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CASE REPORT

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Thrombin generation in a woman with heterozygous factor V Leiden and combined oral contraceptives: A case report

Maxime G. Zermatten MD | Debora Bertaggia Calderara PhD | Alessandro Aliotta MSc | Lorenzo Alberio MD

Division of Haematology and Central Haematology Laboratory, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland

Correspondence
Lorenzo Alberio, Division of Haematology and Central Haematology Laboratory, Lausanne University Hospital, CHUV BH 09 752, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland.
Email: lorenzo.alberio@chuv.ch

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Abstract

Combined oral contraceptives and factor V Leiden mutation are multiplicative risk factors for venous thromboembolism. However, it remains unknown whether this multiplicative effect is reflected in thrombin generation assays. We report here the evolution of the thrombin generation profile while taking combined oral contraceptives and after their discontinuation in a woman with heterozygous factor V Leiden mutation. The proband exhibited a distinctly prothrombotic thrombin generation profile including markedly decreased thrombomodulin (TM) sensitivity, compared to the control population. This profile possibly reflected a high thrombotic risk. After discontinuation of combined oral contraceptives, thrombin generation and TM sensitivity improved greatly, leaving only a slightly prothrombotic profile. Therefore, the multiplied thrombotic risk occurring with simultaneous combined oral contraceptives and factor V Leiden mutation is reflected by a thrombin generation assay performed without and with TM. This could be a promising tool to identify women taking combined oral contraceptives at high risk for venous thromboembolism. Further studies are needed to verify this hypothesis.

KEYWORDS

contraception, factor V, thrombin, thromboembolism, thrombosis, venous

Essentials

- We report thrombin generation in a woman with factor V Leiden taking combined oral contraceptives.
- The thrombin generation profile improved greatly after discontinuation of combined oral contraceptives.
- Thrombin generation reflects the multiplicative effect of combined oral contraceptives and factor V Leiden mutation.
- Thrombin generation may be a promising tool to identify women at high thrombotic risk taking combined oral contraceptives.

1 | INTRODUCTION

Women taking combined oral contraceptives are at increased thrombotic risk.[1,2] This is due to increased levels of fibrinogen; coagulation factors II, VII, VIII, and X; and decreased levels of antithrombin and protein S.[3] The increased levels of factor VIII and decreased levels of protein S lead to an acquired protein C resistance.[4,5] Some genetic polymorphisms add to the thrombotic risk. Factor V Leiden mutation

is the most frequent genetic thrombotic risk factor in Caucasians, particularly in Europe.[6] It consists of a single point mutation in the factor V gene (guanine to adenine in position 1691), leading to a resistance to activated protein C and thus to an increased thrombotic risk.[6] The simultaneous presence of a combined oral contraceptive and factor V Leiden mutation has a multiplicative rather than just an additive prothrombotic effect in clinical studies.[7] However, it remains broadly unknown whether this may be visualized by in vitro thrombin generation. We report here the evolution of thrombin generation profile with and without combined oral contraception in a 30-year-old woman carrying a heterozygous factor V Leiden mutation.

2 | CASE REPORT

A healthy 30-year-old woman was recruited as proband for the pilot phase of the validation of a new fully automated, standardized, and normalized thrombin generation assay, ST Genesia Thrombin Generation System (Stago, Asnière-sur-Seine, France) and reagents ThromboScreen (Stago). In this assay, thrombin generation is measured in the absence and in the presence of thrombomodulin (TM) as a protein C/S system activator. Different parameters were measured, which are listed in the legend of Figure 1 and in Table S1.

The in vitro thrombin generation profile of the woman (Figure 1 and Table S1) was strongly increased in comparison to the rest of the control population (healthy subjects without any medication including combined oral contraception, a personal or family history of thrombohemorrhagic events, or a known pregnancy). In the absence of TM, the velocity index and the peak height of the proband were much higher than in the control population. However, she exhibited an endogenous thrombin potential (ETP) within normal range. In the presence of TM, the velocity index was even higher and the peak height was only slightly decreased compared to the values measured in the absence of TM. Again, these 2 parameters were much higher than in the control population. The ratio of peak height with and without TM was higher than in the control population as well. Of note, the ETP was still within normal ranges, but its TM-mediated inhibition was much lower than observed in the rest of the control population, indicating a protein C resistance (Table S1). Taken together, the proband exhibited a distinctly increased thrombin generation profile with decreased TM-mediated inhibition, which may represent a severe prothrombotic state (see Discussion).

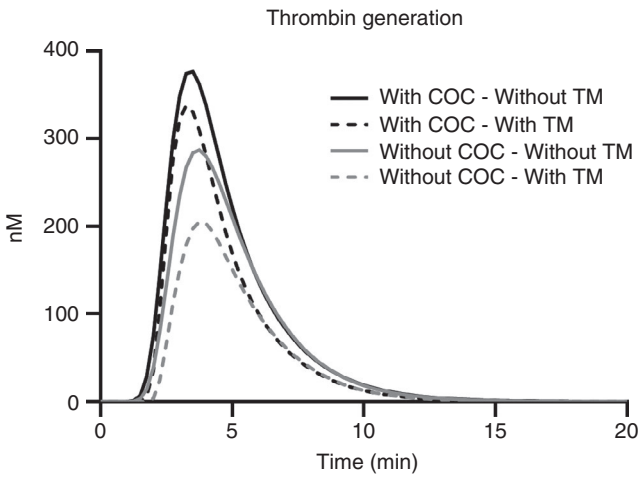

FIGURE 1 Thrombin generation profiles without (continuous lines) and with (interrupted lines) thrombomodulin (TM) before (black lines) and after discontinuation (gray lines) of combined oral contraceptive (COC) in the reported woman. Different parameters are measured by the assay: time until thrombin generation (lag time), maximal concentration of thrombin (peak height), thrombin generation velocity (velocity index), endogenous thrombin potential (ETP; area under the curve of thrombin generation, representing the total amount of thrombin generated) and the TM-mediated inhibition [$(ETP_{-TM} - ETP_{+TM})/ETP_{-TM}$, reflecting the function of the protein C/S system]

To investigate this incidentally diagnosed laboratory prothrombotic profile, history was recorded. The woman had a fully negative personal and familial medical history for venous thromboembolism or other thrombotic events. She had 2 pregnancies without complications and and had given birth to 2 healthy children. She was not pregnant, not breastfeeding, and was in good general condition at the time of blood collection. She was under no medical treatment except a combined oral contraceptive with cyproteron (2 mg) and ethinylestradiol (35 µg). She had been taking combined oral contraceptives for 8 years, from 18 to 26 years of age, and again for the past 18 months. She reported no other risk factors for venous thromboembolism.

Because of the severely increased thrombin generation, further laboratory analyses were performed. She was negative for antiphospholipid antibodies. Antithrombin activity, protein C activity, and free protein S antigen were within normal ranges: 128%, 135%, and 60%, respectively. No prothrombin gene mutation was found. However, a heterozygous factor V Leiden mutation was revealed.

On the basis of history and laboratory analyses, we interpreted the severely increased thrombin generation profile in the frame of the association of combined oral contraceptive and factor V Leiden mutation.

After discussing the thrombotic risk linked to the combination of combined oral contraceptives and factor V Leiden[1,2,7] as well as the laboratory thrombin generation profile, which potentially reflected a prothrombotic state, the woman decided to discontinue the combined oral contraceptive. Thrombin generation was performed again 8 months after discontinuation of the combined oral contraceptive (Figure 1 and Table S1). Velocity index and peak height with and without TM as well as the ratio of peak height with and without TM decreased and were now within reference ranges. Of note, TM-mediated inhibition of the ETP had markedly increased and resulted within the lower limit of the reference range.

In summary, the proband exhibited a severe prothrombotic laboratory profile due to both combined oral contraceptive and factor V Leiden mutation. After discontinuation of the combined oral contraceptive, the prothrombotic profile improved significantly.

3 | DISCUSSION

Combined oral contraceptives and factor V Leiden mutation are multiplicative thrombotic risk factors.[7] The various combined oral contraceptives confer a different thrombotic risk depending on their progestin content.[8,9] We report here the thrombin generation profile of a woman with heterozygous factor V Leiden mutation with and without combined oral contraception (cyproteron and ethinylestradiol). The contraception with cyproteron and ethinylestradiol is known to carry a high risk of venous thromboembolism.[2,9]

In the proband, thrombin generation was strongly increased while taking a combined oral contraceptive compared to the profile observed after its discontinuation, suggesting a possibly severe prothrombotic state. The major prothrombotic alterations under combined oral contraception were an increase of velocity index and peak height as well as a decrease of TM-mediated ETP inhibition. Of note, ETP was within normal limits both under combined oral contraception and after its discontinuation. These analyses are in line with previous studies investigating thrombin generation and activated protein C resistance in women taking combined oral contraceptives. These studies reported increased ETP,[10,11] decreased sensitivity to activated protein C[12,13] (reflected here in the decreased TM-mediated ETP inhibition), and increased peak height.[12] Interestingly, when the proband was taking a combined oral contraceptive, the velocity index increased after addition of TM, while after discontinuation of the combined oral contraceptive, the velocity index tended to decrease. This is possibly due to the decreased protein S induced by combined oral contraception.[3] Indeed, Tripodi et al.[14] also observed an increasing velocity index after addition of TM in patients with protein S deficiency. Based on the extent of the alterations observed in the proband, the thrombin generation profile generated by the ST Genesia Thrombin Generation System appears to detect the multiplicative effect of the coexistence of these 2 risk factors.

Of note, although the ETP is the thrombin generation parameter most frequently analyzed and reported, velocity index and peak height are probably more sensitive biomarkers of hypercoagulability than ETP itself in the presence of both combined oral contraceptives and factor V Leiden mutation (Table S1). A similar observation has been already made by our group and others in other populations.[15–17] It is therefore important to analyze the whole thrombin generation profile and not to focus only on ETP.

What if the woman had not participated in the study? Would she have suffered a thromboembolic event later? The fact that she had a fully negative personal and family history of venous thromboembolism questions the predictive value of the observed severe laboratory prothrombotic profile for the occurrence of venous thromboembolism in women taking combined oral contraceptives. Moreover, some data indicate that the risk of venous thromboembolism in women with factor V Leiden mutation and combined oral contraceptives is far lower than the risk observed during pregnancy and postpartum.[18] Nevertheless, the woman, a physician, after considering the pros and cons, decided to discontinue the combined oral contraceptive. Based on the thrombin generation profile and its evolution after discontinuation, this decision seems to be rational and congruent with an increasing body of evidence for the role of global coagulation assays in identifying a hypercoagulable state and possibly predicting thrombotic risk.[19] Further prospective studies investigating thrombin generation and risk of venous thromboembolism should be performed to assess whether thrombin generation can identify women taking combined oral contraceptives at high thrombotic risk, who would benefit from an alternative contraception. This could improve the safety of combined oral contraceptive users.

Testing for factor V Leiden in her young children was not advised because of the absence of immediate consequences. However, no clear evidence-based recommendation exists yet to clarify whether the woman's daughter should be tested in the future in case of combined oral contraceptive prescription or in case of desire for pregnancy.[20]

Of note, the major limitation of this case report is that blood collection was not repeated while the proband was taking a combined oral contraceptive to assert the reproducibility of the measure. However, the biological reproducibility of the assay as well as the analytical reproducibility of ST Genesia in our laboratory is very good (see Table S3), the thrombin generation results were coherent with the presence of a combined oral contraceptive and factor V Leiden mutation, and no potential influencing factor (particularly no other medication and no recent infection) could be identified. Therefore, we believe that the data presented here are reliable.

The novelty of our case report is the observation that thrombin generation studies performed with and without TM appear to identify the prothrombotic profile known to be induced by the presence of combined oral contraceptives and heterozygous factor V Leiden. However, to assess its clinical significance, this observation needs to be confirmed in additional subjects with these risk factors in various combinations and different outcomes.

In conclusion, we reported here a severely increased thrombin generation profile in a woman with heterozygous factor V Leiden mutation while taking a combined oral contraceptive and a marked improvement of the prothrombotic laboratory profile after its discontinuation. Thrombin generation could be a promising tool to identify women taking combined oral contraceptives possibly at high risk for venous thromboembolism. Further studies are needed to investigate this hypothesis.

RELATIONSHIP DISCLOSURE

The authors declare nothing to report.

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AUTHOR CONTRIBUTIONS

MGZ performed research. MGZ and LA wrote the manuscript. DBC and AA helped perform laboratory analyses and revised the manuscript. All the authors read and approved the final version of the manuscript.

ORCID

Maxime G. Zermatten https://orcid.org/0000-0002-9298-8268
Debora Bertaggia Calderara https://orcid.org/0000-0002-9756-4974
Alessandro Aliotta https://orcid.org/0000-0002-9382-138X
Lorenzo Alberio https://orcid.org/0000-0001-9686-9920

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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