rate, might be a valuable beacon together with the global inhibitor test to evaluate effects of COC in small groups and characterize old and new oral contraceptives.



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A next step of validation would be to test the combination of clot size/growth and APC-resistance in several cohorts with different contraceptives where the VTE risk is known.

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