A retrospective study on the use of low-molecular-weight heparin for prevention of pregnancy-related recurrent venous thromboembolism and obstetrical complications

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Background **The risk of venous thromboembolism (VTE) is increased during pregnancy and it is further increased together with pregnancy complications in women with personal history of VTE and thrombophilia abnormalities. It is unclear how the use of low-molecular-weight heparin (LMWH) may prevent such complications.**

Objective **To evaluate the potential benefits and risks of the use of LMWH for prevention of pregnancy-related VTE and obstetrical complications in the first pregnancy after a previous VTE.**

Methods **This retrospective cohort study includes fertile women referred to the Thrombosis Center from January 2000 to September 2018 for a thrombophilia work-up, after having had at least one previous VTE and one pregnancy thereafter. Data on pregnancy-related recurrent VTE, pregnancy outcomes and the use of LMWH were collected.**

Results **Among 208 women, no thrombosis or major bleeding was recorded in 138 pregnancies conducted with LMWH, whereas 10 VTE (14%) were recorded in 70 pregnancies conducted without. Nine women (90%) with recurrent VTE had had a previous hormone-related event. The incidence of miscarriage was lower in pregnancies with LMWH than in those without (11% vs. 26%, relative risk 0.4, 95% confidence interval: 0.2–0.8), whereas late obstetrical complications and terminations were similar in the two groups. The prevalence of terminations was doubled in women with thrombophilia (12%) than in those without (6%).**

Conclusions **LMWH prophylaxis during pregnancy appears to be effective and safe for the prevention of recurrent VTE and may reduce the incidence of miscarriage.** ***Blood Coagul Fibrinolysis*** **34:111–117** **Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Venous thromboembolism (VTE) is an important cause of maternal morbidity and mortality [1,2] with an estimated incidence of one case every 1000 pregnancies [3–5]. During pregnancy, physiological changes such as increase of procoagulant factors, decrease of the natural anticoagulant proteins and hypofibrinolysis occur together with venous stasis caused by pressure of the uterus on the inferior vena cava and iliac veins and tissue damage at the time of delivery that contributes to increase the risk of VTE. This risk is likely to be further increased by inherited thrombophilia [6]. Furthermore, the risk of recurrence during pregnancy is 3.5-fold increased than in nonpregnant period [7] and women who experienced a previous hormone-related VTE are at higher risk of recurrence during pregnancy than those with a previous nonhormonal related VTE [8,9].

Also, women with thrombophilia abnormalities could have an increased risk of miscarriage and late obstetrical complications owing to the impairment of the placental circulation [10–15].

Low-molecular-weight heparin (LMWH) is the anticoagulant of choice for the prevention and treatment of VTE during pregnancy and it is also thought to be useful in preventing obstetrical complications [16–19]. Limited data are available on the risk of recurrent VTE without the use of LMWH prophylaxis during pregnancy [8,20]. and low certainty evidence exist on the efficacy of LMWH prophylaxis for the prevention of obstetrical complications both in women with the acquired (i.e. antiphospholipid antibodies) [21–23] and with inherited thrombophilia [24,25]. Thus, the use of LMWH prophylaxis during pregnancy should be assessed on an individual basis, as suggested by several guidelines and more recent studies [18,26–29] and data on its use for the prevention of recurrent VTE and obstetrical complications, particularly during the first pregnancy after VTE, are still to be confirmed [30,31].

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With this background our retrospective cohort study is aimed to evaluate the risk of pregnancy-related recurrent VTE and obstetrical complications, and the efficacy of LMWH for their prevention in women with or without thrombophilia.

Methods

Design and study population

This is a retrospective single-center cohort study on women referred to our Centre from January 1, 2000 to September 30, 2018 for a thrombophilia work-up after a previous episode of VTE. Women aged between 15 and 40 years at the time of first VTE, between 18 and 40 years at the time of referral, and with at least one pregnancy occurred after the first VTE within September 2018 were selected. Exclusion criteria were a first index event occurred before the age of 15 or during nonchildbearing age, a VTE event other than deep vein thrombosis (DVT) of the lower limbs or pulmonary embolism (PE), infertility and the antiphospholipid syndrome.

Our clinical practice at the time of the first referral visit is to collect data on previous thrombotic events, previous pregnancies and antithrombotic treatment or prophylaxis. All women were invited to contact the Center in case of symptoms of thrombosis, as well as in high-risk situations such as at the beginning of pregnancy for the prescription of LMWH prophylaxis. In addition, women who were not seen at the Center in 2019 were contacted for the purpose of this study to update their clinical records up to September 2019.

Women with moderate to high risk of recurrence, i.e., those with a prior unprovoked VTE who had discontinued anticoagulant therapy before the onset of the new pregnancy and those with a previous hormonal-related event (pregnancy/puerperium, oral contraceptive use) were prescribed prophylactic doses of enoxaparin (40 mg daily or 60 mg daily if body weight $>$ 80 kg) during pregnancy and puerperium (defined as 6 weeks after delivery), whereas women still on oral anticoagulant therapy or those considered at particularly high thrombotic risk (e.g. previous VTE with severe thrombophilia abnormalities) switched to therapeutic doses of LMWH (twice daily body weight adjusted dose) during pregnancy and resumed oral anticoagulation after delivery. Women at low risk of recurrence (e.g. those with a single episode of VTE associated with a transient risk factor nonhormone related) were prescribed with prophylactic doses of LMWH only during puerperium. The study was approved by Ethics Committee of Milano Area 2 and informed consent was obtained from study participants.

Thrombophilia testing

Blood samples for thrombophilia testing were taken at least 3 months after the index VTE. Thrombophilia work-up included DNA analysis of the gain-of-function mutations, the G1691A substitution in the coagulation factor V gene (factor V Leiden) [32] and the G20210A substitution in the 3'-untranslated region of the prothrombin gene; [33] functional and immunoassays (when required) for plasma antithrombin, protein C and protein S; [34] antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein I immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies) [35]. Patients on vitamin K antagonists at the time of their first visit provided a second blood sample after discontinuation of oral anticoagulant therapy for confirmation of protein C or protein S deficiency. The inheritance of antithrombin, protein C and protein S deficiency was confirmed in a second blood sample and in at least one relative. No woman was pregnant at the time of thrombophilia testing.

Definition of outcomes

Any pregnancy-related VTE event was objectively confirmed by specific diagnostic methods (e.g. compression ultrasonography, lung V/Q scan, angio-CT scan, angio-MR). Pregnancy outcomes were at term pregnancies (defined as delivery occurred after 37th gestational week), miscarriages (defined as pregnancy loss occurring before the 20th gestational week), late obstetrical complications (preterm delivery, intra-uterine growth restriction, small for gestational age, preeclampsia, placental abruption and stillbirth) and terminations (voluntary abortion). Preterm delivery was defined as a delivery before the 37th week of gestation (with or without premature rupture of the membranes), intra-uterine growth restriction as an abnormal fetal growth in utero, small for gestational age as a newborn weight less than 10th percentile for gestational age according to the local referral values [36], preeclampsia as the concomitant presence of arterial hypertension and a significant amount of proteins in the urine [37], and stillbirth as a pregnancy loss that occurred beyond the 20th gestational week.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), and categorical variables as counts and percentages. Comparisons between pregnancies with and without LMWH were performed for the risks of VTE and obstetrical complications, calculating the relative risks and their 95% confidence intervals (CIs). A sensitivity analysis was performed stratifying pregnancies with or without LMWH for the presence of thrombophilia and further analyses were done classifying thrombophilia abnormalities as mild (heterozygous factor V Leiden or prothrombin G20210A mutation) or severe (antithrombin, protein C, protein S deficiencies, homozygous factor V Leiden or prothrombin G20210A mutation, combined abnormalities). The relative risks of full term pregnancy, miscarriage and late obstetrical complications were calculated as the number of pregnancy outcomes on the total number of pregnancies excluding terminations and reported with their 95% confidence intervals. All analyses

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were performed using a spreadsheet for the analysis of epidemiologic data 'Episheet' by Kenneth J. Rothman and John D. Boice, Jr (https://www.rtihs.org/episheet) and the statistical software SPSS (release 26.0, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA).

Results

Patients characteristics

In the inclusion period of this study, 1645 women were referred to our Center, of whom 1385 were excluded for age criteria, not having had pregnancies after VTE, infertility or having antiphospholipid syndrome (Fig. 1). Among 260 women who met the inclusion criteria, 43 were lost to follow up and 9 had an ongoing pregnancy at the time of this analysis. Hence, 208 women represented the final study population.

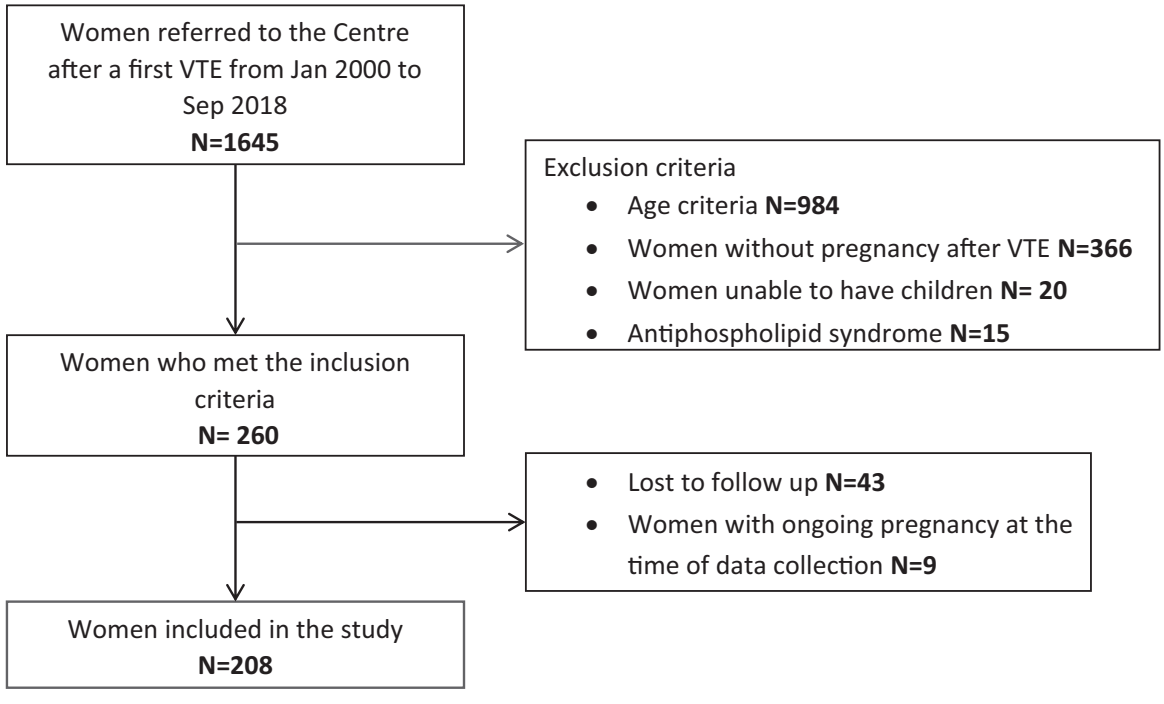
One-hundred and thirty-eight pregnancies were conducted with LMWH and 70 without. Among the latter, 30 women received LMWH prophylaxis only in the puerperium and 40 did not. Their general characteristics are shown in Table 1. The median age at first VTE, the age at index pregnancy, median BMI and the prevalence of hormone-related risk factors at the time of the first VTE, were similar in the two groups, as well as the prevalence of women who had recurrent VTE before the index pregnancy. No patients received concomitant aspirin. nor had diabetes. Previous PE was more prevalent in women who received LMWH prophylaxis during pregnancy than in those who did not (41% vs. 14%). The prevalence of thrombophilia was doubled in women who received LMWH prophylaxis during pregnancy than in those who did not (56% vs. 26%), although the prevalence of severe abnormalities (i.e. Antithrombin, Protein C, Protein S deficiency, homozygous factor V Leiden or prothrombin G20210A mutation, combined abnormalities) was similar (17% vs. 14%) in the two groups.

Among women who did not receive LMWH during pregnancy, 26 were referred to our Center after their first pregnancy after VTE, 20 had the indication to receive LMWH prophylaxis only during puerperium due to a previous VTE associated with nonhormonal transient risk factors, 3 developed VTE at a very early gestational week, 12 had early miscarriages, 3 terminated voluntarily without prior consultation at our Center, and 6 did not come back to the Center when pregnant.

Pregnancy-related recurrent venous thromboembolism

Among 138 pregnancies with LMWH (124 prophylactic and 14 therapeutic doses), no VTE was observed, while 10 of 70 pregnancies without LMWH were complicated by 8 DVT, one PE and one cerebral vein thrombosis, for a risk proportion of 14.3% (95% CI 7.5–24.0%) (Table 2). Five VTE (three DVT, one cerebral vein thrombosis and one PE) occurred in women referred to us after the index pregnancy, three DVT occurred in women at the 7th, 9th and 10th gestational week before the start of LMWH

Fig. 1



Flow chart of the study population.

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Table 1 Baseline characteristics of the study population

	Pregnancies LMWH+	Pregnancies LMWH≥
Number of women, *n*	138	70
Age at first VTE, median (IQR)	27 (23–32)	27 (24–31)
BMI, median (IQR)	21.7 (20.0–25.3)	21.8 (20.0–25.7)
Index event, *n* (%)		
Deep vein thrombosis	81 (59)	60 (86)
Pulmonary embolism	32 (23)	5 (7)
Deep vein thrombosis and pulmonary embolism	25 (18)	5 (7)
Age at first pregnancy after VTE, median (IQR)	33 (29–36)	33 (29–36)
Thrombophilia abnormalities, *n*		
Factor V Leiden	34 (25)	11 (16)
Prothrombin G20210A mutation	26 (19)	9 (13)
AT, PC, PS deficiency	20 (14)	6 (9)
Number of thrombophilia abnormalities[a], *n* (%)		
None	71 (51)	52 (74)
Single	56 (41)	9 (13)
Multiple	11 (8)	9 (13)
Severity of thrombophilia abnormalities[a], *n* (%)		
Mild	43 (31)	8 (11)
Severe	24 (17)	10 (14)
Risk factors at previous VTE, *n* (%)		
None	8 (6)	4 (6)
Oral contraceptive use	96 (70)	44 (63)
Pregnancy	14 (10)	6 (8)
Puerperium	7 (5)	4 (5)
Other transient risk factors	13 (9)	12 (17)
Women with recurrent VTE before pregnancy, n (%)	13 (10)	6 (8)
One recurrence	11 (8 DVT, 2 PE, 1 SVT)	6 (5 DVT, 1SVT)
More than one	2 (DVT)	0

DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SVT, superficial vein thrombosis. [a]Severe thrombophilia includes: antithrombin (AT), protein C (PC), protein S (PS) deficiencies; homozygous factor V Leiden (FVL) or prothrombin (PT) and combined abnormalities.

prophylaxis and the remaining two DVT occurred in women who did not contact us at the time of the index pregnancy. Among 17 women who had already had recurrent events before the index pregnancy, 11 received LMWH prophylaxis during index pregnancy and did not develop thrombotic complications, whereas one of the six who did not receive LMWH had a pregnancy-related recurrence. During puerperium, no women with ($n = 168$) or without ($n = 40$) LMWH prophylaxis developed VTE.

The exposure to hormonal risk factors was the main cause for the first VTE event, with a prevalence of 85% and 77% in women with and without LMWH prophylaxis, respectively. Nine of the 10 women who experienced a recurrent pregnancy-related VTE had had a previous hormone-related event, seven during oral contraceptive intake and two during pregnancy. Additional details of women who recurred during pregnancy are reported in Table 3. Among women who received LMWH during pregnancy, one episode of minor bleeding during delivery and one mild thrombocytopenia after delivery was observed.

Table 2 Prevalence of recurrent venous thromboembolism during pregnancy

VTE, *n* (%)	Pregnancies LMWH + *N* = 138	Pregnancies LMWH- *N* = 70
Deep vein thrombosis	0	8 (11.4)
Pulmonary embolism	0	1 (1.4)
Cerebral vein thrombosis	0	1 (1.4)
Total, *n* (%)	**0**	**10 (14.3%)**

No superficial vein thrombosis was observed. LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Pregnancy outcomes

Overall, 129 (68%) full term pregnancies, 33 (17%) miscarriages, 29 (15%) late obstetrical complications and 17 (8%) terminations were recorded. There was a 20% increased risk for reaching full term and a 60% reduced risk of miscarriages in women who received LMWH than in those who did not, while the prevalence of late obstetrical complications and terminations were similar in the two groups (Table 4). Looking at the previous obstetrical history, for 158 women the index pregnancy was the first ever and we observed similar figures of the main analysis, while 19 of 50 women with at least one pregnancy prior to the index VTE also had a previous obstetrical complication or a termination. Thirteen women had early miscarriages (none had had more than two), two had small for gestational age newborns, two pre-eclampsia and two terminated. Thirteen of the 19 women with a previous history of obstetrical complications received LMWH during the index pregnancy, with the following outcomes: 10 full term pregnancies, one miscarriage, one preterm delivery and one intra-uterine growth restriction. The remaining 6 women who did not receive LMWH during the index pregnancy had 3 full term pregnancies, 2 miscarriages and one preterm delivery with a small for gestational age newborn.

Thrombophilia

Table 5 shows the risk proportions of pregnancy-related VTE and obstetrical complications stratified by the presence of thrombophilia abnormalities. The observed incidence of pregnancy-related recurrent VTE was slightly higher in women with thrombophilia than in those without (17% vs. 13%) with a RR of 1.2 (95% CI 0.4–4.3). The same risks of the main analysis were observed for obstetrical complications. Ten of 85 women with thrombophilia compared to 7 of 123 without chose to terminate their pregnancy (12% vs. 6%, relative risk 2.1; 95% CI 0.8–5.2). A stratified analysis by absence of thrombophilia, mild or severe thrombophilia showed a prevalence of terminations of 5.0% (95% CI 2.0–10.0%), 9.8% (95% CI 3.7–20.4%) and 14.7% (95% CI 5.6–29.6%), respectively.

Discussion

This retrospective cohort study evaluated the risk of recurrent pregnancy-related VTE and the risk of obstetrical complications in the 208 pregnancies following an

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Table 3 Details on women who experienced a pregnancy-related VTE recurrence

Previous event		Age at pregnancy	Thrombophilia abnormalities	Recurrent event
#1	DVT hormone-related (pregnancy)	28	Antithrombin deficiency	DVT
#2	DVT hormone-related	31	None	DVT
#3	DVT hormone-related	24	Double heterozygous (factor V Leiden, prothrombin mutation)	DVT
#4	DVT hormone-related	34	None	DVT
#5	DVT Unprovoked	35	None	DVT
#6	DVT hormone-related	33	None	DVT
#7	DVT hormone-related (pregnancy)	40	None	DVT
#8	PE hormone-related	29	Prothrombin mutation	CVT
#9	DVT +PE hormone-related	33	None	DVT
#10	DVT +PE hormone-related	36	None	PE

CVT, cerebral vein thrombosis; DVT, deep vein thrombosis; DVT+PE, deep vein thrombosis and pulmonary embolism; PE, pulmonary embolism.

episode of VTE, conducted with or without antithrombotic prophylaxis with LMWH. We observed a 14.3% prevalence of recurrent VTE in 70 pregnancies conducted without LMWH, whereas no VTE occurred during pregnancies conducted with LMWH. No recurrent VTE was observed during puerperium, with or without LMWH. Although miscarriages were less frequent in pregnancies conducted with LMWH, the prevalence of obstetrical complications was similar in the two groups.

Previous studies showed a higher prevalence of recurrent VTE in the puerperium than during pregnancy [38], at variance with our findings. Moreover, we found slightly higher prevalence in the antepartum period than previously reported [8,39,40]. This might be due to a relevant loss to follow-up and to a selection bias for referral, including women referred for the index event in pregnancy, or to the fact that our tertiary care Center receives patients with a particularly high risk of recurrent VTE (i.e. women with thrombophilia or a history of recurrent VTE). However, only one woman who recurred was referred for the index event in pregnancy, five had recurrent VTE before the referral and 4 were already followed by us at the time of the index event. Furthermore, excluding women who had had recurrent VTE before the index pregnancy, the proportion of pregnancy-related VTE remained the same.

Table 4 Risk of obstetrical complications

Pregnancy outcome, *n* (%)	Pregnancies LMWH + N = 138[a]	Pregnancies LMWH- N = 70	RR (95% CI)
Full term	92 (67)	37 (53)	1.2 (1.0–1.5)
Miscarriage	15 (11)	18 (26)	0.4 (0.2–0.8)
Late obstetrical complication	21 (16)[b]	8 (13)[c]	1.3 (0.6–2.8)
Termination	10 (7)	7 (10)	0.7 (0.3–1.8)

CI, confidence interval; LMWH, low-molecular-weight heparin; RR, relative risk. [a]14 women were on therapeutic dose: 5 full term, 2 miscarriage, 1 preterm, 1 preeclampsia and 5 termination. [b]1 stillbirth, 4 fetal growth restriction, 1 small for gestational age, 7 preterm (2 with SGA and one with placenta previa), 7 preeclampsia, 1 placental abruption. [c]2 stillbirth, 3 small for gestational age, 2 preterm (one with SGA), 1 preeclampsia, 1 placental abruption.

The prevalence of pregnancy-related recurrent VTE was similar in women with or without abnormalities (17% vs. 13%), in broad agreement with other studies [8,9,41]. Looking at other transient risk factors for pregnancy-related recurrent VTE, we observed that the most prevalent risk factor at the time of the index VTE was hormonal, and that women with a previous hormone-related VTE are at increased risk of recurrence during pregnancy [8,9,42]. Notwithstanding the fact that the absolute risk of antepartum recurrent VTE remains controversial [19], our data suggest that the risk should be carefully evaluated not only during puerperium but also during pregnancy, particularly in women who had had a hormone-related previous VTE, in line with recent recommendations [28]. Some findings support the views that a history of VTE is associated with an increased risk of obstetrical complications [15,43], but the evidence to support the use of LMWH for the prevention of these complications are still poor, with inconsistent results and weak recommendations [2,31]. In our study, pregnancies conducted with LMWH prophylaxis had a lower incidence of miscarriages than those conducted without, particularly in women with thrombophilia, but no differences for the risk of late obstetrical complications were observed in the two groups. This might be explained by different mechanisms underlying obstetrical complications compared to those of VTE. Finally, although all the women in our cohort were informed on the potential benefits and safety of LMWH use during pregnancy, we observed that women with thrombophilia chose termination twice more frequently than those without. Other

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Table 5 Stratification analysis according to the presence of thrombophilia abnormalities

	Thrombophilia + $N=85$			Thrombophilia − $N=123$		
	LMWH + $N=67$	LMWH − $N=18$	RR (95% CI)	LMWH+ $N=71$	LMWH − $N=52$	RR (95% CI)
VTE, *n* (%)	0	3 (17)	0	0	7 (13)	0
Pregnancy outcome, *n* (%)						
Full term	44 (66)	6 (33)	1.7 (0.9–3.1)	48 (67)	31 (60)	1.1 (0.9–1.5)
Miscarriage	7 (10)	6 (33)	0.3 (0.1–0.7)	8 (11)	12 (23)	0.5 (0.2–1.1)
Late obstetrical complication	10 (15)	2 (11)	1.1 (0.3–4.7)	11 (15)	6 (12)	1.3 (0.5–3.4)
Termination	6 (9)	4 (22)	0.4 (0.1–1.3)	4 (6)	3 (6)	1 (0.2–4.2)

VTE, venous thromboembolism; LMWH, low-molecular-weight heparin; RR, relative risk; CI, confidence interval.

than a careful counseling for the available options in order to give birth safely, this finding should raise awareness on the psychological aspect of the communication of the results of thrombophilia screening to women, as this may have negative implications when they became pregnant.

The generalizability of our results, contrary to previous studies conducted in women with obstetric history, can be applied to the first pregnancy after a previous VTE, being the first pregnancy the vast majority of those evaluated in this study. Strengths of our study were the evaluation of a large number of observations (208 first pregnancies following the index VTE with or without LMWH) and a complete thrombophilia work-up performed in all women. However, several limitations must be recognized. The main one is the retrospective nature of the study, with no randomization, a relevant loss to follow up and the possibility to incur into referral bias. The absence of other possible triggering factors for obstetrical complications (e.g. high blood pressure, gynecological comorbidities, and socio-economic status) may limit the interpretation of the results on the efficacy of LMWH in preventing obstetrical complications. In addition, data on pregnancy complications were collected retrospectively and a recall bias cannot be excluded, although we have no reason to think that this bias would differently involve women with or without LMWH prophylaxis. Moreover, the relatively small numbers in the subgroup analysis (i.e., stratification for the presence of thrombophilia) did not allow drawing firm conclusions on the interaction between LMWH and thrombophilia, particularly for obstetrical complications. Because of the small number of women without LMWH during puerperium, this study was underpowered to detect a difference in the prevalence of recurrent VTE during puerperium without LMWH.

In conclusion, this study suggests a reduction in risk of pregnancy-related recurrent VTE associated with the use of LMWH during pregnancy and puerperium, according to previous evidences. In particular, the use of LMWH prophylaxis should be considered in pregnant women who had a previous hormone-related VTE, a condition associated with an increased risk of recurrent VTE during pregnancy and puerperium. LMWH prophylaxis during pregnancy showed a lower incidence of miscarriages, but not of late obstetrical complications. Women with thrombophilia chose termination twice more frequently than those without, an observation that should prompt to evaluate the quality of counseling regarding future pregnancies in women diagnosed as having thrombophilia.

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Authorship contributions: M.A. and I.M. designed the study; M.A. analyzed and interpreted data, drafted and critically revised the manuscript; F.G., A.A., M.C., P.B. and A.C., acquired and interpreted data, and critically revised the manuscript; F.P. and I.M. supervised the work and critically revised the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

A.A. reports nonfinancial support from Bayer and Roche and honoraria from Janssen outside of the submitted work; M.C. reports nonfinancial support from Roche, Novonordisk and Sobi and honoraria from Daiichi Sankyo; F.P. served as a consultant for Kedrion, received honoraria for being a speaker at educational meetings from Ablynx/Sanofi, Grifols, Novo Nordisk, Roche, Shire, and Sobi, and was a member of an advisory board for Ablynx/Sanofi; I.M. reported personal and nonfinancial support from Bayer, Roche, Rovi and Novo Nordisk outside of the submitted work. All other authors have no relevant financial or nonfinancial interests to disclose.

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