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Editorial and Views

APC resistance, oral contraceptive therapy and deep vein thrombosis: settled and unsettled problems

The relationship between oral contraceptive therapy (OCT) and deep vein thrombosis (DVT) in normal women and in women with congenital deficiencies of coagulation inhibitors has drawn a lot of attention in recent days.[1-6] It is widely accepted that women with congenital defects of coagulation inhibitors are particularly prone to thrombotic complications. Patients with factor V Leiden are often also included in this group.[1,5]

In our experience, the factor V Leiden defect does not seem to be so severe as to justify the claims and suggestions made in some papers.[1,5]

Papers dealing with the subject and those suggesting that even homozygous patients can remain asymptomatic after OCT must also be taken into account.[7,8]

In our series of 5 homozygous patients with 6 courses of OCT (one patient underwent two courses of OCT about 23 years apart) only two patients had DVT and in both instances concomitant acquired risk factors were present (Table 1). Furthermore, there seems, from our data, to be no difference in the prevalence of OCT-induced DVT between homozygous and heterozygous patients with this abnormality.[8] The only difference was an earlier onset, after a shorter number of cycles, of DVT in homozygotes as compared to heterozygotes (3.0 cycles vs 14.1 cycles).

It is interesting to note that the mean number of cycles needed to *cause* a venous thrombosis in the heterozygous was similar to that seen in normal women (13.0 cycles) (Table 1). This seems to suggest that venous thrombosis in these patients has little, if anything, to do with the factor V Leiden defect.

Some patients, both homozygotes and heterozygote remained asymptomatic even after up to 4 years of continued OCT.[8]

We are convinced that the defect is mild and that additional triggering factors have to be present for DVT to develop during oral contraception. That the defect is mild is well demonstrated also by a recent prospective study which showed that, excluding the propositi, the prevalence of thrombosis in affected and non-affected family members of probands was approximately the same.[9]

It is clear that these observations cast serious doubts about the role of factor V Leiden defect in the pathogenesis of OCT-induced or associated venous thrombosis.

The risk is definitively lower than that seen in patients with antithrombin or protein C deficiencies.[10-12] Therefore there are settled and unsettled problems with regard to this problem. It still needs to be explained why so many patients with this abnormality, both heteroygotes and even homozygotes, may remain asymptomatic even after long-term administration of OCT.

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Table 1. Prevalence of DVT in patients homozygous and heterozygous for factor V Leiden and in a control group.

	No. of patients	*No. of patients with DVT*	*Associated risk factors°*	*Average no. of cycles before DVT*
Control group*	31	1(3.2%)	None	13.0
Homozygous APC resistance	6#	2 (33.3%)	2	3.0
Heterozygous APC resistance	16	7 (43.7%)	2	14.1

**Control patients were tested for antithrombin, protein C, protein S deficiences and for factor V Leiden defect. °Associated risk factors: trauma, surgery, immobilization. #One patient had two courses of OCT.*

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Refining prognosis of acute myeloid leukemia patients

Estey *et al.*[1] present interesting data suggesting that the prognosis within each of the cytogenetic subsets of acute myeloid leukemia (AML) needs to be refined. Mandelli *et al.*,[2] in this journal, recently discussed the role of genetic characterization in the therapy of AML, and the investigative efforts needed for the design of tailored treatment for each and every AML patient. They concluded that the prognostic role of genetic lesions, currently identified by karyotyping studies, needs to be validated in large series of AML patients prospectively characterized by advanced molecular/cytogenetic analyses and treated uniformly. In addition, searches for new clinically relevant genetic abnormalities, and diagnostic tools for their rapid identification are urgently needed to identify prognostic categories better. Other studies in this journal have emphasized the same need in AML and myelodysplastic syndromes.[3-8] The final target is, however, to identify the AML gene alterations in order to develop new drugs targeted to the specific lesion in the individual patient.

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