

Treatment of venous thromboembolism in pregnancy: findings from the RIETE Registry

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Dear Editor,

Venous thromboembolism (VTE) is one of the leading cardiovascular etiologies of maternal morbidity and mortality.¹ Indeed, pulmonary embolism (PE) accounts for ap-

proximately 9% of pregnancy-related deaths.² In addition, pregnancy-related deep-vein thrombosis (DVT) can lead to (severe) post-thrombotic syndrome.³

The optimal management of pregnancy-related VTE has never been addressed by proper investigations. Virtually all major international guidelines suggest the use of full-dose low-molecular-weight heparin (LMWH) for as long as the pregnancy lasts and at least the first six weeks after delivery.⁴⁻⁶ This indication, however, is not supported by scientific evidence. Besides, it contrasts with the modalities of LMWH treatment that are adopted in clinical conditions other than pregnancy. For example, based on the findings of clinical trials conducted in patients with active cancer, which is by far the condition at the highest risk of recurrent VTE while on anticoagulation,⁷ the initial intensive LMWH dose is generally reduced by approximately one fourth after the first 3 to 4 weeks.⁸⁻¹⁰ And in patients without cancer, whenever LMWH is used as a standalone therapy in place of vitamin K antagonists for the initial and long-term treatment of VTE, the shift from therapeutic to subtherapeutic doses is generally made after one or two weeks.¹¹⁻¹³

While the risk of VTE is expected to increase at the end of pregnancy and in the first six weeks after delivery,¹ the reasons why pregnant women with VTE should afford the potential risks and the inconveniences of uninterrupted full-dose LMWH for as long as the pregnancy lasts are unclear. Not surprisingly, in clinical practice several clinicians do not comply with these indications and give their patients lower doses of LMWH after an initial variable period of intensive treatment.¹⁴ While it would be interesting to know if this approach is reasonably effective and safe, this information is lacking. As in the framework of the international RIETE registry, aimed at collecting information on the initial and long-term follow-up of unselected patients with VTE, several women with pregnancy-related VTE had their therapy managed with lower than conventional doses of LMWH, we report here the main findings achieved in these women.

The Computerized Registry of Patients with Venous

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Thromboembolism (RIETE, NCT: 02832245) is a large prospective registry that since 2001 has been enrolling consecutive patients, including pregnant women, with objectively confirmed VTE.¹⁵ The main objective of RIETE is to provide information to help physicians to improve their knowledge on the natural history of thromboembolic disease, including epidemiologic, diagnostic, prophylactic and therapeutic information. Participants in the RIETE registry are requested to provide accurate information on patient's short and long-term outcome after the index event. All recurrent symptomatic VTE events are diagnosed according to objective tests and validated criteria for their interpretation. All enrollees provide written or verbal informed consent according to the local ethics protocols of enrolling centers. The institutional review board at each enrolling center approves participation in RIETE for the site investigators and allows the entry of de-identified patient information into the RIETE database.

Out of 641 patients with pregnancy-related acute VTE who visited a RIETE center between January 2001 and April 2021 and were managed with LMWH, 201 (31.4%) had the initial full dose reduced by 25 to 50% after a period ranging between one and two weeks, and were followed up for as long as antithrombotic therapy was needed, thus covering at least the first six weeks after delivery. Table 1 shows the main demographic and clinical characteristics of these women.

Table 1. Main characteristics of the study patients

Features	Patients (N=201) N. (%)
Age, years (mean \pm SD)	33 \pm 6
Body weight \geq 90 Kg	27 (13.4)
Varicose veins	44 (21.9)
Previous VTE	13 (6.5)
Family history of VTE	8 (4.0)
Thrombophilia*	52 (25.9)
Additional risk factors	
Active cancer	1 (0.5)
Recent surgery	8 (4.0)
Immobilization (\geq 4 days)	21 (10.4)
Prolonged travel	3 (1.5)
Type of VTE	
Proximal \pm calf DVT	138 (68.7)
Isolated calf DVT	23 (11.4)
PE \pm DVT	40 (19.9)
Trimester of pregnancy	
First	66 (32.8)
Second	44 (21.9)
Third	91 (45.3)

*Antithrombin, protein C or S deficiency, factor V Leiden, prothrombin G20210A mutation, antiphospholipid antibody syndrome. SD=standard deviation; VTE=venous thromboembolism; DVT=deep-vein thrombosis; PE=pulmonary embolism.

During the follow-up period, objectively confirmed recurrent VTE developed in two of the 201 women (1.0%): in none during 69.13 patient-years before delivery, and in two during 25.13 patient-years after delivery (a nonfatal PE and a left proximal DVT occurring after three and 10 days, respectively). Accordingly, the annual rate of VTE complications was 0.00% (95% CI: 0.00 to 0.05) and 0.08% (95% CI: 0.02 to 0.25) before and after delivery, respectively. Major bleeding complications, defined according to the ISTH classification, developed in one woman (0.5%) during the overall 94.26 patient-years of follow-up (a vaginal bleeding soon after delivery), accounting for an annual rate of 0.01% (95% CI: 0.00 to 0.06). No patient died during the follow-up period.

As far as we know, this is the first report dealing with the long-term follow-up of a considerable number of women with pregnancy-related VTE who were managed with sub-therapeutic doses of LMWH following an initial short period of intensive treatment. Our findings suggest that in patients with pregnancy-related VTE, the efficacy of sub-therapeutic doses of LMWH following an initial intensive treatment may not be lower than that of an uninterrupted full-dose scheme before delivery, while it is expected to decline after delivery.¹ Of course, our findings should be interpreted with caution, because of the uncontrolled nature of our observation and of the potential for selection bias, as the therapeutic choices were left to discretion of attending physicians. Accordingly, our findings should be intended as hypothesis generating. A randomized clinical trial addressing the comparison between uninterrupted full-dose LMWH and a more prudent anti-partum strategy in the management of VTE-related pregnancy is desirable.

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