on the role played by the GPIb-IX-V complex in megakaryocyte development. There are several new clues: (1) A time course analysis indicates that expression of the von Willebrand factor receptor and filamin A starts in immature megakaryocytes and increases just before proplatelet extension. (2) The association of GPIbα to actin cytoskeleton occurs only in mature megakaryocytes and is filamin A–dependent, as in platelets. (3) GPIbα expression on filamin A–null megakaryocyte membranes is similar to controls, in contrast with filamin A–null platelets that have decreased GPIbα surface levels. All together, these data point out the importance of a correct association between the actin–rich membrane skeleton and the plasma membrane to platelet production. It looks like macrothrombocytopenia is always accompanied by a defect in some cytoskeletal components (ie, tubulin, myosin IIα, filamin A). Megakaryocytes have to be in “perfect” shape to release functional platelets.

The increase of the microtubular mass in giant platelets may be ascribed to the incapacity of pro–platelets to undergo the final step that occurs in circulation and leads to production of correct numbers of normal-sized platelets. Alternatively, giant platelets may stay giant to have a thicker microtubule coil as a sort of protection of their fragile structure. Finally, filamin A–null platelets undergo microvesiculation while they lose von Willebrand factor receptor components on the membrane surface. This may be explained by the fact that, in the absence of filamin A, ADAM17 and MMP9 metalloproteinases are more expressed and, in turn, GPIbα is more cleaved. Furthermore, the formation of annexin–V4 microvesicles was strongly associated with the activity of the protease calpain. Thus, filamin A acts to maintain the synergy between cellular mechanics and signaling systems that is required to regulate the production of structured and functional platelets.

Beside GPIbα and von Willebrand factor, filamin A interacts with several proteins that regulate cell adhesion, including β1 integrin and several protein kinases.2 Megakaryocyte adhesion and migration on extracellular matrices are key factors in the regulation of platelet formation by the bone marrow environment. Interestingly, Falet et al recently demonstrated that filamin A is required in signaling by direct interaction with Syk in platelet activation through the immunoreceptor tyrosine-based activation motif (ITAM)– and ITAM–like–mediated signal receptors GPVI and C-type lectin-like receptor 2.2 This observation, together with the knowledge that filamin A regulates cell adhesion strength, raises a variety of very interesting questions about the role of filamin A in the interaction of megakaryocytes with bone marrow matrices, such as collagen I. Little is known about the transmission of force between hemopoietic stem cells and their niche, and the question on how biochemical and biomechanical signals cooperate to generate force and, ultimately, to regulate megakaryocyte fate, is still open.

The study by Jurak Begonja et al clearly demonstrates that, despite their tight affinity, megakaryocytes do not always behave like platelets and that platelet formation is the consequence of a variegated sequence of events. Thus, only the fine-tuning of the different elements of the orchestra will lead to the release of functional platelets.

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**REFERENCES**


**Comment on van Vlijmen et al, page 2055**

**The risks of informed decision-making**

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In this issue of *Blood*, van Vlijmen and colleagues provide data from a retrospective family cohort study on the absolute risks of venous thromboembolism (VTE) during combined oral contraceptive use and the pregnancy/postpartum period in relatives of symptomatic probands with the factor V Leiden or prothrombin gene mutations.1

Using these absolute risks and reported failure rates with various contraceptive methods, the authors demonstrate in a modeling exercise that if both the risks of contraceptive-related and pregnancy-related VTE resulting from contraceptive failure are taken into account, the overall risks of VTE are lower in thrombophilic women with combined oral contraceptive use than when condoms are used. The lowest overall risks are seen with intrauterine devices.

Although combined oral contraceptives are associated with a 3–6-fold increase in the risk of VTE in the general population,2,3 these agents remain widely accepted because they are effective and convenient, and the low average annual incidence of VTE among women of reproductive age means that absolute risk of combined oral contraceptive–associated VTE is only 3 to 4 per 10 000 person-years for current users.2 Women with hereditary thrombophilia who use combined oral contraceptives appear at greater risk of VTE.4 These risks are most marked in women with antithrombin, protein C, or protein S deficiency,5 while thrombotic risks are much more modest in women with the common mild thrombophilias of heterozygosity for factor V Leiden or the prothrombin gene mutation.6

In recent years, laboratory testing for thrombophilia has been performed on increasing numbers of patients, including...
asymptomatic individuals with a family history of VTE or with a family member known to have a thrombophilia. Proposed benefits of thrombophilic screening in this population include the prevention of VTE through primary anticoagulant prophylaxis and avoidance of risk factors, like oral contraceptives. Although guidelines for the investigation and management of patients with thrombophilia in the presence and absence of a thrombosis history exist, it is not known whether the proposed benefits of screening justify the potential drawbacks of testing, which include negative psychological effects, difficulties with insurability, bleeding risks with primary prophylaxis, additional medical expenditures, false reassurance from a negative test result, and the effect of incorporating this information into important life decisions including pregnancy, surgery, and contraceptive choice. Few studies have investigated the impact of counseling based on the results of thrombophilia testing, data supporting a reduction in thrombotic risk in heterozygous carriers of the factor V Leiden or prothrombin gene mutation who are denied combined oral contraceptives are lacking.

In this retrospective cohort study, van Vlijmen and colleagues investigated 798 female relatives of symptomatic patients who were heterozygous, double heterozygous, or homozygous for factor V Leiden or the prothrombin gene mutation. Probands were excluded from the analysis to avoid bias, as were female relatives with deficiencies of the natural anticoagulants because these are strong risk factors for VTE. The absolute risk of VTE during oral contraceptive use was 0.19 per 100 pill-years for relatives with no defects, compared with 0.49 for those heterozygous for factor V Leiden or prothrombin gene mutation and 0.86 with homozygous or combined heterozygous defects. With respect to pregnancy and the postpartum period, the incidence per 100 pregnancy-years was 0.73, 1.97, and 7.65 for relatives with no, single, or combined/homozygous mutations, respectively. These results support previous research demonstrating a higher risk of VTE during the pregnancy and postpartum period than during combined oral contraceptive use. The most novel aspect of this report is the calculation of overall venous thromboembolic incidences in users of combined oral contraceptives and in those using alternative contraceptive methods that takes into account not only contraceptive-related thrombosis but also those events developing during unintended pregnancies caused by contraceptive failure. The estimated incidence of VTE per 100 000 women-years in thrombophilic relatives was 536 in users of combined oral contraceptives, compared with 586 in condom users, 290 in those with copper intrauterine devices, and 270 with the levonorgestrel intrauterine device. Although anticoagulant prophylaxis can reduce the risk of venous thrombosis in thrombophilic women who become pregnant, it is onerous and not without risk. High-quality data supporting its use are lacking.

Careful readers will note that the baseline risk of VTE in the control relatives without thrombophilia (0.13/100 person-years) is higher than the age-equivalent rates usually reported in the literature. This may be because of the high frequency of concomitant elevations in factor VIII levels. Previous studies have reported that a family history of VTE increases thrombotic risk regardless of the presence of a known hereditary thrombophilic defect, likely as a result of the concomitant presence of other genetic or environmental risk factors within the family. In this study, van Vlijman and colleagues demonstrate that the confounding effect of high factor VIII levels on reported VTE risks was small.

Although the current study is limited by its retrospective nature; multiple interventions were incorporated into the study design to limit recall bias and improve the accuracy of the data, including reconfirmation of information by written questionnaire, review of medical records, and contacting family practitioners. Of available relatives, 21% were deceased and could not be investigated. It is possible that the reported VTE incidences are underestimated by early deaths in those with thrombophilia; however, previous studies have documented normal life expectancies in these individuals.

The results obtained by van Vlijman et al do not allow physicians to advocate the use of combined oral contraceptives in asymptomatic heterozygous carriers of the factor V Leiden or prothrombin gene mutation; however, they do make clear that strictly contraindicating these agents may be inappropriate. Determination of the potential benefits of modifying the management of asymptomatic family members based on thrombophilic testing requires carefully designed randomized trials of screening and intervention. Such studies have been difficult to conduct. In the interim, knowledge of the interaction between the risks of VTE, hereditary thrombophilia, and oral contraceptive use may help women make an informed decision about contraceptive choices. However, if all potential benefits and risks of various contraceptives are not disclosed, the outcome can be unsatisfactory, despite our best intentions.

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REFERENCES

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