Position Paper on the Management of Pregnancy-Associated Superficial Venous Thrombosis. Balkan Working Group for Prevention and Treatment of Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE) is a multifactorial disease that can possibly affect any part of venous circulation. The risk of VTE increases by about 2 fold in pregnant women and VTE is one of the major causes of maternal morbidity and mortality. For decades superficial vein thrombosis (SVT) has been considered as benign, self-limiting condition, primarily local event consequently being out of scope of well conducted epidemiological and clinical studies. Recently, the approach on SVT has significantly changed considering that prevalence of lower limb SVT is twice higher than both deep vein thrombosis (DVT) and pulmonary embolism (PE). The clinical severity of SVT largely depends on the localization of thrombosis, when it concerns the major superficial vein vessels of the lower limb and particularly the great saphenous vein. If untreated or inadequately treated, SVT can potentially cause DVT or PE. The purpose of this review is to discuss the complex interconnection between SVT and risk factors in pregnancy and to provide evidence-based considerations, suggestions, and recommendations for the diagnosis and treatment of this precarious and delicate clinical entity.

Keywords

superficial vein thrombosis, venous thrombembolic disease, pregnancy, thrombosis

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Introduction

Venous thromboembolism (VTE) is a multifactorial disease that can possibly affect any part of venous circulation. Pathogenesis of VTE involves blood hypercoagulability, vascular damage and flow alterations. According to the localization of thrombosis in the venous system, VTE may manifest as (a) deep vein thrombosis (DVT) which may involve the distal or the proximal veins of the lower limb, the iliac veins and the inferior vena cava (b) pulmonary embolism (PE), (c) venous thrombosis of rare localization (i.e. splanchnic vein thrombosis, cerebral vein thrombosis etc.), (d) upper limb vein thrombosis, (e) superficial vein thrombosis (SVT).

For decades SVT has been considered as benign, self-limiting condition, primarily local event consequently being out of scope of well conducted epidemiological and clinical studies.² Recently, the approach on SVT has changed and it is perceived as manifestation of blood hypercoagulability interconnected with inflammation of vessel wall.³ The prevalence of lower limb SVT is twice higher than both DVT and PE since it ranges from 3% to 11% in the general population.⁴⁻⁶

Superficial vein thrombosis is considered as benign and less hazardous manifestation of VTE as compared to DVT since it is less frequently complicated with PE. Though, the clinical severity of SVT largely depends on the localization of thrombosis when it concerns the major superficial vein vessels of the lower limb and particularly the saphenous vein. If untreated or inadequately treated, SVT will cause DVT or PE in 10% of patients within 90 days from symptoms onset. Nevertheless, asymptomatic DVT was found in 18.1%, and PE in 6.9%, of patients with SVT indicating that in a non-negligible number of patients SVT is a clinical manifestation of venous thromboembolic disease.

Saphenous veins are almost unavoidable anatomical entities affected in patients with SVT. Great saphenous vein (GSV) is affected in 60%-80% of cases while small saphenous vein (SSV) is less frequently affected, with prevalence of 10%-20%. Clinical presentation of SVT varies and is characterized by non-specific symptoms. Most usually, SVT is presented with localized pain, redness of the skin, warm and tender cord along the vein. Characteristics of surrounding area are edema and erythema. The diagnosis of SVT is based on the abovementioned clinical signs and symptoms and it is documented by imaging methods. Compression ultrasound (CUS) is the method of choice for objective documentation of SVT. In addition, assessment with CUS aims to determine the length of the thrombus and most importantly its location, i.e. the proximity of thrombus to the saphenofemoral junction (SFJ) or saphenopopliteal junction, where superficial vein confluences anastomosed with the deep venous system, since this element is determinant for the hazardous evolution of SVT to DVT. The concern is raised about SVT when it is 3 cm or less close to the deep vein, which is considered as equivalent to DVT. 10

SVT demands attention for some additional reasons:

- 1. SVT can be indicative for coexisting DVT or PE,
- isolated SVT can be complicated by extension to DVT and/or PE,
- SVT is confirmed as risk factor for recurrence of DVT or PE.¹¹⁻¹³

SVT might be the first clinical manifestation of an underlying pathology related with high risk of VTE such as antiphospholipid syndrome, malignancy or autoimmune disease.

By consensus, SVT is classified into ¹⁴: 1. *primary SVT in varicose vein* (VV-SVT) followed by sterile inflammation of the vein wall (varicophlebitis), and 2. *non varicose vein SVT* (NV-SVT), which represents a whole group of different disorders, with variable dominance between thrombus and inflammation. A particular form of SVT is Mondor's disease (MD), a specific sclerosing thrombophlebitis of the superficial veins which is divided into 3 categories: original MD of anterolateral chest wall, penile MD and axillary web syndrome affecting mid-upper arm after axillary surgery. ¹⁵

Pregnancy associated SVT is of particular interest since it is an underestimated but frequent problem that impacts women during pregnancy. The prevalence of SVT in pregnancy is about 0.1%. Though, the risk of VTE increases by about 2 fold in pregnant women with SVT with an incidence ranging from 0.82 to 1.99 per 1000 deliveries/pregnancies/women. However, the accuracy of this estimation is questioned due to methodological issues of the studies published so far. Similarly, the evidence for the optimal prevention and treatment of SVT and the prevention of SVT recurrence during pregnancy are extremely limited yielding its management a real challenge for the treating physician.

Risk Factors for Pregnancy Associated SVT

Risk factors for SVT are quite overlapping with those for DVT and PE. Age, female gender, recent trauma, pregnancy and lactation, chronic vein disease, personal or family history of VTE, presence of active malignancy, hereditary or acquired thrombophilia, use of contraceptive drugs or hormonal replacement therapy, obesity, infectious diseases and cellulites which affect the lower limb (i.e. erysipelas) and cardiac and/or respiratory failure are common risk factors for both SVT and DVT/PE. Common risk factors for VTE such as obesity, metabolic syndrome and restricted mobilization as well cardiovascular risk factors are also associated with the risk of SVT during pregnancy. ²¹⁻²³ In pregnant women, recent surgery, within past 1-3 months, immobilization lasting more than 3 days as well as traumatic injury of limbs further increase the risk of SVT. ⁹

These risk factors are all superimposed on the physiological hypercoagulable state that occurs during pregnancy. There is an increase of concentrations of several coagulation factors (V, VII, VIII, IX, XI, XII), von Willebrand factor (vWF) and fibrinogen, and a reduction of the anticoagulant protein C pathway due to diminished protein C receptors and lower protein S concentrations. Due to increase of plasminogen activator

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inhibitor 1 and 2 (PAI-1, PAI-2), there is also an inhibition of endogenous fibrinolysis. Last, but not least, during late pregnancy there are some venous flow changes due to compression.²⁴

The Balkan Working Group for the Prevention and Treatment of Venous Thromboembolism, taking into consideration that the thrombotic burden through pregnancy is increased during all 3 trimesters and launched immediately after labor and for at least 6 weeks postpartum,

- 1. encourages routine evaluation of the risk of VTE and SVT in pregnant women
- suggests duplex ultrasound investigation of superficial and deep venous system, when there are clinical signs and symptoms of SVT in or close to the great or lesser saphenous vein
- stresses out the need for careful measurement of thrombus length and thrombus localization regarding its distance from the SFJ
- considers that mechanical thromboprophylaxis, such as elastic garments, is needed especially if there is chronic vein disease or varicose veins.

Management of SVT in Pregnancy

Pregnancy associated SVT impacts mother's morbidity. A limited number of studies reviewed in 2 recent meta-analyses^{25,26} investigated the efficacy and safety of antithrombotic treatment in patients with SVT. To the best of our knowledge, none of them focused on pregnancy associated SVT.

The international retrospective study published by Nelson-Piercy et all., has been focused exclusively on pregnant women,²⁷ with primary aim to evaluate maternal, fetal and neonatal safety of tinzaparine use as VTE prophylaxis or treatment. Participants have been divided in 2 groups: prophylaxis (n = 1013) and treatment (n = 254) group. Tinzaparin safety profile in pregnancy appeared to be equivalent to other low molecular heparins (LMWH). Out of 1256 pregnancies included in the study, VTE rate was 2% (1% in prophylaxis group and 2% in treatment group).

The LMWH enoxaparin was the first antithrombotic agent studied in the treatment of SVT in a prospective randomized clinical trial elaborated by the Superficial Thrombophlebitis Treated By Enoxaparin Study Group in 2003. That study with a double-blind design enrolled 427 patients with documented acute symptomatic SVT of the legs, which were randomly assigned to receive subcutaneous enoxaparin 4000 anti-Xa IU subcutaneously (s.c.) once daily (o.d.) or enoxaparin 150 anti-Xa IU/kg s.c. o.d. or oral tenoxicam or placebo, once daily for 8 to 12 days. The primary efficacy outcome was DVT between days 1 and 12, defined as DVT detected by ultrasonography between days 8 and 12 or earlier if clinically indicated, or documented symptomatic pulmonary embolism. The incidence of DVT and SVT by day 12 was significantly reduced in all active treatment groups, from 30.6% (34 of 111 patients) in the placebo group to 8.3% in the 40-mg enoxaparin (p < 0.001), 6.9% in the enoxaparin 150 anti-Xa IU/kg group (p < 0.001), and 15% in the tenoxicam (p < 0.01) group.²⁸

The SeVEN study retrospectively analyzed medical records of 296 patients with documented SVT who received treatment with intermediate dose tinzaparin (10000 anti-Xa IU s.c. o.d.) for a maximum period of 5 weeks. The presence of thrombus above the knee and restricted daily activity were associated with longer period of treatment. Only one case with minor bleeding was observed. Recurrence of thrombosis over a 12-week follow-up period occurred in 6% (SVT in 14 (4.7%), DVT in 3 (1%) and thrombus extension in the superficial veins in 1 (0.3%)). However, the retrospective design of this study is a major limitation. Extended 3-month treatment with intermediate dose of tinzaparin was found to be more effective than a shorter course of treatment in the prevention of recurrent SVT and DVT. 30

The efficacy and safety of the LMWH dalteparin (200 anti-Xa IU/kg s.c. first dose then 10000 anti-Xa IU s.c. daily) was compared to anti-inflammatory agent ibuprofen in the treatment of symptomatic documented SVT in a small study that enrolled 72 patients. The study was a randomized, controlled, double-blind, double-dummy trial. The duration of treatment was 7 days. The primary outcome measure was the incidence of extension of thrombus or new symptomatic VTE during the 14-day at 3-month follow-up period. Four patients receiving ibuprofen compared with no patients receiving dalteparin had thrombus extension at 14 days (p = 0.05). However, there was no difference in thrombus extension at 3 months. Both treatments significantly reduced pain. There were no episodes of major or minor bleeding during the treatment period. 31

The CALISTO trial,³² performed in patients with documented SVT in the legs, compared the efficacy and safety of treatment with fondaparinux (a specific antithrombin-dependent factor Xa inhibitor) to placebo in reducing symptomatic VTE complications or death (from any cause). Administration of fondaparinux 2.5 mg per day subcutaneously for 45 days significantly reduced the risk of VTE event or death in patients with SVT of the legs, comparing to placebo. Equally important was finding that there was not increased risk of major bleeding.

Although the CALISTO trial established the efficacy and safety of fondaparinux in the treatment of SVT, pregnant women were excluded. Taking into consideration that some traces of fondaparinux can pass the placenta barrier and can be found in embryos' blood the findings of the CALISTO trial cannot be extrapolated in pregnant women and fondaparinux should not be considered as first line antithrombotic treatment in pregnancy.³³ Consequently, fondaparinux is not recommended as first line antithrombotic treatment in pregnant women with SVT.

A post-hoc analysis of the CALISTO trial,³⁴ stratified patients in 4 groups: 1. patients with symptomatic SVT, 2. patients with SVT initially associated with DVT or PE, 3. patients with SVT which involves SFJ and 4. patients with isolated SVT not involving SFJ. Symptomatic treatment of SVT included anti-inflammatory drugs (NSAID) or topical heparin formulations.

Anticoagulant therapy or surgical saphenofemoral ligation was suggested for patients with SVT involving SFJ.

In a recent review *Di Nisio* et al²⁵ analyzed data from 33 different randomized clinical trials considering the treatment of lower extremity SVT (Table 1). This analysis confirmed that the available evidences support the favorable benefic/risk ratio of antithrombotic treatment with fondaparinux at prophylactic dose of 2.5 mg s.c. once daily for 45 days in patients with SVT. The systematic review and meta-analysis presented Duffet et al suggested the same regiment of fondaparinux.²⁶ This conclusion has been endorsed by the most recent guidelines from the American Society of Hematology (ASH) for the management of VTE. 35 Though, the ASH guidelines highlight the absence of publications focused specifically on pregnant patients with SVT. Although the level of evidence is low, the ASH guidelines recommend treatment with LMWH over no anticoagulant treatment in pregnant women with diagnosed SVT (conditional recommendation, low certainty in evidence about effects; Table 1). The question of side effects of LMWH therapy is raised. The ASH guidelines confirmed that treatment with LMWH does not significantly increase the risk of clinically relevant bleeding. ASH guidelines did not end up on any recommendation on LMWH dosing or duration for this indication specific to pregnancy, based on the fact that there are no data reported on the literature. ASH panel generally agreed that SVT should be treated for the remainder of pregnancy and for 6 weeks postpartum, but regarding the dosing there was no agreement with options of prophylactic dose, intermediate dose, or intermediate dose decreasing to prophylactic dose once symptom resolution advanced.

Two meta-analyses showed that LMWH diminish the probability of extension or recurrence of SVT, but does not preclude VTE in patients with SVT. ^{25,26}

Mechanical means of thromboprophylaxis might be an alternative to LMWH. The usage of elastic compression stockings remains controversial and their effect in the treatment of SVT in pregnancy has not been studied.

The Balkan Working Group for the Prevention and Treatment of Venous Thromboembolism, based on the pathophysiology of VTE and the alterations of the coagulation system and the veins anatomy during pregnancy, agreed on the following suggestions:

- 1. It is crucial to treat SVT during pregnancy, as the thrombotic risk will remain increased till the end of the pregnancy and at least for the 6 weeks postpartum.
- 2. Veins' functional status should be evaluated by CUS every 3-4 months.
- 3. The first line treatment for SVT during pregnancy is LMWH. Fondaparinux 2.5 mg once daily should be considered as an alternative in case of allergic reaction or intolerance to LMWH.
- 4. SVT located below the knee or at the superficial veins of the upper limb: treatment with prophylactic dose of LMWM is suggested for a duration of 6 weeks. The continuation of the treatment beyond the 6 weeks

- should be considered if the patient has additional thromboembolic risk factors (i.e immobilization, known thrombophilia, pregnancy related vascular complications, infections, inflammatory syndrome, cancer, autoimmune pathology, personal history of VTE).
- 5. SVT located above the knee, up to 10 cm before the SVJ, or SVT situated below the knee but 5 cm before the small saphenous vein (SSV): treatment with intermediate dose of LMWH is suggested during all pregnancy and for 6 weeks post-partum.
- 6. SVT located at distance less than 10 cm of the SVJ or less than 5 cm of the SSVJ: treatment with therapeutic dose of LMWH is suggested during all pregnancy and for 6 weeks post-partum.
- Mechanical means of thromboprophylaxis (i.e. elastic compression stocking) should be considered in the presence of chronic vein disease.

Laboratory Monitoring of LMWH Treatment of SVT During Pregnancy

The inherent risk of VTE related to SVT and the complexity of the management of pregnancy associated SVT as well as the lack of evidence regarding the optimal dosage and duration of the treatment with LMWH raise the question about the place of biological monitoring of LMWH therapy. The publications considering this particular issue in pregnancy are rare. Suggestions for general population receiving LMWH is to be monitored for signs and symptoms of bleeding, but routine anti-Xa monitoring is not recommended. Complete blood count and serum creatinine levels should be periodically evaluated. ⁴⁶

Although some articles point out potential benefit from anti-Xa monitoring in specific population groups including pregnant patients, ⁴⁷ latest guidelines from ASH 2018 for management of VTE in the context of pregnancy suggest against routine monitoring of the anti-Xa activity and dose adjustment in pregnant patients receiving LMWH therapy. ⁴⁸

The Balkan Working Group for the Prevention and Treatment of Venous Thromboembolism, agreed on the above statements—suggestions:

Prophylactic, intermediate or therapeutic dose of LMWH do not require any laboratory monitoring for dose adjustment. The suggested doses are summarized in Table 2.

In women with SVT with extreme body weight, renal or hepatic insufficiency, measurement of anti-Xa activity in plasma at 4 hours after the subcutaneous injection and dose adjustment should be considered.

Thrombophilia Screening in Pregnant Women With SVT

The panel of inherited and acquired thrombophilia screening in pregnant women is composed of

Table I. Parenteral Anticoagulants for the Treatment of SVT.²⁵

			VTE, no	VTE, no./total no.	
Source	Parenteral anticoagulant	Comparison	Treatment	Comparison	RR (95% CI)
Decousus, 2010 ³²	2.5 mg/d of fondaparinux for 45 d	Fondaparinux Placebo I owMolerular-Weight Hebarin	3/1502	20/1500	0.15 (0.04-0.5)
Stenox, 2003 ²⁸		Placebo	011/9	5/112	1.22 (0.38-3.89)
Cosmi, 2012 ^{36,37}	1.5 mg/kg/d of enoxaparin for 8-12 d 8500 IU/d of parnaparin for 10 d and then 6400 II for 20 d	Placebo 4250 IU/d of parnaparin for 30 d	4/106 4/219	5/112 7/217	0.85 (0.23-3.06) 0.57 (0.17-1.91)
	4250 IU/d of parnaparin for 10 d and then 6400 IU for 20 d	8500 IU/d of parnaparin for 10 d	7/2/7	11/212	0.62 (0.25-1.57)
	8500 IU/d of parnaparin for 10 d and then 6400 IU for 20 d	8500 IU/d of parnaparin for 10 d	4/219	11/212	0.35 (0.11-1.09)
Vesalio, 2005 ³⁸	Weight-adjusted dose of nadroparin for 10 d and then half dose for 20 d	2850 IU/d of nadroparin for 30 d	2/81	4/83	0.51 (0.10-2.72)
Spirkoska, 2015 ³⁹ Gorski, 2005 ⁴⁰	5000 IU/d of dalteparin for 6 wk 40 mg/d of enoxaparin for 7-14 d	10 000 IU/d of dalteparin for 6 wk Heparin spray gel for 7-14 d	1/33	2/35 3/21	0.30 (0.03-2.70)
Katzenschlager, 2003 ⁴¹	40 mg/d of enoxaparin for 7-14 d	Heparin spray gel 7-14 d	0/21	0/18	
Stenox, 2003 ²⁸	40 mg/d of enoxaparin for 8-12d	20 mg/d of tenoxicam for 8-12 d	011/9	4/99	1.35 (0.39-4.64)
!	1.5 mg/kg/d of enoxaparin for 8-12 d	20 mg/d of tenoxicam for 8-12 d	4/106	4/99	0.93 (0.24-3.63)
Titon, 1994 ⁴²	6150 IU/d of nadroparin for 6 d	500 mg/d of naproxen for 6 d	0/38	0/35	
Ç	61.5 IU/kg/d of nadroparin for 6 d	500 mg/d of naproxen for 6 d	98/0	0/35	
Lazano, 2003 ⁴³	I mg/kg of enoxaparin twice per day for I wk and then I mg/kg/d for 3 wk	Saphenofemoral disconnection	0/30	2/30	0.20 (0.01-4.00)
Uncu, 2009 ⁴⁴	190 IU/kg/d of canadroparin for 10 d	190 IU/kg/d of canadroparin plus 60 mg of acemetacin twice/d for 10d	0/25	0/25	
Belcaro, 1999 ⁴⁵	Prophylactic LMWH plus GCS	Graduated compression stockings (GCS)	9//0	8//9	0.08 (0-1.38)
SEVEN 2018 ²⁹ and Nikolakopoulos, 2018 ³⁰	Variable dose of tianzaparin	Standardized intermediate dose of tianzaparin	15/98	0/49	
Rathbun, 2012³¹	dalteparin 200 units/kg s.c. first dose	ibuprofen 800 mg given orally 3 times	I month	I month	
	then 10,000 units s.c. daily for	daily for 7 days	0/37	4/35	
	6 additional doses		II month 4/37	ll month 6/35	

Abbreviations: LMWH, low-molecular-weight heparin; RR, risk ratio; VTE, venous thromboembolic event; s.c., subcutaneous; IU, international unit; d, day; wk, week.

	Prophylactic dose	Intermediate dose	Therapeutic dose
Dalteparin	5000 IU SC daily or twice daily > 20 weeks Obesity: 7500 IU SC daily	100 IU/kg SC daily or 5000 IU SC twice daily	200 IU/kg daily or 100 IU/kg SC twice daily
Enoxaparin	40 mg SC daily or 30 mg SC twice daily Obesity: 60 mg SC daily	40 mg SC twice daily	I mg/kg SC twice daily or I.5 mg/kg SC daily
Nadroparin	2850 IU SC daily	Not applicable	171 IU/kg SC daily
Tinzaparin	4500 IU SC daily Obesity: 75 IU/kg daily	4500 IU SC twice daily or 9000 IU SC daily	175 IU/kg SC daily
Danaparoid	750 IU SC twice daily	Not applicable	2000 IU SC twice daily

Table 2. Prophylactic, Intermediate and Therapeutic Dosage of LMWH.

Abbreviations: LMWH, low-molecular-weight heparin; SC, subcutaneous; IV, intravenous; aPTT, activated partial thromboplastin time; IU, international unit.

- a. the genetic research for factor V Leiden mutation and prothrombin G20210A mutation,
- the measurement of the natural inhibitors of blood coagulation protein C, and antithrombin. Due to normal decrease of protein S levels during pregnancy the measurement of this natural coagulation inhibitor is not recommended.
- the level of anticardiolipin antibodies IgG and IgM and anti-beta-2 glycoprotein 1 IgG and IgM antibodies as well as the testing for lupus anticoagulant.⁴⁹

Though, thrombophilia screening in patients with VTE is a controversial issue among experts.

Latest guidelines considering inherited thrombophilias in pregnancy issued by The American College of Obstetricians and Gynecologists (ACOG) defines clinical scenarios in which assessment of thrombophilia screening in pregnancy is recommended⁵⁰:

- 1. personal history of VTE, with or without risk factors, without previous testing,
- 2. first-degree relative with history of high-risk inherited thrombophilia(s).

The Balkan Working Group for the Prevention and Treatment of Venous Thromboembolism, regarding the need of thrombophilia testing in women with SVT during pregnancy or lactation agreed on the following statements—suggestions:

- testing for different types of inherited thrombophilia, is not necessary to be performed at diagnosis of SVT, as these results are not going to influence the therapeutic strategy regarding the initiation of the anticoagulant treatment, the intensity and its duration through pregnancy and lactation.
- The testing for lupus anticoagulant and antibodies related with the antiphospholipid syndrome (APLS) might influence the decision regarding the dose of LMWH (i.e. in case of positive test administration of therapeutic dose of LMWH could be considered) or the addition of aspirin.

3. From this point of view, the Balkan Working Group proposes that the research for lupus anticoagulant and APLS related antibodies to be performed early after the diagnosis of the SVT.

Conclusion and Future Directions

Management of pregnant women with superficial vein thrombosis is a challenging issue because the burden and the morbidity of the disease are not negligible and the available data from clinical trials are extremely poor to support an evidencebased approach. Facing this clinical need, the Balkan Working Group on the Prevention and Treatment of Venous Thromboembolism presents a comprehensive strategy for the diagnosis and treatment of pregnant women with SVT. The basic principle adopted by the Group is that SVT in pregnancy is the resultant of intrinsic risk factors of vascular and/or hematological origin combined with the hypercoagulable state of pregnancy. The Balkan Working Group on the Prevention and Treatment of Venous Thromboembolism proposes antithrombotic treatment based on the use of LMWH. Acknowledging the absence of clinical trials specific for the antithrombotic treatment in pregnancy related SVT the Group proposes an extrapolation of the therapeutic schemas that have been studied in non pregnant patients with SVT. Though, in women with SVT, pregnancy per se is an independent risk factor for thrombosis recurrence and even pulmonary embolism leading to application of more intensive antithrombotic treatment as compared to that applied in SVT without pregnancy. Due to the particularities in the pharmacokinetics and pharmacodynamics of the LMWHs in pregnant women, the Group endorses a strategy based on a close biological and clinical follow up of the women being on antithrombotic treatment for pregnancy associated SVT and stresses out the limitations on the use of antithrombotic agents that cross the placenta.

The Balkan Working Group on the Prevention and Treatment of Venous Thromboembolism underlines that pregnancy associated thrombosis has major impact on public health but lacks good quality clinical data for evidence based management. Moreover the design and realization of clinical trials to evaluate the efficacy and safety of the various antithrombotic

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strategies in pregnancy is a difficult and complex task that involves major ethical issues. The set-up of an international database and the application of artificial intelligence and machine learning methods might be a realistic strategy to respond to the unmet need for optimization of the management of pregnant women with thrombosis, and particularly those with SVT.

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