Venous thromboembolism in women

Venous thromboembolism in women – A focus on unusual sites, pregnancy and thrombophilia

Maria Abbattista

Venous thromboembolism in women – A focus on unusual sites, pregnancy and thrombophilia

Thesis Maastricht University
ISBN: 978-94-6423-526-5

Cover: Vincent van Gogh - Almond blossom, 1890

Venous thromboembolism in women – A focus on unusual sites, pregnancy and thrombophilia

DISSERTATION

To obtain the degree of Doctor of Philosophy at the Maastricht Univeristy, on the authority of the Rector Magnificus,
Prof. Dr. Pamela Habibovic
in accordance with the decision of the Board of Deans,
to be defended in public on
Friday 11th of February 2022, at 10:00 hours

By

Maria Abbattista

(born on May 14th, 1988 in Foggia)

Supervisor

Prof. Dr. H. ten Cate

Co-supervisors

Prof. Dr. P.M. Mannucci (University of Milan)
Dr. I. Martinelli (Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan)

The Assesment Committee

Prof. Dr. A. Kroon (Chair)
Dr. A. J. ten Cate-Hoek
Prof. Dr. S. Eichinger (Medical University Vienna)
Prof. Dr. M. Spaanderman
Dr. F.A. Klok (Leiden University Medical Center)

Contents

Chapter 1

General introduction

General introduction

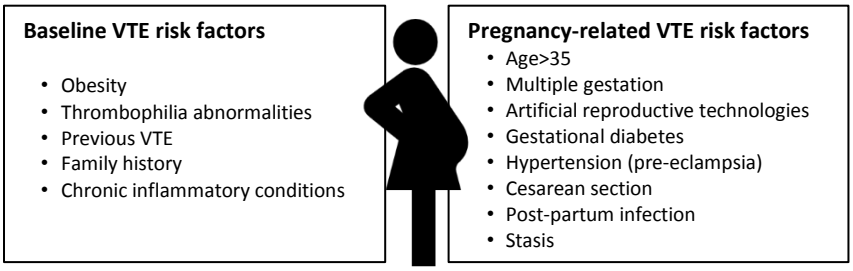
Venous thromboembolism (VTE) is a medical condition caused by the presence of a blood clot in the veins that could partially or completely occlude the vessel lumen. Deep vein thrombosis of the lower limbs and pulmonary embolism are the most common manifestations of VTE, representing the third most frequent cardiovascular disease, after myocardial infarction and stroke.[1] VTE is a multicausal disease and its incidence varies widely depending on its etiology (provoked vs. unprovoked), the period of life to which it refers (pediatric, adult or reproductive, and older age), and if it is the first episode or a recurrence. The annual incidence of VTE is approximately 1 per 1000 person-years [2,3], it is rare in children, and increases with age over 80 years up to 6-fold.[2] About 25-30% of people with a previous VTE are at risk of recurrence [4], with similar rate between men and women.[5] The overall incidence of VTE is similar between sexes [6], notwithstanding sex-related differences have been shown in incidence rate and clinical presentation according to the age group and sex-related exposures. Although male sex is a well-known risk factor for VTE, particularly at increasing age, women are at higher risk than men during reproductive age.[2,7,8] Indeed, the increased risk of VTE in women during childbearing age is mainly attributable to female-related risk factors such as hormonal contraceptive use, pregnancy or puerperium (defined as the 6 weeks period after delivery). Sex also appears to modulate the presentation of VTE. Data from three registries showed a 10% more frequent pulmonary embolism in women compared to men.[9]

Other than the most common manifestations, VTE may involve any district of the venous system and in 10% of cases can occur at such unusual sites as the deep circulation of the upper extremities (i.e., subclavian, axillary, and brachial veins), the splanchnic circulation (i.e., portal, mesenteric, splenic vein, and Budd-Chiari syndrome involving the small hepatic veins), cerebral circulation (i.e., cerebral veins and dural venous sinuses), renal, ovarian and retinal circulation. VTE at unusual sites is rare in the general population (1-5 cases per million persons)[10], but it is more common in other and some sex-specific differences exist. This is valid in particular for cerebral vein thrombosis (CVT), whose estimated annual incidence is between 2 to 15 cases per million persons[11-13], but it is a female-specific manifestation with a frequency 3 times higher in women than in men because of its strong association with oral contraceptive use and pregnancy.[14] Historically, there are three factors, known as the Virchow's triad that predispose to thrombosis: endothelial damage on the vessel walls, blood flow stasis and

hypercoagulability. The hypercoagulable state can be due to both acquired or inherited conditions. Inherited forms of hypercoagulability, known as thrombophilia abnormalities, are consistently associated with a 2- to 10-fold increased risk of developing VTE.[15] They can be rare and severe as the deficiencies of the naturally occurring anticoagulant proteins antithrombin, protein C and protein S (0.2%-0.02% prevalence), or common and mild as the heterozygous mutation of factor V Leiden (3-7%) and prothrombin gene G20210A (0.7-4%). Acquired hypercoagulability is far more common and consists of recent transient inflammatory conditions such as surgery, trauma, or infection, and chronic inflammatory conditions (e.g., obesity, diabetes, autoimmune disease, cancer).

Women have additional acquired provoking risk factors, such as oral contraceptives use, pregnancy, puerperium, and hormonal replacement therapy. The use of oral contraceptives or hormonal replacement therapy shifts the hemostatic balance to a procoagulant condition through increased plasma concentration of procoagulant factor II, VII, VIII, X, and fibrinogen, while natural anticoagulant protein S and antithrombin are reduced, as well as the fibrinolytic activity.[16] Similarly, during pregnancy and puerperium, several hemostatic changes occur, inducing a physiological procoagulant state that reflects all the three elements of the Virchow's triad. These changes probably indicate a protective evolutionary adaptation against bleeding at the time of delivery or miscarriage. Women on oral contraceptive are at 2 to 6-fold increased risk of VTE compared to non-users[17] and pregnant women have a 4-fold increased risk to develop VTE compared to non-pregnant women of similar age.[18] Moreover, in 25% of cases during pregnancy, women may develop a pulmonary embolism that could be fatal in up to 11%.[19] The concomitant presence of one or more risk factors for VTE during pregnancy (Figure 1) can further increase the risk. Additionally, the risk of recurrent VTE during pregnancy is increased in women who had had a previous hormonal-related event [20,21] or in those with a personal history of VTE.[22]

Figure 1: Prothrombotic risk factors during pregnancy



VTE during pregnancy could be a serious complication and constitutes a diagnostic and therapeutic challenge. As a result, the use of antithrombotic prophylaxis as preventive strategy during pregnancy deserves a separate discussion. Low molecular weight heparin (LMWH) is the mainstay of anticoagulation in pregnant women, because of its safety profile, not crossing the placenta. Several guidelines on the use of LMWH as anticoagulant prophylaxis to prevent pregnancy -related VTE have been produced by different hematological and obstetrical/gynecological scientific societies.[23-25] Moreover, women at increased risk of pregnancy related-VTE appear also at increased risk of other vascular obstetrical complications, that can lead to adverse pregnancy outcomes such as miscarriage, preeclampsia, stillbirth and intrauterine growth restriction.[26-29] Although these complications can be in part explained by an impaired placental circulation associated with the presence of thrombophilia abnormalities [29,30], it is controversial whether there is an association between thrombophilia and uteroplacental thrombosis that leads to adverse pregnancy outcomes. However, it has been suggested that antithrombotic prophylaxis, preventing placental thrombosis, might also prevent recurrent placenta-mediated pregnacy complications.[27,31] Hence, the efficacy of anticoagulant prophylaxis during pregnancy should consider both outcomes of mother and fetus.

Outline and aims of the thesis

This thesis aims to summarize several epidemiological and clinical aspects of venous thrombosis in women focusing on VTE at unusual sites such as cerebral vein thrombosis and female-related prothrombotic risk factors. In particular, this thesis is structured as follows: **Chapter 2**

summarizes clinical features, symptoms, risk factors and the therapeutic approach of rare thrombotic manifestations including ovarian vein thrombosis and cerebral vein thrombosis as female-specific events. CVT, the rare thrombotic manifestation that affects particularly young women, is broadly described in **Chapter 3**. The case-control study on **Chapter 4** focuses on a female-related risk factor, namely the duration of oral contraceptive use, to evaluate its association with the thrombotic risk. Pregnancy-related VTE and pregnancy outcomes after a previous episode of CVT have been investigated in **Chapter 5** and **Chapter 6.** Then, the incidence of pregnancy-related VTE, pregnancy outcomes and the effectiveness of low molecular weight heparins during pregnancy have been evaluated in **Chapter 7,** that is focused on a rare population of pregnant women with antithrombin deficiency (the most severe thrombophilia abnormality) and in **Chapter 8,** that consider the first pregnancy after a previous VTE in a broad population. A general discussion and summary of the outcomes described in this thesis is provided in **Chapter 9**.

References

1. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008;28(3):370-372.
2. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692-699.
3. Arshad N, Isaksen T, Hansen JB, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. Eur J Epidemiol. 2017;32(4):299-305.
4. Spiezia L, Campello E, Bon M, et al. ABO blood groups and the risk of venous thrombosis in patients with inherited thrombophilia. Blood Transfus. 2013;11:250-253.
5. Giustozzi M, Valerio L, Agnelli G, et al. Sex-specific differences in the presentation, clinical course, and quality of life of patients with acute venous thromboembolism according to baseline risk factors. Insights from the PREFER in VTE. Eur J Intern Med. 2021;88(March):43-51.
6. Tormene D, Ferri V, Carraro S, Simioni P. Gender and the risk of venous thromboembolism. Semin Thromb Hemost. 2011;37(3):193-198.
7. Roach REJ, Lijfering WM, Rosendaal FR, Cannegieter SC, Le Cessie S. Sex difference in risk of second but not of first venous thrombosis: Paradox explained. Circulation. 2014;129(1):51-56.
8. Bleker SM, Coppens M, Middeldorp S. Sex, thrombosis and inherited thrombophilia. Blood Rev. 2014;28(3):123-133.
9. Scheres LJJ, Brekelmans MPA, Beenen LFM, Büller HR, Cannegieter SC, Middeldorp S. Sex- specific differences in the presenting location of a first venous thromboembolism. J Thromb Haemost. 2017;15(7):1344-1350.
10. Ageno W, Dentali F, Pomero F, et al. Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari Syndrome. Thromb Haemost. 2017;117(04):794-800.
11. Stam J. Thrombosis of the Cerebral Veins and Sinuses. N Engl J Med. 2005;352(17):1791-1798.
12. Bousser M-G, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2):162-170.
13. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral Venous Sinus Thrombosis Incidence is Higher Than Previously Thought: A Retrospective Population-Based Study. Stroke. 2016;47(9):2180-2182.
14. Maali L, Khan S, Qeadan F, Ismail M, Ramaswamy D, Hedna VS. Cerebral venous thrombosis: continental disparities. Neurol Sci. 2017;38(11):1963-1968.
15. Middeldorp S, Van Hylckama Vlieg A. Does thrombophilia testing help in the clinical management of patients? Br J Haematol. 2008;143(3):321-335.
16. Bremme KA. Haemostatic changes in pregnancy. Best Pract Res Clin Haematol. 2003;16(2):153-168.
17. van Hylckama VA, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ. 2009;339:b2921.
18. Heit JA. Trends in the Incidence of Venous Thromboembolism during Pregnancy or Postpartum: A 30-Year Population-Based Study. Ann Intern Med. 2005;143(10):697.
19. Abe K, Kuklina E V., Hooper WC, Callaghan WM. Venous thromboembolism as a cause of severe maternal morbidity and mortality in the United States. Semin Perinatol. 2019;43(4):200-204.
20. Pabinger I, Grafenhofer H, Kaider A, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J Thromb Haemost. 2005;3(5):949-954.

21. Stefano V De, Martinelli I, Rossi E, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br J Haematol. 2006;135(3):386-391.
22. Galambosi PJ, Ulander VM, Kaaja RJ. The incidence and risk factors of recurrent venous thromboembolism during pregnancy. Thromb Res. 2014;134(2):240-245.
23. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2):e351S-e418S.
24. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2(22):3317-3359.
25. Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018;132(5):e197-e207.
26. Walker ID. Thrombophilia in pregnancy. J Clin Pathol. 2000;53(8):573-580.
27. Rodger MA, Carrier M, Le Gal G, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. Blood. 2014;123(6):822-828.
28. Hansen AT, Schmidt M, Horváth-Puhó E, et al. Preconception venous thromboembolism and placenta-mediated pregnancy complications. J Thromb Haemost. 2015;13(9):1635-1641.
29. Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: A systematic review. Br J Haematol. 2006;132(2):171-196.
30. Rodger MA, Langlois NJ, Ip De Vries J, et al. Low-Molecular-Weight Heparin for Prevention of Placenta-Mediated Pregnancy Complications: Protocol for a Systematic Review and Individual Patient Data Meta-Analysis (AFFIRM). Syst Rev 2014; 3: 69
31. De Santis M, Cavaliere AF, Straface G, Di Gianantonio E, Caruso A. Inherited and acquired thrombophilia: Pregnancy outcome and treatment. Reprod Toxicol. 2006;22(2):227-233.

Chapter 2

Treatment of unusual thrombotic manifestations

Abbattista M, Capecchi M, Martinelli I.

Blood. 2020 Jan 30;135(5):326-334. doi: 10.1182/blood.2019000918. PMID: 31917405.

Summary

Venous thrombosis rarely occurs at unusual sites such as cerebral, splanchnic, upper-extremity, renal, ovarian, or retinal veins. Clinical features, symptoms, and risk factors of rare thrombotic manifestations are heterogeneous and in large part differ from those typical of the commonest manifestations of venous thrombosis at the lower extremities. The therapeutic approach also varies widely according to the affected site, whether cerebral, abdominal, or extra-abdominal.

To date, anticoagulant therapy for thrombosis at unusual sites is generally accepted, but the optimal therapeutic approach remains challenging. This review is focused on the treatment of unusual thrombotic manifestations as reported in the most recent guidelines and according to the updated scientific literature.

Introduction

Thrombosis at unusual sites accounts for ≈~10% of all cases of venous thrombosis, affecting any venous region other than the deep or superficial veins of the lower limbs or those involved in pulmonary circulation. Its annual incidence varies from 1 to 2 cases per 1 million individuals for splanchnic vein thrombosis to 5 per 1000 individuals for retinal vein thrombosis.[1,2] Cerebral venous sinus thrombosis (CVST) occurs more often in young women because of its strong association with oral contraceptive use and pregnancy.[3] Splanchnic vein thrombosis (SVT) often complicates underlying diseases such as liver cirrhosis, myeloproliferative neoplasms (particularly those bearing the Janus kinase 2 V617F mutation), paroxysmal nocturnal hemoglobinuria, Behçet's disease, inflammatory bowel diseases, or abdominal cancers.[4] Upper extremity deep vein thrombosis (UEDVT) is defined as primary when resulting from effort (Paget-Schrotter syndrome) or thoracic outlet syndrome or when unprovoked and as secondary when caused by triggering factors, mainly indwelling central venous catheters (CVCs)[5,6] but also pacemakers and cancer. Renal vein thrombosis (RVT) is the most common thrombotic manifestation in neonates, particularly those born prematurely, accounting for 16% to 20% of all thromboembolic events,[7] and is mainly related to umbilical or femoral indwelling catheters reaching the inferior vena cava, whereas in adults, it is mainly associated with cancer (66%) and nephrotic syndrome (20%), as well as renal transplantation (0.5%) and local trauma (surgery or venous catheters).[8] Ovarian vein thrombosis (OVT) is usually associated with pregnancy or the postpartum setting, pelvic inflammation, abdominal cancer, and pelvic surgery.[9] Retinal vein occlusion (RVO) involving the central or branch veins or, more rarely, the hemicentral vein is mainly caused by intraocular hypertension or glaucoma or, in contrast to venous thrombosis at other sites, by the systemic risk factors for arterial thrombosis (i.e., arterial hypertension, diabetes, hyperlipidemia).[10,11]

To date, anticoagulant therapy with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) followed by vitamin K antagonists (VKAs) is generally accepted in patients with thrombosis at unusual sites. With the exception of 4 small randomized controlled trials (RCTs) in patients with CVST, 1 in those with OVT, and 3 in those with RVO, no RCTs have been performed in patients with unusual thrombotic manifestations, whose treatment remains challenging in the absence of high-quality evidence.

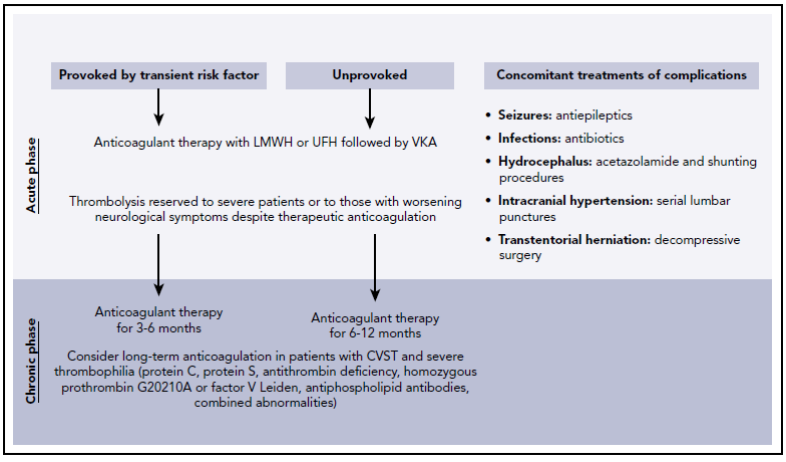
The aim of this review is to summarize the therapeutic options for thrombosis at unusual sites, examining the existing guidelines published by various scientific societies and screening their relative references. In addition, we consulted 2 databases of evidence-based content (Trip Medical Database and Dynamed Plus) and searched PubMed for relevant scientific literature on thrombosis at unusual sites after the publication date of the most recent guidelines.

CVST

A meta-analysis of 2 small and older RCTs showed that treatment of CVST with LMWH or UFH in the acute phase is safe and efficacious in terms of mortality and disability[12-14] and does not enhance the risk of intracranial hemorrhage.[15] Therefore, heparin is recommended by several neurological guidelines[16-18] and by the American College of Chest Physicians (ACCP),[19] even in the presence of intracranial hemorrhage. Two more recent RCTs and a metaanalysis favored LMWH over UFH,[20-22] although the small sample size of the studies allowed recommendations of only moderate-quality evidence. UFH, with its shorter half-life and easier reversibility, should be preferred in patients with unstable cases or in those requiring invasive procedures. Endovascular treatment with local thrombolysis (urokinase, streptokinase, or recombinant tissue plasminogen activator) or mechanical thrombectomy has been investigated only in small case series and seems associated with a high risk of intracranial haemorrhage (7.6%) and mortality (9.2%).[23] Local thrombolysis was compared with heparin treatment in the TO-ACT trial (registered at www.clinicaltrials.gov as #NCT01204333), which was prematurely interrupted because of futility (no difference in the primary outcome disability) after the inclusion of 67 patients.[24,25] A systematic review of 26 patients treated with systemic thrombolysis (mainly urokinase) reported an extracranial or intracranial hemorrhage in 30.7% of patients and partial or complete recanalization in 61.5%.[26] Hence, local or systemic thrombolysis should be reserved for patients with severe cases or those with worsening neurological symptoms despite therapeutic anticoagulation.[27] In the acute phase, complications could require specific management with antiepileptic drugs in the case of seizures[17]; acetazolamide and
shunting procedures to drain excess cerebrospinal fluid in the case of hydrocephalus with neurological deterioration; serial lumbar punctures in the case of intracranial hypertension, papilledema, or reduced visual acuity[18]; or

decompressive hemicraniectomy as a lifesaving procedure in the rare case of transtentorial herniation resulting from large hemorrhagic infarcts. The DECOMPRESS-2 registry is an ongoing prospective evaluation of patients with CVST undergoing decompressive surgery, and the interim analysis of 22 patients showed a 6-month mortality rate of 23.8% in patients treated vs 100% in those not treated.[28] After the acute phase, anticoagulant therapy is administered for secondary prevention of CVST or venous thrombosis at other sites. The risk of recurrent thrombosis is low, and long-term anticoagulation should be reserved for patients with persistent and unmodifiable risk factors such as severe thrombophilia and solid or hematological neoplasms.[29,30] The American Heart Association and American Stroke Association guidelines recommend that patients with CVST secondary to a transient risk factor receive anticoagulant therapy with VKAs for 3 to 6 months, whereas those with unprovoked CVST should receive such therapy for 6 to 12 months.[17] Figure 1 summarizes the recommendations for treatment of CVST. For patients with no recognized thrombophilia abnormalities, the same guidelines recommend a switch to antiplatelet therapy, but in the absence of controlled trials or observational studies, this recommendation seems unsupported.31 The ongoing EXCOA-CVT study (registered at http://www.isrctn.com as #ISRCTN25644448) comparing short (3-6 months) with long (12 months) duration of oral anticoagulant therapy in patients with CVST will provide new insights.[32]

Figure 1. Recommendations for treatment of CVST

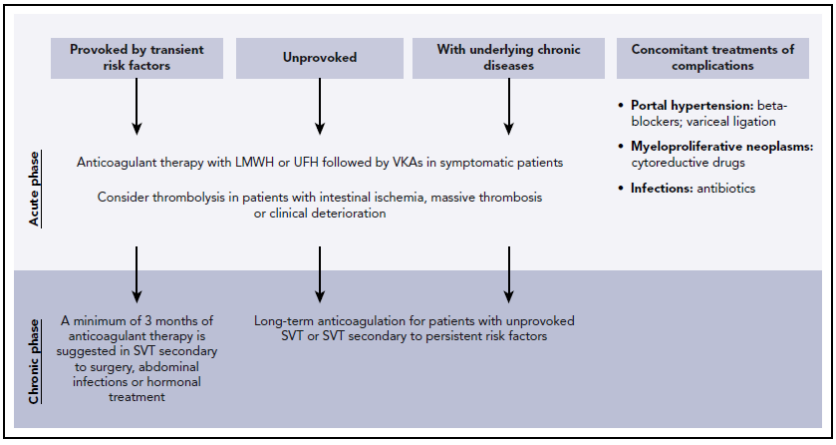


SVT

On the basis of observational studies, anticoagulant therapy in patients with SVT (portal intra- or extrahepatic, superior mesenteric, and splenic vein) is recommended by the ACCP guidelines only in symptomatic cases and not in those incidentally detected, unless in the case of extensive thrombosis, thrombus progression, or active cancer.[33] This approach is in accordance with the evidence indicating that symptomatic patients have a double risk of recurrent thrombosis rather than bleeding, whereas asymptomatic patients have similar risks.[34,35] In contrast, the American Association for the Study of Liver Diseases guidelines recommend anticoagulation for all patients with acute portal vein thrombosis, including asymptomatic patients.[36] For patients with isolated portal or splenic vein thrombosis, some authors suggest a watchful waiting approach, based on a retrospective study showing spontaneous thrombus regression in 47% of patients, stability in 45%, and progression in only 7%.[37] An exception is acute mesenteric vein thrombosis, which may represent an emergency, requiring prompt initiation of anticoagulation together with support therapy because of the high 30-day mortality (20%) despite treatment.[38] The European Society of Vascular Surgery recommends anticoagulation with heparin as first-line treatment followed by oral anticoagulants, in the absence of major contraindications.[39] In patients with intestinal ischemia, local catheter–directed thrombolysis should be considered with the aim of avoiding ischemic bowel resection.[40] Thrombolysis should also be considered in patients with particularly extended thrombosis or clinical deterioration despite anticoagulant therapy, if their bleeding risk is low. There are insufficient data to suggest local catheter–directed over systemic thrombolysis.[40] The optimal duration of anticoagulant therapy is not established, but a minimum of 3 months is suggested for patients with SVT associated with transient risk factors.[36] Patients with persistent risk factors, such as myeloproliferative neoplasms or cirrhosis, or those with idiopathic thrombosis should continue anticoagulant therapy for life.[36,41] An international prospective cohort study of 604 patients with SVT showed incidence rates per 100 patient-years of 3.8 for major bleeding and 7.3 for recurrent thrombosis, 3.9 and 5.6 during anticoagulation, and 1.0 and 10.5 after anticoagulation discontinuation, respectively. The highest incidence rates of major bleeding and thrombosis were observed in patients with cirrhosis (10.0 and 11.3 per 100 patient-years, respectively).[42] The recanalization rates after 1 year of anticoagulant therapy with VKAs were 38%, 61%, and 54% for

portal, mesenteric, and splenic veins, respectively.[43] These figures indicate indefinite anticoagulation in most patients. However, many patients have risk factors for bleeding, such as liver cirrhosis, possibly associated with portal hypertension and esophageal varices; splenomegaly, possibly associated with thrombocytopenia; or cancer. A large Danish cohort study of 1915 patients followed for 10 years reported higher bleeding rates in patients with all-cause SVT than in those with lower-extremity DVT (LEDVT) or pulmonary embolism.[44] However, the risk of bleeding in cirrhotic patients seems to be lower than expected (,5%)[45] and is further reduced during anticoagulation.[46,47] Hence, esophageal varices and liver dysfunction–associated coagulopathy do not represent absolute contraindications to anticoagulation, as confirmed by a recent meta-analysis, which showed higher recanalization rates and lower variceal bleeding rates in patients with portal vein thrombosis and liver cirrhosis who received anticoagulant therapy compared with those who did not.[48] To reduce the bleeding risk, patients with liver cirrhosis often benefit from prophylaxis for variceal bleeding with nonselective b-blockers and/or endoscopic variceal ligation. Regarding anticoagulant treatment in patients with SVT and moderate to severe thrombocytopenia, evidence is limited to expert opinion. In the absence of bleeding complications, the intensity of anticoagulation can be reduced to half therapeutic doses, if platelet counts are between 50 and 100 x 10^9/L, and to prophylactic doses, if platelet counts are between 30 and 50 x 10^9/L. In the presence of severe thrombocytopenia (<30 x 10^9/L), some experts recommend against anticoagulation.[40] Recommendations for treatment of SVT are summarized in Figure 2.

Figure 2. Recommendations for treatment of SVT



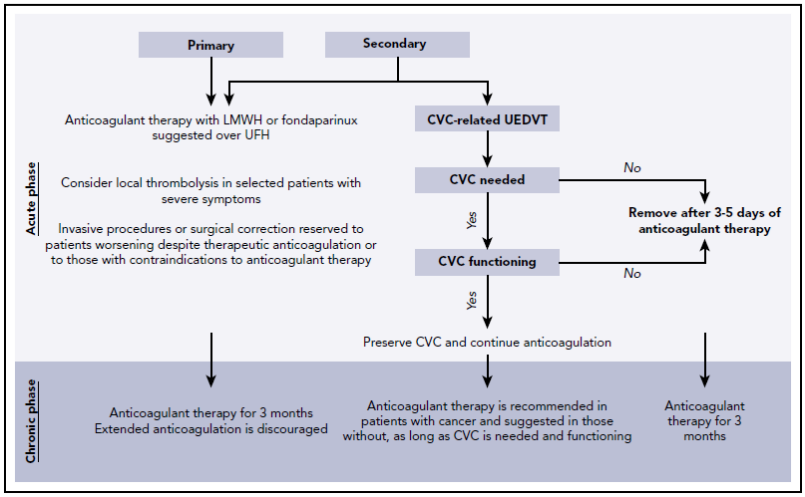
UEDVT

On the basis of moderate-quality and indirect evidence from the treatment of LEDVT, the ACCP guidelines recommend parenteral anticoagulation in the acute phase of primary UEDVT involving the axillary or more proximal veins and suggest LMWH or fondaparinux over UFH or thrombolysis for a minimum duration of 3 months.[33] Uncertainty remains regarding full-dose anticoagulation in patients with isolated primary brachial vein thrombosis, a treatment favored only in severe symptomatic patients; for the others, clinical surveillance, LMWH, or fondaparinux at prophylactic doses for 3 months or therapeutic doses for <3 months is suggested.[33] Selected patients with severe cases may benefit from catheter-directed thrombolytic treatment, encouraged over systemic thrombolysis.[33,49] Like LEDVT, UEDVT may be complicated by post thrombotic syndrome (PTS). Because no RCTs on the prevention of PTS with compression sleeves or venoactive medications are available, the ACCP guidelines recommend against their use, but anecdotal evidence supports bandages or compression sleeves.[33] A recent metaanalysis compared the rates of PTS, recurrent thrombosis, and major bleeding in patients with primary or secondary UEDVT treated conservatively with anticoagulant therapy or invasively with thrombolytic therapy and/or decompressive surgery. Patients receiving anticoagulant therapy had a higher risk of PTS (23.2% vs 11.8%), similar risk of recurrent thrombosis (7.6% vs 7.5%), and lower risk of bleeding (1.3% vs 3.8%) than those treated invasively; the frequency of PTS was higher in patients with primary than in those with secondary UEDVT.[50] Hence, the decision for aggressive treatment should be weighed against the risk of bleeding and that of PTS, but because the latter is unpredictable, more data are necessary before making recommendations.
Limited data are available on percutaneous mechanical thrombectomy, angioplasty along with endovascular stenting, filter insertion, and resection of the first rib for decompression in the presence of thoracic outlet syndrome,[51] none of which are routinely recommended in the acute phase; these should be reserved for exceptional cases such as patients for whom anticoagulant therapy fails or those in whom anticoagulant therapy is contraindicated.[33]

The optimal treatment duration of primary UEDVT beyond 3 months is still debated. A majority of patients are managed with heparin followed by VKAs for up to 3 or 6 months, as recommended.[50] Although a prospective population-based study showed a similar rate of recurrent thrombosis in patients with UEDVT and in those with LEDVT,[52] a direct comparison

between unprovoked UEDVT and LEDVT showed a lower recurrence rate in those with UEDVT (4% vs 19%) over a 5-year period.[53] Hence, unlike in LEDVT, extended anticoagulation is discouraged in patients with unprovoked UEDVT.[33] For secondary CVC-related UEDVT, the ACCP guidelines support maintaining the CVC if still functioning and needed, despite the presence of the thrombus. Anticoagulation is recommended as long as the CVC remains in place in patients with cancer and suggested in those without.[33,54] If the CVC is not functioning or no longer required, it can be removed after a short period of anticoagulation (3-5 days)[54]; thereafter, 3 months of anticoagulant therapy are suggested in patients with cancer and recommended in those without.[33,54] Figure 3 summarizes the recommendations for treatment of primary and secondary UEDVT.

Figure 3. Recommendations for treatment of UEDVT



RVT

RVT is frequently encountered in neonates, for whom current guidelines provide recommendations; however, its management in adults is not specifically addressed. The pivotal recommendation of the American Society of Hematology for the management of RVT in neonates is to involve a multidisciplinary team that includes neonatologists, radiologists, hematologists, and nephrologists.[55] According to the ACCP guidelines, unilateral RVT can be managed only with supportive therapy and radiologic monitoring.

Anticoagulant therapy is suggested in patients with thrombus extension as well as in patients with RVT and nephrotic syndrome (pulmonary embolism is reported in up to 76% of cases), impairment of renal function, or extension into the inferior vena cava. In the case of unilateral RVT in monokidney patients or those receiving kidney transplants, worsening RVT despite adequate anticoagulant therapy or life-threateningn bilateral RVT with severe renal deterioration, thrombolysis as well as the placement of a temporary suprarenal inferior vena cava filter should be considered.[55,56] In neonates, thrombolysis is complicated by a 21% rate of major bleeding.[55] In general, when using heparin, one should consider that neonates have a high clearance and often reduced antithrombin plasma levels (physiologically or resulting from proteinuria in the presence of nephrotic syndrome), so higher heparin doses than those for adults and perhaps antithrombin concentrate may be needed. In contrast, in the frequent clinical case of RVT presenting with renal function impairment, particular attention should be given to anticoagulant dose adjustment to avoid drug accumulation. Despite the scarce evidence, it seems that the same outcome in terms of mortality, resolution of RVT, long-term renal impairment, and hypertension is achieved regardless of the use of anticoagulant therapy.[55] The suggested duration of anticoagulant therapy in neonates with RVT secondary to transient risk factors varies from 6 weeks to 3 months, whereas those with unprovoked or nephrotic syndrome–associated RVT should continue until resolution of proteinuria.[56,57]

OVT

In a vast majority of cases, OVT is a complication of pregnancy or postpartum conditions. Six retrospective studies, 1 prospective study, and a small RCT on the management of pregnancy- and postpartum-associated OVT were included in a systematic review.[58] Interventions included mainly antibiotic and/or anticoagulant therapy, the latter for a median duration of 3 months, as reported in the 2 largest cohorts of 13 and 74 patients, respectively.[59,60] Concerning the type of anticoagulant therapy, the most frequently used was LMWH, but warfarin[58,60,61] and, rarely, an anti–factor Xa oral anticoagulant were also used.[9,62]

On the basis of this evidence and extrapolating the duration of anticoagulant therapy from the ACCP guidelines on the treatment of LEDVT,[49] 3 months are suggested for symptomatic postpartum OVT, with the addition of

antibiotic therapy, if needed.[58] Among the gynecological guidelines, OVT is mentioned
only by the Canadian Society of Obstetricians and Gynecologists, which recommends parenteral broad-spectrum antibiotic therapy until 2 days after resolution of symptoms and anticoagulant therapy for 1 to 3 months.[63] Anticoagulant therapy is discouraged in asymptomatic postpartum-associated OVT with no evidence of thrombus extension or pulmonary embolism.[58] Data on treatment of OVT outside of pregnancy or the postpartum setting are limited to small case series[60,64] and do not allow for recommendations.

RVO

The current treatment options for RVO recommended by the Royal College of Ophthalmologists include the use of intravitreal antivascular endothelial growth factor agents if RVO is complicated by macular edema, along with laser photocoagulation of ischemic areas and/or corticosteroids.[65] A recent meta-analysis showed that antivascular endothelial growth factor agents are the most effective therapy for macular edema secondary to both central and branch RVO.66 Anticoagulant treatment is a parallel option, although it is not routinely recommended by the Royal College of Ophthalmologists guidelines[65] or by the Anticoagulation Forum[40] because of the lack of evidence, but it may be limited to patients without local risk factors, with recent onset of symptoms, or with major risk factors for thrombosis (e.g., antiphospholipid antibodies). For the latter, long-term anticoagulant therapy may be considered.[67] In the most rigorous RCT of 58 patients with early-onset (within 15 days) RVO, treatment with therapeutic doses of LMWH for 7 days and half therapeutic doses thereafter for a total of 3 months was more effective than aspirin in preventing visual loss.[68] A meta-analysis including 3 RCTs comparing the effect of LMWH vs aspirin in patients with RVO favoured LMWH, which improved visual acuity and was associated with a 78% reduction in the risk of developing adverse ocular outcomes. [69] A large prospective cohort study of 686 patients with RVO showed no benefit and even worse visual outcomes in patients receiving aspirin or other antiplatelet drugs compared with nontreated patients.[70] Hence, LMWH is suggested for a period of 1 to 3 months in RVO patients with recent onset of symptoms, no local risk factors (i.e., glaucoma), and no contraindications,[40,67,71] with therapeutic doses for 10 to 15 days, followed by half therapeutic doses for up to 3 months.[67] Fondaparinux was also reported to be safe and effective in

resolving recent-onset RVO in 13 consecutive patients.[72] Local thrombolytic therapy should be considered only in selected cases with total visual loss.[40]

Thrombophilia testing

The different guidelines considered in this review do not address specifically the benefits of thrombophilia testing in patients with thrombosis at unusual sites. At present, one should approach testing in thrombosis at unusual sites as in LEDVT, although even in thrombosis at such a common site, the issue of testing is debated. Only severe thrombophilia abnormalities (e.g., homozygous factor V Leiden or G20210A prothrombin mutation; antithrombin, protein C, or protein S deficiency; antiphospholipid antibodies; or combined abnormalities) may influence the duration of anticoagulant treatment, because they are associated with a higher risk of recurrent venous thrombosis than the common heterozygous mutations in factor V and II. Whether patients with severe thrombophilia may benefit from a longer or indefinite duration of anticoagulant therapy should be investigated in an RCT, but an RCT is almost unfeasible considering the rarity of severe abnormalities.[73] In this panorama, routine thrombophilia testing is usually discouraged, because it would not influence patient management. For thrombosis at unusual sites, which often involves local or systemic conditions triggering the event, testing for thrombophilia seems even less useful. It can be reserved for selected patients with unexplained events, young age, or positive family history of thrombosis, with careful consideration given to the interpretation of the results.[73]

Cancer screening

Apart from myeloproliferative neoplasms, screening for which should be conducted in patients with unprovoked SVT and, to a lesser extent, in those with unprovoked cerebral venous thrombosis (CVT), extensive screening for occult cancer is not recommended in patients with thrombosis at unusual sites.[74] Given that radiologic imaging is required for the diagnosis of CVT, SVT, UEDVT, RVT, and OVT, it is usually enough to detect regional occult cancer. Extensive diagnostic cancer screening is also not warranted in patients with RVO, who do not have an increased risk of cancer, as shown in a Danish nationwide population-based cohort study.[75]

Role of DOACs

Because the phase 3 RCTs conducted on direct oral anticoagulants (DOACs) did not include patients with unusual thrombotic manifestations,76 their safety and efficacy in this setting needs to be proven in dedicated clinical trials, and at present, their use should be discouraged. Limited data are available from 7 case series[77-83] reporting on 44 patients with CVST treated with DOACs for a period varying from 3 to 19 months, with complete or partial recanalization achieved in ~80% of cases without bleeding complications. Table 1 lists the ongoing clinical trials on treatment of CVST with DOACs. Regarding SVT, the only RCT of 80 patients comparing 10 mg of rivaroxaban with warfarin at a 1:1 ratio showed favorable safety and efficacy profiles for rivaroxaban.[84] A total of 92 patients with SVT were treated with DOACs in 8 case reports or case series, and 4 major gastrointestinal bleedings and 2 cases of recurrent thrombosis were reported.[85-92] On the basis of this evidence and considering the increasing amount of data in patients with cancer (often associated with SVT), the use of DOACs has been suggested in patients with SVT.[93] In addition, a pilot prospective single-arm cohort study of patients with SVT and no cirrhosis treated with rivaroxaban is ongoing (registered at www.clinicaltrials.gov as #NCT02627053). The use of DOACs was reported in a retrospective study of 55 patients with UEDVT who developed 1 recurrent UEDVT (2%) and 1 clinically relevant nonmajor bleeding episode (2%) during treatment.[94] A pilot study in patients with cancer and CVC-associated UEDVT treated with rivaroxaban has completed recruitment (registered at www.clinicaltrials.gov as #NCT01708850). Two other phase 4 single-arm studies of apixaban for the treatment of UEDVT, 1 in patients with cancer (registered at www.clinicaltrials. gov as #NCT03100071) and 1 in those without (registered at www. clinicaltrials.gov as #NCT02945280), are ongoing. Only 4 cases of RVT treated with DOACs (rivaroxaban and apixaban) have been reported so far, with no evidence of increased risk of bleeding or recurrence.[62,95] There is still no experience with DOACs in the treatment of RVO, and their use is discouraged. The only prospective study comparing the use of DOACs (rivaroxaban or apixaban) in patients with thrombosis at unusual sites, including CVST, SVT, OVT, and RVT, and in those with thrombosis t common sites showed comparable safety and efficacy; moreover, the rates of bleeding and recurrent thrombosis in patients treated with DOACs were similar to those in patients treated with enoxaparin.[62] Finally, an international registry on DOACs for treatment of all unusual thrombotic

manifestations included in this review except for UEDVT is ongoing and will provide new insights (registered at www.clinicaltrials.gov as #NCT03778502).

Table 1. Ongoing clinical trials with DOACs in patients with CVST

Title	Study type	Intervention	Main outcome	N° of patients	Start date	Recruitment status
A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis (RE-SPECT CVT) (NCT02913326)	Interventional (phase 3), randomized, parallel assignment, open label	Dabigatran etexilate vs warfarin for 6 mo	Composite rate of major bleeding and venous Thromboembolism	120	13 Dec 2016	Completed
The Efficacy and Safety of Dabigatran Etexilate for the Treatment of Cerebral Venous Thrombosis (NCT03217448)	Interventional (phase 3), randomized, parallel assignment, open label, single blind (outcomes assessor)	Dabigatran etexilate vs warfarin for 6 mo	Recanalization after 6 mo	80	30 Oct 2017	Recruiting
Comparison of the Efficacy of Rivaroxaban to Coumadin (Warfarin) in Cerebral Venous Thrombosis (NCT03191305)	Interventional, nonrandomized, parallel assignment, single blind (participants)	Rivaroxaban vs warfarin	Hemorrhage or recurrent CVT based on repeated MRI at 6 mo	50	-	Not yet recruiting
Study of Rivaroxaban for CeREbral Venous Thrombosis (SECRET) (NCT03178864)	Interventional (phase 2), randomized, parallel assignment, open label, single blind (outcomes assessor)	Rivaroxaban vs standard of care	Composite rate of all-cause mortality, symptomatic intracranial bleeding, and major extracranial bleeding at 6 mo	380	12 Mar 2019	Recruiting
Comparing Treatment Outcomes in CVT Patients Who Were Treated With Warfarin and Rivaroxaban in Isfahan, Iran (NCT03747081)	Interventional (phase 1/2), randomized, parallel assignment, open label	Rivaroxaban vs warfarin for 3 mo	Modified Rankin scale at 3 mo	50	1 Sep 2018	Recruiting

References

1. Ageno W, Dentali F, Pomero F, et al. Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari syndrome. Thromb Haemost. 2017;117(4):794-800.
2. Rogers S, McIntosh RL, Cheung N, et al; International Eye Disease Consortium. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology. 2010;117(2):313-319.e1.
3. Bousser MG, Crassard I. Cerebral venous thrombosis, pregnancy and oral contraceptives. Thromb Res. 2012;130(suppl 1): S19-S22.
4. De Stefano V, Martinelli I. Splanchnic vein thrombosis: clinical presentation, risk factors and treatment. Intern Emerg Med. 2010;5(6): 487-494.
5. Joffe HV, Kucher N, Tapson VF, Goldhaber SZ; Deep Vein Thrombosis (DVT) FREE Steering Committee. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. Circulation. 2004;110(12): 1605-1611.
6. Muñoz FJ, Mismetti P, Poggio R, et al; RIETE Investigators. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. Chest. 2008; 133(1):143-148.
7. Brandão LR, Simpson EA, Lau KK. Neonatal renal vein thrombosis. Semin Fetal Neonatal Med. 2011;16(6):323-328.
8. Wysokinski WE, Gosk-Bierska I, Greene EL, Grill D, Wiste H, McBane RD II. Clinical characteristics and long-term follow-up of patients with renal vein thrombosis. Am J Kidney Dis. 2008;51(2):224-232.
9. Lenz CJ, Wysokinski WE, Henkin S, et al. Ovarian vein thrombosis: incidence of recurrent venous thromboembolism and survival. Obstet Gynecol. 2017;130(5):1127-1135.
10. Cheung N, Klein R, Wang JJ, et al. Traditional and novel cardiovascular risk factors for retinal vein occlusion: the multiethnic study of atherosclerosis. Invest Ophthalmol Vis Sci. 2008;49(10):4297-4302.
11. O'Mahoney PRA, Wong DT, Ray JG. Retinal vein occlusion and traditional risk factors for atherosclerosis. Arch Ophthalmol. 2008; 126(5):692-699.
12. Einhaupl KM, Villringer A, Meister W, et al.Heparin treatment in sinus venous thrombosis. Lancet. 1991;338(8767):597-600.
13. de Bruijn SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke. 1999;30(3): 484-488.
14. Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. Cochrane Database Syst Rev.2011;(8):CD002005.
15. Ghandehari K, Riasi HR, Noureddine A, et al. Safety assessment of anticoagulation therapy in patients with hemorrhagic cerebral venous thrombosis. Iran J Neurol. 2013;12(3):87-91.
16. Einhaupl K, Stam J, Bousser M-G, et al; European Federation of Neurological Societies. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. Eur J Neurol. 2010;17(10):1229-1235.
17. Saposnik G, Barinagarrementeria F, Brown RD Jr., et al; American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart ssociation/American Stroke Association. Stroke. 2011;42(4):1158-1192.
18. Ferro JM, Bousser M-G, Canhão P, et al; European Stroke Organization. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24(10): 1203-1213.
19. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 suppl):e601S-e636S.
20. Misra UK, Kalita J, Chandra S, Kumar B, Bansal V. Low molecular weight heparin versus unfractionated heparin in cerebral venous sinus thrombosis: a randomized controlled trial. Eur J Neurol. 2012;19(7):1030-1036.

21. Afshari D, Moradian N, Nasiri F, Razazian N, Bostani A, Sariaslani P. The efficacy and safety of low-molecular-weight heparin and unfractionated heparin in the treatment of cerebral venous sinus thrombosis. Neurosciences (Riyadh). 2015;20(4):357-361.
22. Al Rawahi B, Almegren M, Carrier M. The efficacy and safety of anticoagulation in cerebral vein thrombosis: A systematic review and meta-analysis. Thromb Res. 2018; 169(April):135-139.
23. Dentali F, Squizzato A, Gianni M, et al. Safety of thrombolysis in cerebral venous thrombosis. A systematic review of the literature. Thromb Haemost. 2010;104(5):1055-1062.
24. Coutinho JM, Ferro JM, Zuurbier SM, et al. Thrombolysis or anticoagulation for cerebral venous thrombosis: rationale and design of the TO-ACT trial. Int J Stroke. 2013;8(2): 135-140.
25. Coutinho JM, Ferro J, Zuurbier S, et al. Thrombolysis or anticoagulation for cerebral vein thrombosis (TO-ACT): a randomized controlled trial. Eur Strok J. 2017;2(1 suppl): 479.
26. Viegas LD, Stolz E, Canhão P, Ferro JM. Systemic thrombolysis for cerebral venous and dural sinus thrombosis: a systematic review. Cerebrovasc Dis. 2014;37(1):43-50.
27. Eskey CJ, Meyers PM, Nguyen TN, et al; American Heart Association Council on Cardiovascular Radiology and Intervention and Stroke Council. Indications for the performance of intracranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association. Circulation. 2018;137(21):e661-e689.
28. The´ audin M, Crassard I, Bresson D, et al. Should decompressive surgery be performed in malignant cerebral venous thrombosis? A series of 12 patients. Stroke. 2010;41(4): 727-731.
29. Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannucci PM. Longterm evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. Circulation. 2010;121(25):2740-2746.
30. Dentali F, Poli D, Scoditti U, et al; CErebral VEin Thrombosis International Study Investigators. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study [published correction appears in J Thromb Haemost. 2013;11(2):399]. J Thromb Haemost. 2012;10(7):1297-1302.
31. Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in Stroke. 2015;46(2):e54]. Stroke. 2014;45(7):2160-2236.
32. Miranda B, Aaron S, Arauz A, et al. The benefit of EXtending oral antiCOAgulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. Int J Stroke. 2018;13(7):771-774.
33. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl): e419S-e496S.
34. Tufano A, Ageno W, Di Micco P, et al; RIETE Investigators. Outcomes during anticoagulation in patients with symptomatic vs. incidental splanchnic vein thrombosis. Thromb Res. 2018;164:69-74.
35. Riva N, Ageno W, Schulman S, et al; International Registry on Splanchnic Vein Thrombosis (IRSVT) study group. Clinical history and antithrombotic treatment of incidentally detected splanchnic vein thrombosis: a multicentre, international prospective registry. Lancet Haematol. 2016;3(6): e267-e275.
36. DeLeve LD, Valla DC, Garcia-Tsao G; American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatology. 2009;49(5):1729-1764.
37. Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol. 2013;108(4):568-574.
38. Hedayati N, Riha GM, Kougias P, et al. Prognostic factors and treatment outcome in mesenteric vein thrombosis. Vasc Endovascular Surg. 2008;42(3):217-224.

39. Bjo¨ rck M, Koelemay M, Acosta S, et al; Esvs Guidelines Committeee. Editor's choice - management of the diseases of mesenteric arteries and veins: clinical practice guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4): 460-510.
40. Ageno W, Beyer-Westendorf J, Garcia DA, Lazo-Langner A, McBane RD, Paciaroni M.Guidance for the management of venous thrombosis in unusual sites. J Thromb Thrombolysis. 2016;41(1):129-143.
41. European Association for the Study of the Liver. EASL clinical practice guidelines: vascular diseases of the liver. J Hepatol. 2016; 64(1):179-202.
42. Ageno W, Riva N, Schulman S, et al. Longterm clinical outcomes of splanchnic vein thrombosis results of an international registry. JAMA Intern Med. 2015;175(9):1474-1480.
43. Plessier A, Darwish-Murad S, Hernandez- Guerra M, et al; European Network for Vascular Disorders of the Liver (EN-Vie). Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology. 2010;51(1):210-218.
44. Søgaard KK, Adelborg K, Darvalics B, et al. Risk of bleeding and arterial cardiovascular events in patients with splanchnic vein thrombosis in Denmark: a population-based cohort study. Lancet Haematol. 2018;5(10): e441-e449.
45. Huard G, Bilodeau M. Management of anticoagulation for portal vein thrombosis in individuals with cirrhosis: a systematic review. Int J Hepatol. 2012;2012:672986.
46. Senzolo M, M Sartori T, Rossetto V, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver Int. 2012;32(6):919-927.
47. SenzoloM, Riva N, Dentali F, et al; IRSVT study investigators. Long-term outcome of splanchnic vein thrombosis in cirrhosis. Clin Transl Gastroenterol. 2018;9(8):176.
48. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology. 2017;153(2):480-487.e1.
49. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report [published correction appears in Chest. 2016;150(4):988]. Chest. 016;149(2):315-352.
50. Thiyagarajah K, Ellingwood L, Endres K, et al. Post-thrombotic syndrome and recurrent thromboembolism in patients with upper extremity deep vein thrombosis: A systematic review and meta-analysis. Thromb Res. 2019; 174:34-39.
51. Grant JD, Stevens SM, Woller SC, et al. Diagnosis and management of upper extremity deep-vein thrombosis in adults. Thromb Haemost. 2012;108(6):1097-1108.
52. Isma N, Svensson PJ, Gottsa¨ ter A, Lindblad B. Upper extremity deep venous thrombosis in the population-based Malmo¨ thrombophilia study (MATS). Epidemiology, risk factors, recurrence risk, and mortality. Thromb Res. 2010;125(6):e335-e338.
53. Lechner D, Wiener C, Weltermann A, Eischer L, Eichinger S, Kyrle PA. Comparison between idiopathic deep vein thrombosis of the upper and lower extremity regarding risk factors and recurrence. J Thromb Haemost. 2008;6(8): 1269-1274.
54. Zwicker JI, Connolly G, CarrierM, Kamphuisen PW, Lee AY. Catheter-associated deep vein thrombosis of the upper extremity in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12(5):796-800.
55. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv. 2018;2(22):3292-3316.
56. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl): e737S-e801S.
57. Zhang LJ, Zhang Z, Li SJ, et al. Pulmonary embolism and renal vein thrombosis in patients with nephrotic syndrome: prospective evaluation of prevalence and risk factors with CT. Radiology. 2014;273(3):897-906.

58. Bannow BTS, Skeith L. Diagnosis and management of postpartum ovarian vein thrombosis. Hematology Am Soc Hematol Educ Program. 2017;2017(1):168-171.
59. Salomon O, Dulitzky M, Apter S. New observations in postpartum ovarian vein thrombosis: experience of single center. Blood Coagul Fibrinolysis. 2010;21(1):16-19.
60. Rottenstreich A, Da'as N, Kleinstern G, Spectre G, Amsalem H, Kalish Y. Pregnancy and non-pregnancy related ovarian vein thrombosis: clinical course and outcome. Thromb Res. 2016;146:84-88.
61. Assal A, Kaner JD, Danda N, Cohen HW, Billett HH. Risk factors and prognosis of ovarian vein thrombosis. Blood Coagul Fibrinolysis. 2017;28(6):468-474.
62. Janczak DT, Mimier MK, McBane RD, et al. Rivaroxaban and apixaban for initial treatment of acute venous thromboembolism of atypical location. Mayo Clin Proc. 2018;93(1):40-47.
63. Chan WS, Rey E, Kent NE, et al; Society of Obstetricians and Gynecologists of Canada. Venous thromboembolism and antithrombotic therapy in pregnancy. J Obstet Gynaecol Can. 014;36(6):527-553.
64. Kodali N, Veytsman I, Martyr S, Lu K. Diagnosis and management of ovarian vein thrombosis in a healthy individual: a case report and a literature review. J Thromb Haemost. 2017;15(2):242-245.
65. Sivaprasad S, Amoaku WM, Hykin P; RVO Guideline Group. The Royal College of Ophthalmologists guidelines on retinal vein occlusions: executive summary [published correction appears in Eye (Lond). 2016;30(4):642]. Eye (Lond). 2015;29(12):1633-1638.
66. Qian T, Zhao M, Xu X. Comparison between anti-VEGF therapy and corticosteroid or laser therapy for macular oedema secondary to retinal vein occlusion: a meta-analysis. J Clin Pharm Ther. 2017;42(5):519-529.
67. Garcia-Horton A, Al-Ani F, Lazo-Langner A. Retinal vein thrombosis: the internist's role in the etiologic and therapeutic management. Thromb Res. 2016;148:118-124.
68. Ageno W, Cattaneo R, Manfredi E, et al. Parnaparin versus aspirin in the treatment of retinal vein occlusion. A randomized, double blind, controlled study. Thromb Res. 2010; 125(2):137-141.
69. Lazo-Langner A, Hawel J, Ageno W, Kovacs MJ. Low molecular weight heparin for the treatment of retinal vein occlusion: a systematic review and meta-analysis of randomized trials. Haematologica. 2010;95(9):1587-1593.
70. Hayreh SS, Podhajsky PA, Zimmerman MB. Central and hemicentral retinal vein occlusion: role of anti-platelet aggregation agents and anticoagulants. Ophthalmology. 2011;118(8): 1603-1611.
71. Tait C, Baglin T, Watson H, et al; British Committee for Standards in Haematology. Guidelines on the investigation and management of venous thrombosis at unusual sites. Br J Haematol. 2012;159(1):28-38.
72. Steigerwalt RD Jr., Pascarella A, De Angelis M, Ciucci F, Gaudenzi F. An ultra-low-molecular weight heparin, fondaparinux, to treat retinal vein occlusion. Drug Discov Ther. 2016;10(3): 167-171.
73. Connors JM. Thrombophilia testing and venous thrombosis. N Engl J Med. 2017;377(12): 1177-1187.
74. Delluc A, Antic D, Lecumberri R, Ay C, Meyer G, Carrier M. Occult cancer screening in patients with venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2017;15(10):2076-2079.
75. Hansen AT, Veres K, Prandoni P, Adelborg K, Sørensen HT. Retinal vein thrombosis and risk of occult cancer: a nationwide cohort study. Cancer Med. 2018;7(11):5789-5795.
76. van Es N, Coppens M, Schulman S, Middeldorp S, Bu¨ ller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968-1975.
77. Geisbu¨ sch C, Richter D, Herweh C, Ringleb PA, Nagel S. Novel factor xa inhibitor for the treatment of cerebral venous and sinus thrombosis: first experience in 7 patients. Stroke. 2014;45(8):2469-2471.
78. Mutgi SA, Grose NA, Behrouz R. Rivaroxaban for the treatment of cerebral venous thrombosis. Int J Stroke. 2015;10(SA100 suppl A100):167-168.

79. Mendonça MD, Barbosa R, Cruz-e-Silva V, Calado S, Viana-Baptista M. Oral direct thrombin inhibitor as an alternative in the management of cerebral venous thrombosis: a series of 15 patients. Int J Stroke. 2015;10(7):1115-1118.
80. Anticoli S, Pezzella FR, Scifoni G, Ferrari C, Pozzessere C. Treatment of cerebral venous thrombosis with rivaroxaban. J Biomed Sci. 2016;5(3):1-2.
81. Amemiya T, Uesaka T, Kameda K, et al. Usefulness of edoxaban for deep cerebral venous sinus thrombosis with hemorrhagic infarction: a case report [in Japanese]. No Shinkei Geka. 2017;45(7):607-613.
82. Talamo L, Douvas M, Macik BG, Ornan D. Successful treatment with apixaban of sinus venous thrombosis due to pegylated asparaginase in a young adult with T cell acute lymphoblastic leukemia: case report and review of management. Ann Hematol. 2017; 96(4):691-693.
83. Covut F, Kewan T, Perez O, Flores M, Haddad A, Daw H. Apixaban and rivaroxaban in patients with cerebral venous thrombosis. Thromb Res. 2019;173:77-78.
84. Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. Vascul Pharmacol. 2019;113:86-91.
85. Intagliata NM, Henry ZH, Maitland H, et al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci. 2016;61(6):1721-1727.
86. Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. Eur J Haematol. 2017;98(4):393-397.
87. De Gottardi A, Trebicka J, Klinger C, et al; VALDIG Investigators. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver Int. 2017;37(5):694-699.
88. Lenz K, Dieplinger B, Buder R, Piringer P, RauchM, Voglmayr M. Successful treatment of partial portal vein thrombosis (PVT) with low dose rivaroxaban. Z Gastroenterol. 2014; 52(10):1175-1177.
89. Pannach S, Babatz J, Beyer-Westendorf J. Successful treatment of acute portal vein thrombosis with rivaroxaban. Thromb Haemost. 2013;110(4):626-627.
90. Yang H, Kim SR, Song MJ. Recurrent acute portal vein thrombosis in liver cirrhosis treated by rivaroxaban. Clin Mol Hepatol. 2016;22(4): 499-502.
91. Nery F, Valadares D, Morais S, Gomes MT, De Gottardi A. Efficacy and safety of direct-acting oral anticoagulants use in acute portal vein thrombosis unrelated to cirrhosis. Gastroenterol Res. 2017;10(2):141-143.
92. Parthvi R, Mehra S. Use of rivaroxaban for mesenteric vein thrombosis secondary to diverticulitis: a case report. Am J Ther. 2017; 24(5):e629-e630.
93. Finazzi G, De Stefano V, Barbui T. Splanchnic vein thrombosis in myeloproliferative neoplasms: treatment algorithm 2018. Blood Cancer J. 2018;8(7):64.
94. Montiel FS, Ghazvinian R, Gottsa¨ ter A, Elf J. Treatment with direct oral anticoagulants in patients with upper extremity deep vein thrombosis. Thromb J. 2017;15:26.
95. Date Y, Nagamine H, Hara H, Kawase Y. Renal vein thrombosis after open repair of abdominal aortic aneurysm successfully treated by direct oral anticoagulants. Vasc Endovascular Surg. 2019;53(5):408-410.

Chapter 3

Cerebral venous sinus thrombosis

Capecchi M, Abbattista M*, Martinelli I.*

J Thromb Haemost. 2018 Oct;16(10):1918-1931. doi: 10.1111/jth.14210. Epub 2018 Jul 11.

**contributed equally*

Summary

The cerebral venous system is an unusual site of thrombosis, with a particularly high incidence in young adults. This incidence has increased in past decades because of the improvement of neuroradiological techniques. Risk factors for cerebral venous sinus thrombosis overlap with those of other venous thromboembolism sites, however, some are specific for this particular anatomical district. Prognosis is favorable in most cases if diagnosis is made rapidly and treatment is promptly initiated, even if acute complications or chronic invalidity still occur in a quarter of patients. The mainstay of treatment is anticoagulation, which is necessary in order to block clot propagation and obtain recanalization. Intracranial bleeding does not contraindicate anticoagulation. Endovascular procedures are reserved for patients with a particularly severe presentation or rapidly declining neurological symptoms despite appropriate anticoagulation, although data from clinical trials are lacking. Specifically, this review addresses the epidemiology, clinical presentation and course, risk factors, and treatment of cerebral venous sinus thrombosis, with a special focus on the pediatric population.

Anatomy

The cerebral venous system can be divided into two major compartments considering the anatomic and functional characteristics of the blood vessels: the cerebral veins and the dural venous sinuses (Fig. 1). Considering the topographic distribution, a superficial and a deep system can be distinguished. The superficial system drains blood from the cerebral cortex mainly into the superior sagittal sinus, which in turn drains into the transverse sinuses. The deep system drains blood from the deep white matter and the basal ganglia to the inferior sagittal sinus, that continues into the straight sinus and then into the transverse sinuses. From the transverse and the straight sinuses blood flows out of the sigmoid sinuses, passing through the sinus confluence (torcular herophili), and finally into the internal jugular veins. Many anastomoses exist between the cerebral veins from the fetal period onwards. The dural venous sinuses are delimited by the superficial (periosteal) and the deep (meningeal) layer of the dura mater and their walls are composed of only the dura mater layer lined with endothelium, hence lacking the tunica media. Additionally, these sinuses lack valves. Dural venous sinuses drain blood from the cerebral veins and the cerebrospinal fluid from the subarachnoid space, via the arachnoid pacchionian granulations, which are present particularly in the superior sagittal sinus. The classic anatomy varies considerably among individuals and the knowledge of such variations is essential for a correct interpretation of radiological images. The most frequent anatomic variants are: asymmetries of transverse sinuses, observed in nearly 50% of patients; hypo-/aplasia of all or part of the transverse sinuses, observed in nearly 20% of patients; and less frequently hypo-/aplasia of the frontal part of the superior sagittal sinus.[1]

Pathophysiology

The formation of a thrombus in the cerebral venous circulation leads to an increase in the hydrostatic pressure in the veins and capillaries upstream to the occlusion. However, because of the anastomotic circuit of the cerebral venous system, the increased venous pressure is usually compensated to some extent. If the increase in the venous pressure overcomes the compensation capacity the following can occur: blood-brain barrier disruption, extravasation of fluids into the cerebral parenchyma and consequent localized edema. Furthermore, if the venous pressure exceeds the arterial pressure, a reduction

of arterial flow and consequent arterial ischemia can occur and, if not adequately treated, it may progress to hemorrhagic infarction.[2] A peculiar characteristic that distinguishes vasogenic (due to venous occlusion) from cytotoxic (due to arterial occlusion) edema, is that in the former the perfusion pressure is not usually reduced and therefore irreversible brain tissue damage is unlikely. Indeed, in venous stroke a resolution of thrombi and a favorable prognosis are more likely than in arterial stroke. The peculiarity of venous occlusion is the reduction of cerebrospinal fluid reabsorption, by reducing cerebrospinal fluid access to the arachnoidal pacchionian granulations, leading to intracranial hypertension.[3] This scenario is more frequent with superior sagittal sinus occlusion (where arachnoidal pacchionian granulations are present), but can also occur in the occlusion of other sinuses.

Epidemiology

Cerebral venous sinus thrombosis (CVST) is a rare manifestation of thrombosis with an incidence that varies between studies. In adults, the annual incidence of CVST is 2–5 cases per million individuals,[3,4] but it is likely underestimated because of the lack of well-designed epidemiological studies. Two recent studies in the Netherlands and Southern Australia found a higher incidence than previously reported of 13.2 and 15.7 annual cases per million, respectively.[5,6] The high prevalence of infection-related CVST can determine even higher figures in others countries (18% in Pakistan), but the exact incidence among different ethnic groups is pending investigation.[7–9] At variance with arterial stroke that is more prevalent in the elderly, CVST typically affects young adults with a mean age of 35 years and is more common in women than in men (2.2:1) because of sex-specific risk factors.[10] The superior sagittal and the transverses are the most frequently involved sinuses (60% of patients), followed by the internal jugular and cortical veins (20%). In almost two-thirds of patients CVST involves more than one sinus.

Epidemiology in children and neonates

The annual incidence of CVST in the pediatric population is approximately 7 cases per million and is higher in neonates than in children.[11–14] The sex ratio seems balanced because of the absence of sex-specific risk factors.[12] Similarly to adults, the superficial sinuses are the most frequently involved (particularly

the superior sagittal and the transverse sinus) and the transverse sinus is more frequently involved in children older than 2 years of age (60% vs 39%).[11,15]

Clinical presentation

Since symptoms of CVST are variable and aspecific, diagnosis is often delayed to a median period of 7 days from the onset of clinical manifestations.[16] The International Study on Cerebral Venous and Dural Sinus Thrombosis (ISCVT) that included 624 patients, described the following as the most common presenting symptoms: headache (88.8%), seizures (39.3%), paresis (37.2%), papilledema (28.3%), and mental status changes (22%).[16]Headache is usually the first symptom at onset of CVST. In only 10% of cases does the headache have a thunderclap outbreak, mimicking a subarachnoid hemorrhage.[17] Because of its aspecific nature, physicians must have a high suspicion of CVST when dealing with a new onset and progressively increasing intensity of headache; that is the only presenting symptom in about 32% of patients.[17] The location of the headache is not informative as it does not correlate with the thrombosis site. The absence of headache is typical of elderly patients, especially men,[18] and in those with cortical vein thrombosis who have normal cerebrospinal fluid homeostasis. The pathophysiologic mechanism of headache in CVST is the increase in intracranial pressure due to reduced cerebrospinal fluid reabsorption. For this reason, the intensity of the headache typically increases when patients lie down and after the Valsalva maneuver. For reasons not yet fully understood, headache is more common in patients with CVST than in those with arterial stroke (25% of cases).[19] Seizures are focal in one quarter of patients, in another quarter they begin as focal and then generalize and in the remaining half, seizures are generalized ab initio.[20] Seizures are more frequent in patients with CVST than in those with arterial stroke (2–9%), [20] perhaps as a consequence of the accumulation of catabolic products due to venous stasis.

Focal neurological deficits such as paresis, dysarthria, and aphasia are due to localized damage in the cerebral cortex, secondary to a venous infarction. Focal deficits are more frequent in patients with thrombosis of the superficial system with involvement of the parasagittal cortex, where the motor and sensory areas are located. Papilledema is the consequence of intracranial hypertension and can cause diplopia and visual loss. Patients with thrombosis of the cavernous sinus may also develop proptosis, orbital pain, chemosis, and ophthalmoplegia secondary to a palsy of the oculomotor (III), trochlear (IV)

and abducens (VI) cranial nerves. Mental status changes such as amnesia, mutism, confusion, or delirium are seen in patients with thrombosis of the deep system, particularly those with large venous infarctions or bilateral edema of the basal ganglia and thalami. The most severe cases can have a rapid neurological deterioration, leading to coma and death.

Clinical presentation in children and neonates

In children symptoms at onset are even more aspecific than in adults and are frequently attributable to more common diseases such as infections or dehydration, making the suspicion and diagnosis of CVST particularly difficult. In general, symptoms in children are the same as in adults, but generalized neurological deficits are more common and seizures are more frequent in neonates. [11]

Diagnosis

When CVST is suspected in adults the first line imaging technique is unenhanced computed tomography (CT) scan; this allows for the ruling out of brain tumors, abscesses, or arterial stroke. In the acute phase, CVST is seen in unenhanced CT scans as a hyperdense signal in the vessel lumen, that becomes iso- and then hypodense after the first week. Depending on the location of CVST, two specific radiological signs are described: the "dense triangle sign" when thrombosis is located in the superior sagittal sinus, and the "dense cord sign" when located in a cortical or deep vein [3] (Fig. 2a). However, such signs are rarely described (considering that the unenhanced CT scan has a low sensitivity) resulting positive in only 30% of patients with CVST.[21] The addition of contrast agent increases the sensitivity to 99% for sinus thrombosis and 88% for vein thrombosis, figures similar to those obtained with magnetic resonance imaging (MRI). [22,23] In the presence of the contrast agent, a specific radiological sign is the "empty delta sign", a filling defect in the middle of the venous lumen with a peripheral enhancement (Fig. 2b). Advantages of CT scanning are the availability in an emergency and the ability to show the presence of local complications associated to CVST, such as subarachnoid or intraparenchymal hemorrhage or cerebral edema. Disadvantages are the exposure to ionizing radiation and the need of contrast agent to increase the accuracy. Currently, MRI is the gold standard imaging technique for diagnosis of CVST, despite exact sensitivity and specificity are not known because of the

lack of proper comparative studies with catheter angiography. Catheter angiography was the historical gold standard technique that to date, due to its invasiveness, is reserved for patients with an inconclusive CT scan and MRI or for candidates to endovascular procedures.[24,25] Maximum accuracy is obtained with the combination of classic MRI sequences, which are able to show the thrombus, together with venography, which can show reduction or absence of flow and therefore distinguish hypoplastic sinuses, partial sinus occlusion, thrombosis of cortical cerebral veins, or filling defects due to hyperplastic arachnoid granulations (Fig. 3).[26] The advantages of MRI are the absence of both radiation exposure and intravenous contrast agent, and the ability to establish the age of the clot. Finally, when D-dimer is high it increases the likelihood of deep vein thrombosis of the lower limbs or pulmonary embolism; it has been investigated in several studies as a predictive factor for CVST, but has consistently shown a low sensitivity and specificity.[27] Despite of this, the ESO guidelines suggest to measure D-dimer before neuroimaging in patients with suspected CVST, except in those with isolated headache and in case of prolonged duration of symptoms (i.e. > 1 week). The quality of evidence is low and the strength of recommendation is weak.[28]

Diagnosis in children and neonates

In children imaging techniques for diagnosis are the same as in adults, while in neonates the first choice is the transfontanellar doppler ultrasound, which has the advantage of being extensively available and non-invasive, albeit strongly operator-dependent. In case of inconclusive results and a persistent clinical suspicion of CVST, enhanced CT scan and MRI must be performed.

Prognosis

For a long time CVST has been considered a life-threatening condition, but the case fatality rate has decreased proportionally over time from more than 50% to 5–10%.[29] Increased clinical awareness, the advancement of neuroimaging techniques, and the improvement in therapeutic management has enabled for earlier diagnosis and identification of less severe cases, ensuring a better prognosis. However, data on clinical outcome stem from studies with small sample sizes, which suffer from methodological heterogeneity and are usually referred to follow-up visits up to only 12 months. The clinical course of the acute phase is unpredictable and in

approximately 5% of patients intracranial hemorrhage followed by herniation, seizures, pulmonary embolism, or severe comorbidity can be fatal.[16,30,31] A minority of patients with CVST (15-20%), have different degrees of permanent disability or die.[16,32] A meta-analysis reported an overall mortality of 9.4% (122 deaths among 1303 patients), although the causes of death during follow-up were mainly related to concomitant diseases (e.g., cancer) rather than to CVST itself.[30,33] The majority of patients who recover completely achieve relative independence, usually expressed as between 0 and 2 on the modified Rankin Scale (mRS), although mild residual symptoms, such as headache, motor deficits, linguistic difficulties, impaired vision or cognition often remain.[16,34–36] Only 5–10% of patients who survive the acute phase remain moderately or severely dependent (mRS 3 or 4),[16,34] however, this proportion increases up to 34% in those with massive CVST.[37]

Recanalization

To date, few studies with small sample sizes have investigated the recanalization rate of CVST. Differences in the definition of recanalization and time of evaluation across studies make it difficult to pool data and to provide homogenous results. With these limitations, the rate of recanalization (complete or partial) is around 85%, ranging between 73% and 93%.[30,38] Almost 50% of cases achieve a complete recanalization after a median time of 6 months. Recanalization occurs mainly in the first months after CVST and is a dynamic process continuing up to 12 months later, whereas recanalization after one year is rare. [30,38,39] A late recanalization has been described in patients with CVST occurring during hormonal treatment.[39] Controversial and limited data are available regarding the influence of the degree of recanalization on functional outcome.[40,41] One study reported a greater chance of good functional outcome associated with complete recanalization, [38] while others did not confirm this finding.[39,42] A recent large study including 508 patients showed a high recanalization rate at 3 months after CVST (81%)and an independent association between recanalization and a favorable neurological outcome.[43]

Recurrence rate

Data on recurrent venous thrombosis derive mainly from studies with small sample sizes and retrospective design, underpowered to detect potential

risk factors for recurrence. The overall incidence of recurrent venous thrombosis within the first year after a first episode of CVST is estimated at around 4 per 100 patient-years (p-y),[44] that of recurrent CVST is 0.5% to 2.2% p-y and that of recurrent deep vein thrombosis of the lower limbs and/or pulmonary embolism is 1.1% to 5.0% p-y.[16,44–47] Notably, male sex is associated with a 7-fold increased risk of recurrence.[44,46] Cohort studies on long-term evaluation of the risk of recurrent thrombosis after anticoagulant therapy discontinuation showed higher figures in the first period (5.0% p-y, 2.6% p-y, and 1.7% p-y in the first, third, and tenth year after discontinuation, respectively) for an overall risk of 2 to 3.5 per 100 p-y.[46,47]

Prognosis in children and neonates

The mortality rate varies from 5% to 10% and increases up to 25% in newborns.[48] Few studies have investigated the clinical outcome of neonates and children who survive the acute phase of CVST and no data on their subsequent neurodevelopment are available. The longest observational period was described in a large prospective study that included 104 neonates followed for a median period of 2.5 years (range 6 months to 15 years).[49] Prognosis in children seems worse than in adults, with 20–70% of patients presenting residual neurological deficits.[13,49,50] In a series of 42 neonates, one died and only 21% of those who completed 2 years of follow-up recovered completely.[51] A European cohort study reported a recanalization rate of 69% (46% complete and 42% partial) between 3 and 6 months after CVST,[52] and another recent study found a rate of 85% at 3 months in neonates compared to 56% in children.[53]

Despite the limited data, complete recanalization seems to occur earlier in children than in adults, particularly in neonates.[53] The recurrence rate of thrombosis varies between 0% and 20% [15,48–50] with the highest figures in children older than 2 years,[11,52] this is mainly due to underlying systemic diseases (e.g., lupus erythematosus and Behçet disease).[54] The avoidance of anticoagulant therapy, the lack of recanalization, and the presence of the G20210A prothrombin gene mutation have all been associated with an increased risk of recurrence of 11.2-, 4.1- and 4.3-fold, respectively.[38,52]

Risk factors

Like any thrombosis, CVST has a multifactorial etiology (Table 1). In 85% of patients at least one risk factor is identified and 50% of events are triggered by the interaction of more risk factors. A small proportion of cases remains idiopathic, i.e., no direct cause or risk factor can be identified.[16,55]

Sex-related

CVST is more common in women of reproductive age than in men, as a result of the use of oral contraceptives or hormone replacement therapy, pregnancy, and puerperium.[56] Oral contraceptive use is by far the most common risk factor, reported in more than 80% of women in various series and associated with a pooled estimate of approximately 6-fold increased risk of CVST.[57] A recent case-control study showed that overweightness and obesity in women using oral contraceptives further increased the risk of CVST up to 30-fold in a dose-dependent manner.[58] An increase in risk also occurs with the multiplicative interaction between oral contraceptive use and the presence of thrombophilia abnormalities.[59,60] Pregnancy or puerperium are responsible for 5–20% of CVST, with an incidence of 12 cases per 100,000 deliveries.[4,56,61]

Thrombophilia abnormalities

Inherited thrombophilia abnormalities, that is, the common gain-of-function mutations in factor V and factor II (factor V Leiden and prothrombin G20210A mutation) and the rare lack-of-function deficiencies in antithrombin, protein C, and protein S, are well-established risk factors for venous thromboembolism, including CVST. Heterozygous factor V Leiden or prothrombin mutation are reported in 6–24% of patients with CVST, with the latter being more prevalent in several case series.[16,62,63] A recent meta-analysis that included 23 cohort and 33 case-control studies, reported a solid risk estimate of CVST for prothrombin mutation (OR 6.05, 95%CI 4.12-8.90) and factor V Leiden (2.89, 95%CI 2.10-3.97), and a strong estimate for protein C (OR 8.35, 95%CI 2.61-26.67) and protein S (OR 6.45, 95%CI 1.89-22.03) deficiency.[62] With regard to the severe acquired thrombophilia due to the presence of antiphospholipid antibodies, data on the association with CVST are lacking and only case reports or small case series are available. [30,63–65] A study of 163 patients with CVST and 163 with deep vein thrombosis showed a

stronger association of anticardiolipin antibodies with the former rather than the latter (17% vs 4%).[65] Data are scanty for other thrombophilia markers such as high factor VIII and hyperhomocysteinemia. Only one case-control study investigated the association between high factor VIII and CVST, showing higher levels in patients than controls.[66] Hyperhomocysteinemia is associated with a 3-fold increased risk of CVST,[62,64] however the homozygous MTHFR C677T polymorphism, a genetic determinant of homocysteine levels, does not independently increase the risk of CVST. [64,67]

Cancer

Approximately 7% of patients with CVST have a concomitant solid (cerebral or non-cerebral) or hematological cancer.[16,47] In a recent case-control study, among 594 patients with CVST the prevalence of cancer was 8.9%, for a nearly 5-fold increased risk (OR 4.86, 95%CI 3.46-6.81).[33] Moreover, CVST can be a complication of chemotherapy with L-asparaginase. Out of 706 treated patients 22 (3.1%) developed CVST, 20 of whom during L-asparaginase.[68] Although the incidence rate of CVST in patients with myeloproliferative neoplasms is around 1%, approximately 4% of patients with CVST have an overt myeloproliferative neoplasm.[69–71] Hence, such diseases must be suspected and appropriately searched for in patients with CVST.

Systemic diseases and infections

CVST occurs in 0.5–7.5% of patients with chronic inflammatory bowel diseases, as a complication of the hypercoagulable state due to mucosal inflammation that leads to upregulation of tissue factor, high platelet count, and impaired fibrinolysis.[72,73] Additional systemic conditions are vasculitis, especially Behçet disease, with an incidence rate of CVST of 3 per 1000 p-y [74], whereas few data are available on systemic lupus erythematosus and nephrotic syndrome.[75] A local infection becomes a strong risk factor for CVST through endothelial injury and activation of procoagulant pathways. The most common are otitis, mastoiditis, sinusitis, meningitis, skin or dental infections. However, in the antibiotic era the prevalence of infection-related CVST has dropped to 8–12%, although it remains higher in less developed countries.[9,16,47]

Other risk factors

Additional mechanical risk factors for CVST include neurosurgery, internal jugular catheterization, and lumbar puncture.[3,4] Regarding genetic causes, several loci on chromosome 6 (within the human histocompatibility complex) and chromosome 9 (close to the ABO gene) have been involved in the development of CVST,[76] although these associations remain to be confirmed in large genome-wide association studies.[77] The association of CVST with other candidate genes, such as plasminogen activator inhibitor-1 4G/5G polymorphism,[78] protein Z G79A polymorphism[79] remains controversial. Janus Kinase-2 (JAK2) V617F somatic mutation, primary molecular marker of Philadelphia-negative MPN, is also present in a small percentage (0-6.2%) of CVST without an overt MPN and it could be linked to an increased risk of cerebral thrombosis.[80,81]

Risk factors in children and neonates

As in adults, CVST in children and neonates has a multifactorial etiology. Compared to adults, children develop idiopathic events less frequently and have a partially different set of risk factors due to anatomical and rheological characteristics of the cerebral circulation. The hemostatic system in children is in a dynamic state, with quantitative and qualitative differences in coagulation factors compared to adults. In neonates the hemostatic system it is accelerated as a result of decreased levels of the natural anticoagulant proteins (antithrombin, protein C, and protein S) that physiologically raise up to physiological adults levels at approximately 6 months after birth.[82,83] Despite this, neonates have a good hemostatic balance that can be altered by concomitant comorbidities such as systemic or local infections, dehydration, chronic renal failure, and brain tumors.[84,85] In neonates there are also obstetrical predisposing conditions, including premature rupture of the membrane, infections, gestational diabetes, hypertension, and hypoxic ischemic injury.[86] Specifically, the compression of the skull bones during delivery can result in damage of the dural venous sinuses and this, together with typical neonatal dehydration, can increase the risk of CVST development.[24,87] Additionally, the usual supine position assumed by neonates has a major influence on intracranial venous outflow, contributing to local venous stasis. This happens particularly in the thrombosis of the superior sagittal sinus (OR 2.5, 95%CI 1.07-5.67).[84] In children and adolescents, head and neck infections (otitis media, mastoiditis, and sinusitis) are the most common risk factors for CVST. [11,13,85,88] Other risk factors

observed in more than 50% of cases include underlying chronic diseases such as nephrotic syndrome (that confers an acquired prothrombotic state due to urinary loss of anticoagulant proteins),[89] liver disease,[11] systemic lupus erythematosus,[90] malignancy,[15,91] head trauma, or neurosurgery.[48,49] CVST has also been reported in children with iron deficiency anemia and to a lesser extent with hemolytic anemia, β-thalassemia, and sickle cell disease.[15] Inherited thrombophilia has been poorly investigated in pediatric CVST and reported in 20% to 62% of cases.[11,12,15,48] The association of CVST with factor V Leiden and prothrombin G20210A mutation appears weaker in children than in adults.[12,15,92] The combination of acquired thrombophilia and underlying conditions provides a major contribution to the pathogenesis of pediatric CVST.[12,89]

Treatment of the acute phase

Anticoagulant treatment

The use of heparin was first described in 1942 by a British gynecologist who successfully treated a puerpera with CVST.[93] The initial indication of anticoagulation in patients with CVST comes from two small randomized controlled trials performed in the 1990s that compared heparin with a placebo. The first included 20 patients and was prematurely stopped because of safety concerns due to 3/10 intracranial hemorrhages in the placebo group compared to 0/10 in the unfractionated heparin (UFH) arm.[94] The second study included 59 patients and showed a better outcome in the low molecular weight heparin (LMWH) arm (death or dependence rate 13% vs 21%).[95] A subsequent meta-analysis of the two trials showed a 13% reduction in the risk of death or dependency in patients treated with heparin.[96] None of the 18 patients with intracranial hemorrhage included in the two studies cited above and treated with heparin worsened bleeding.[94,95] An observational study including 102 CVST patients with hemorrhagic venous infarction or subarachnoid hemorrhage treated with LMWH or UFH showed a deterioration in clinical course only in 11% of patients, without difference between the two treatment group.[97] Based on these data, current guidelines state that intracranial hemorrhage does not represent a contraindication to anticoagulant therapy in the acute phase of CVST.[28] Our personal opinion is to use sub-therapeutic doses (i.e., 50–75% of the full dose) of LMWH in case of vast intracranial hemorrhage. No consensus exists on the superiority of one

type of heparin over the other. The first indirect comparison between LMWH and UFH in patients with CVST was made in the framework of the ISCVT study and showed a lower incidence of disability at 6 months in the LMWH group, without differences in the overall survival.[98] Subsequently, two randomized controlled trials compared LMWH and UFH. The first showed a significantly lower mortality rate in the LMWH group (0% vs 18.8%),[99] while the second showed no differences between the two groups in mortality (3,8% vs 5,6%) and in new symptomatic intracranial hemorrhage (none in both groups).[100] Unfractionated heparin, with its shorter half-life and easier reversibility, can be preferred in unstable patients or in those requiring invasive procedures.

Thrombolysis and endovascular treatment

No randomized clinical trials have assessed the role of systemic thrombolysis in CVST. The most recent systematic review on this issue included only case reports and case series for a total of 26 patients.[101] Urokinase was the most frequently administered thrombolytic agent (73.1%), while streptokinase and rt-PA were used in 7.7% of cases each. Extracranial hemorrhage occurred in 5 patients (19.2%) and intracranial in 3 (11.5%), with 2 deaths. Partial or complete recanalization occurred in 16 patients (61.5%). Only case reports and small case series are available in the literature on endovascular treatment of CVST with local thrombolysis (urokinase, streptokinase, or recombinant tissue-plasminogen activator) and mechanical thrombectomy. This treatment should be reserved for patients with a very severe presentation or rapidly declining neurological symptoms despite appropriate anticoagulant therapy, after exclusion of other causes of deterioration. Endovascular treatment is associated with a high risk of intracranial hemorrhage (7.6%) and mortality (9.2%), half due to new onset or worsening of pre-existing intracranial hemorrhage.[102] These estimates are likely underestimated because of the publication bias in favor of successful case reports. The randomized controlled trial TO-ACT (NCT01204333) comparing local thrombolysis and heparin treatment has been prematurely interrupted after the inclusion of 67 patients because of no difference in primary outcome (mRS 0-1 at 12 months).[103] Hence, currently available data raise concerns about safety of thrombolysis and endovascular treatment in patients with CVST.

Treatment of complications

The most severe patients present complications in the acute phase that requires specific management. In case of seizures, antiepileptic drugs are indicated to prevent recurrences, although the optimal duration of this therapy and its use as primary prophylaxis are not well established. In case of hydrocephalus associated to neurological deterioration, shunting procedures to drain excess cerebrospinal fluid are required after temporary withdrawal of anticoagulation. Intracranial hypertension does not usually require treatment, but in symptomatic cases shunting procedures or serial lumbar puncture are required to promptly reduce intracranial pressure in case of papilledema and reduced visual acuity. Acetazolamide can be also administered to reduce cerebrospinal fluid production.[28] Rarely, patients with CVST present transtentorial herniation in the acute phase and need decompressive surgery, a lifesaving procedure. A prospective evaluation of the outcome of patients with CVST undergoing decompressive surgery is ongoing (DECOMPRESS-2 registry) and the interim analysis on 22 patients showed a 6-month mortality rate of 23.8% in patients treated versus 100% in those not treated.[104] The role of steroids to reduce vasogenic edema is controversial, their use is not suggested in acute CVST, particularly in patients without parenchymal lesions while is recommended in CVST with an associated inflammatory disease (e.g. Behçet's disease).[28]

Treatment of the chronic phase

The optimal duration of anticoagulant therapy for secondary prevention of CVST should be decided for the single patient evaluating the risk-benefit ratio. The absolute risk of recurrent thrombosis is low and long-term anticoagulation is reserved to patients with persistent and unmodifiable risk factors (e.g., severe thrombophilia, and solid or hematological neoplasms) and to those with recurrent CVST. Whether also patients with unprovoked CVST should continue anticoagulation is not known (Fig. 4). AHA/ASA guidelines recommend that patients with CVST secondary to a transient risk factor receive anticoagulant therapy with a vitamin K antagonist for 3 to 6 months, maintaining an INR range between 2 and 3, while those with unprovoked CVST for 6 to 12 months.[24] An exception is CVST during pregnancy, that requires therapeutic doses of LMWH possibly adjusted for body weight to ensure efficacy until delivery[28] because of the teratogenic effect

of vitamin K antagonists. AHA/ASA guidelines recommend antiplatelet therapy after a period of anticoagulation in patients with CVST without a recognized thrombophilia, although in the absence of controlled trials or observational studies this indication sounds arbitrary.[106] In line with studies conducted in patients with venous thromboembolism, we might accept the recommendation for patients with unprovoked events. Randomized clinical trials are required and the ongoing EXCOA-CVT study (ISRCTN25644448) comparing a short (3-6 months) with a long (12 months) duration of oral anticoagulant therapy in patients with CVST will provide new insights into this crucial issue.[107] Recanalization of CVS T can be considered among criteria potentially helping the decision on the optimal duration of anticoagulant therapy. Repeating imaging (CT or MRI) is recommended at 3-6 months from index event or in case of persistence or recurrent symptoms suggestive of CVST during anticoagulation therapy.[24] In case of complete recanalization further neuroimaging is not required, whereas in case of partial recanalization we suggest to consider the possibility to prolong anticoagulation until a reassessment at 12 months from the event. Another emerging issue in the treatment of CVST is the role of direct oral anticoagulants (DOACs), that showed a similar efficacy and a better safety profile compared to vitamin K antagonists in patients with proximal deep vein thrombosis of the lower limbs or pulmonary embolism. All phase III clinical trials on the use of DOACs excluded patients with CVST and we thus have no certainties of their appropriateness for these patients, although a case series of only 7 patients treated with rivaroxaban confirmed its safety.[108] Clinical trials comparing efficacy and safety of dabigatran etexilate or rivaroxaban with warfarin or standard of care are ongoing (Table 2).

Secondary prevention

Concerning antithrombotic prophylaxis for prevention of thrombosis after a first episode of CVST, it has been suggested to follow suggestions reported in guidelines on extra-cranial venous thrombosis.[24] Concerning pregnancy and puerperium, prophylactic dose of LMWH for women who discontinued oral anticoagulation or therapeutic doses for those who remain pregnant during oral anticoagulation are suggested prophylaxis.[28]

Treatment in children and neonates

In children, the correction of concomitant conditions such as dehydration or infections is of crucial importance, even more so than in adults. When CVST is secondary to otitis media complicated by mastoiditis, antibiotic treatment with cephalosporins is indicated. Antibiotics are also used in patients with infection-related jugular vein thrombosis (Lemierre's syndrome), in particular against anaerobic microorganisms such as Fusobacterium necrophorum. In the absence of randomized controlled trials on anticoagulant treatment in children with CVST, current guidelines recommend therapeutic heparin doses independently of concomitant intracranial hemorrhage and endovascular treatment for patients with rapidly deteriorating neurological functions despite adequate anticoagulation, similarly to adults.[109] For neonates there is no consensus on the management of the acute phase, and both anticoagulation or a conservative approach should be considered, treating concomitant illnesses. A promising alternative to the parenteral heparin or vitamin K antagonists that require laboratory monitoring (very uncomfortable in the pediatric population) are the DOACs, at present under investigation in any phase trials.[110] The optimal duration of anticoagulant treatment is not well established, however 6 weeks to 3 months are recommended for neonates, and 3 to 6 months for children.[111] Thrombolysis should be used only in highly selected patients because of the bleeding risk, which is particularly high in neonates due to their immature hemostatic system. Moreover, the naturally low levels of plasminogen in neonates may decrease the efficacy of chemical thrombolysis and some authors suggest infusion of plasminogen through fresh frozen plasma before the procedure.[109]

Conclusions

Despite its low incidence rate, CVST represents one of the leading causes of stroke in young adults. A prompt diagnosis is necessary to avoid acute complications and long-term disabilities. The mainstay of therapy is anticoagulation, even if the optimal duration of treatment is currently under investigation. DOACs represent a fascinating option for treatment of CVST considering their safety profile and the lack of laboratory monitoring. Clinical trials with DOACs are currently ongoing in adults and children and their results will help in decision-making.

References

1. Goyal G, Singh R, Bansal N, Paliwal VK. Anatomical Variations of Cerebral MR Venography : Is Gender Matter ? 2016; : 92–8.
2. Schaller B, Graf R. Cerebral venous infarction: the pathophysiological concept. Cerebrovasc Dis 2004; 18: 179–88.
3. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005; : 1791–8.
4. Bousser M-G, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol 2007; 6:162–70.
5. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: A cross-sectional study. Stroke 2012; 43: 3375–7.
6. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral Venous Sinus Thrombosis Incidence is Higher Than Previously Thought: A Retrospective Population-Based Study. Stroke 2016; 47: 2180–2.
7. Janghorbani M, Zare M, Saadatnia M, Mousavi SA, Mojarrad M, Asgari E. Cerebral vein and dural sinus thrombosis in adults in Isfahan, Iran: Frequency and seasonal variation. Acta Neurol Scand 2008; 117: 117–21.
8. Khealani BA, Wasay M, Saadah M, Sultana E, Mustafa S, Khan FS, Kamal AK. Cerebral venous thrombosis: A descriptive multicenter study of patients in Pakistan and Middle East. Stroke 2008; 39: 2707–11.
9. Sidhom Y, Mansour M, Messelmani M, Derbali H, Fekih-Mrissa N, Zaouali J, Mrissa R. Cerebral venous thrombosis: Clinical features, risk factors, and long-term outcome in a Tunisian cohort. J Stroke Cerebrovasc Dis Elsevier Ltd; 2014; 23: 1291–5.
10. Maali L, Khan S, Qeadan F, Ismail M, Ramaswamy D, Hedna VS. Cerebral venous thrombosis: continental disparities. Neurol Sci Neurological Sciences; 2017; 38: 1963–8.
11. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, Camfield CS, David M, Humphreys P, Langevin P, MacDonald EA, Meaney B, Shevell M, Sinclair DB, Yager J, Gillett J. Cerebral Sinovenous Thrombosis in Children. N Engl J Med 2001; 345: 417–23.
12. Heller C, Heinecke A, Junker R, Knöfler R, Kosch A, Kurnik K, Schobess R, Von Eckardstein A, Sträter R, Zieger B, Nowak-Göttl U. Cerebral venous thrombosis in children: A multifactorial origin. Circulation 2003; 108: 1362–7.
13. Suppiej A, Gentilomo C, Saracco P, Sartori S, Agostini M, Bagna R, Bassi B, Giordano P, Grassi M, Guzzetta A, Lasagni D, Luciani M, Molinari AC, Palmieri A, Putti MC, Ramenghi LA, Rota LL, Sperlì D, Laverda AM, Simioni P. Paediatric arterial ischaemic stroke and cerebral sinovenous thrombosis. Thromb Haemost 2015; 113: 1270–7.
14. Sirachainan N, Limrungsikul A, Chuansumrit A, Nuntnarumit P, Thampratankul L, Wangruangsathit S, Sasanakul W, Kadegasem P. Incidences, risk factors and outcomes of neonatal thromboembolism. J Matern Neonatal Med Informa UK Ltd.; 2017; 0: 1–5.
15. Sébire G, Tabarki B, Saunders DE, Leroy I, Liesner R, Saint-Martin C, Husson B, Williams AN, Wade A, Kirkham FJ. Cerebral venous sinus thrombosis in children: Risk factors, presentation, diagnosis and outcome. Brain 2005; 128: 477–89.
16. Ferro JM, Canhão P, Stam J, Bousser M-G, Barinagarrementeria F, ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004; 35: 664–70.
17. De Bruijn SFTM, Stam J, Kappelle LJ. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. Lancet 1996; 348: 1623–5.
18. Coutinho JM, Stam J, Canhão P, Barinagarrementeria F, Bousser MG, Ferro JM. Cerebral venous thrombosis in the absence of headache. Stroke 2015; 46: 245–7.
19. Vestergaard K, Andersen G, Nielsen MI, Jensen TS. Headache in stroke. Stroke 1993; 24: 1621–4.
20. Davoudi V, Keyhanian K, Saadatnia M. Risk factors for remote seizure development in patients with cerebral vein and dural sinus thrombosis. Seizure 2014; 23: 135–9.
21. Leach JL, Fortuna RB, Jones B V., Gaskill-Shipley MF. Imaging of Cerebral Venous Thrombosis: Current Techniques, Spectrum of Findings, and Diagnostic Pitfalls1. Radiographics 2006; 26: S19–41.
22. Linn J, Ertl-Wagner B, Seelos KC, Strupp M, Reiser M, Brückmann H, Brüning R. Diagnostic value of multidetector-row CT angiography in the evaluation of thrombosis of the cerebral venous sinuses. AJNR Am J Neuroradiol 2007; 28: 946–52.
23. Kunal A, Kathy B, John F. R. Cerebral Sinus Thrombosis. Headache 2016; 63: 138–1333.
24. Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, Deveber G, Ferro JM, Tsai FY. Diagnosis and management of cerebral venous thrombosis: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42: 1158–92.
25. Bonneville F. Imaging of cerebral venous thrombosis. Diagn Interv Imaging Elsevier Masson SAS; 2014; 95: 1145–50.

26. Weimar C. Diagnosis and treatment of cerebral venous and sinus thrombosis. Curr Neurol Neurosci Rep 2014; 14: 417.
27. Crassard I, Soria C, Tzourio C, Woimant F, Drouet L, Ducros A, Bousser MG. A negative D-dimer assay does not rule out cerebral venous thrombosis: A series of seventy-three patients. Stroke 2005; 36: 1716–9.
28. Ferro JM, Bousser M-G, Canhão P, Coutinho JM, Crassard I, Dentali F, di Minno M, Maino A, Martinelli I, Masuhr F, Aguiar de Sousa D, Stam J. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol 2017; 24: 1203–13.
29. Coutinho JM, Zuurbier SM, Stam J. Declining mortality in cerebral venous thrombosis: A systematic review. Stroke 2014; 45: 1338–41.
30. Dentali F, Gianni M, Crowther MA, Ageno W. Natural history of cerebral vein thrombosis: a systematic review. Blood 2006; 108: 1129–34.
31. Haghighi AB, Edgell RC, Cruz-Flores S, Feen E, Piriyawat P, Vora N, Callison RC, Alshekhlee A. Mortality of cerebral venous-sinus thrombosis in a large national sample. Stroke 2012; 43: 262–4.
32. Breteau G, Mounier-Vehier F, Godefroy O, Gauvrit JY, Mackowiak-Cordoliani MA, Girot M, Bertheloot D, Hénon H, Lucas C, Leclerc X, Fourrier F, Pruvo JP, Leys D. Cerebral venous thrombosis: 3-Year clinical outcome in 55 consecutive patients. J Neurol 2003; 250: 29–35.
33. Silvis SM, Hiltunen S, Lindgren E, Jood K, Zuurbier SM, Middeldorp S, Putaala J, Cannegieter SC, Tatlisumak T, Coutinho JM. Cancer and risk of cerebral venous thrombosis: a case-control study. J Thromb Haemost 2017; : 90–5.
34. Hiltunen S, Putaala J, Haapaniemi E, Tatlisumak T. Long-term outcome after cerebral venous thrombosis: analysis of functional and vocational outcome, residual symptoms, and adverse events in 161 patients. J Neurol Springer Berlin Heidelberg; 2016; 263: 477–84.
35. Koopman K, Uyttenboogaart M, Vroomen PC, Meer J van der, De Keyser J, Luijckx GJ. Long-Term Sequelae after Cerebral Venous Thrombosis in Functionally Independent Patients. J Stroke Cerebrovasc Dis Elsevier Ltd; 2009; 18: 198–202.
36. Bugnicourt JM, Guegan-Massardier E, Roussel M, Martinaud O, Canaple S, Triquenot-Bagan A, Wallon D, Lamy C, Leclercq C, Hannequin D, Godefroy O. Cognitive impairment after cerebral venous thrombosis: A two-center study. J Neurol 2013; 260: 1324–31.
37. Kowoll CM, Kaminski J, Weiß V, Bösel J, Dietrich W, Jüttler E, Flechsenhar J, Guenther A, Huttner HB, Niesen WD, Pfefferkorn T, Schirotzek I, Schneider H, Liebig T, Dohmen C. Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis. Neurocrit Care 2016; 25: 392–9.
38. Arauz A, Vargas-González J-C, Arguelles-Morales N, Barboza MA, Calleja J, Martínez- Jurado E, Ruiz-Franco A, Quiroz-Compean A, Merino JG. Time to recanalisation in patients with cerebral venous thrombosis under anticoagulation therapy. J Neurol Neurosurg Psychiatry 2016; 87: 247 LP-251.
39. Herweh C, Griebe M, Geisbüsch C, Szabo K, Neumaier-Probst E, Hennerici MG, Bendszus M, Ringleb PA, Nagel S. Frequency and temporal profile of recanalization after cerebral vein and sinus thrombosis. Eur J Neurol 2016; 23: 681–7.
40. Strupp M, Covi M, Seelos K, Dichgans M, Brandt T. Cerebral venous thrombosis: correlation between recanalization and clinical outcome--a long-term follow-up of 40 patients. J Neurol 2002; 249: 1123–4.
41. Stolz E, Trittmacher S, Rahimi A, Gerriets T, Rottger C, Siekmann R, Kaps M. Influence of Recanalization on Outcome in Dural Sinus Thrombosis: A Prospective Study. Stroke 2004; 35: 544–7.
42. Gazioglu S, Eyuboglu I, Yildirim A, Aydin CO, Alioglu Z. Cerebral venous sinus Thrombosis: Clinical Features, Long-Term outcome and recanalization. J Clin Neurosci Elsevier Ltd; 2017; 45: 248–51.
43. Rezoagli E, Martinelli I, Poli D, Scoditti U, Passamonti SM, Bucciarelli P, Ageno W, Dentali F. The effect of recanalization on long-term neurological outcome after cerebral venous thrombosis. J Thromb Haemost 2018; : [Epub ahead of print].
44. Miranda B, Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, Scoditti U. Venous thromboembolic events after cerebral vein thrombosis. Stroke 2010; 41: 1901–6.
45. Gosk-Bierska I, Wysokinski W, Brown RD, Karnicki K, Grill D, Wiste H, Wysokinska E, McBane RD. Cerebral venous sinus thrombosis: Incidence of venous thrombosis recurrence and survival. Neurology 2006; 67: 814–9.
46. Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannuccio Mannucci P. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. Circulation 2010; 121: 2740–6.
47. Dentali F, Poli D, Scoditti U, di Minno MND, Stefano VD, Siragusa S, Kostal M, Palareti G, Sartori MT, Grandone E, Vedovati MC, Ageno W, Falanga A, Lerede T, Bianchi M, Testa S, Witt D, McCool K, Bucherini E, Grifoni E, et al. Long-term outcomes of patients with cerebral vein thrombosis: A multicenter study. J Thromb Haemost 2012; 10: 1297–302.
48. Wasay M, Dai AI, Ansari M, Shaikh Z, Roach ES. Cerebral Venous Sinus Thrombosis in Children: A Multicenter Cohort From the United States. J Child Neurol 2008; 23: 26–31.
49. Moharir MD, Shroff M, Pontigon A-M, Askalan R, Yau I, MacGregor D, DeVeber GA. A Prospective Outcome Study of Neonatal Cerebral Sinovenous Thrombosis. J Child Neurol 2011; 26: 1137–44.

50. De Schryver EL, Blom I, Braun KP, Jaap Kappelle L, Rinkel GJ, Boudewyn Peters A, Jennekens-Schinkel A. Long-term prognosis of cerebral venous sinus thrombosis in childhood. Dev Med Child Neurol 2004; 46: 514–9.
51. Fitzgerald KC, Williams LS, Garg BP, Carvalho KS, Golomb MR. Cerebral sinovenous thrombosis in the neonate. Arch Neurol 2006; 63: 405–9.
52. Kenet G, Kirkham F, Niederstadt T, Heinecke A, Saunders D, Stoll M, Brenner B, Bidlingmaier C, Heller C, Knöfler R, Schobess R, Zieger B, Sébire G, Nowak-Göttl U. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. Lancet Neurol 2007; 6: 595–603.
53. Moharir MD, Shroff M, Stephens D, Pontigon AM, Chan A, MacGregor D, Mikulis D, Adams M, DeVeber G. Anticoagulants in pediatric cerebral sinovenous thrombosis a safety and outcome study. Ann Neurol 2010; 67: 590–9.
54. Dlamini N, Billinghurst L, Kirkham FJ. Cerebral Venous Sinus (Sinovenous) Thrombosis in Children. Neurosurg Clin N Am Elsevier Ltd; 2010; 21: 511–27.
55. Canhão P, Ferro JM, Lindgren AG, Bousser MG, Stam J, Barinagarrementeria F. Causes and predictors of death in cerebral venous thrombosis. Stroke 2005; 36: 1720–5.
56. Bousser MG, Crassard I. Cerebral venous thrombosis, pregnancy and oral contraceptives. Thromb Res Elsevier Ltd; 2012; 130: S19–22.
57. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: A meta-analysis. Blood 2006; 107: 2766–73.
58. Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MR, Meisterernst J, Nemeth B, Meulendijks ER, Stam J, Cannegieter SC, Coutinho JM. Risk of cerebral venous thrombosis in obese women. JAMA Neurol 2016; 73: 579–84.
59. Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. Arterioscler Thromb Vasc Biol 1999; 19: 700–3.
60. Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP, Investigation O. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. Arch Intern Med 2000; 160: 49–52.
61. Coutinho JM, Ferro JM, Canhão P, Barinagarrementeria F, Cantú C, Bousser MG, Stam J. Cerebral venous and sinus thrombosis in women. Stroke 2009; 40: 2356–61.
62. Lauw M, Barco S, Coutinho J, Middeldorp S. Cerebral Venous Thrombosis and Thrombophilia: A Systematic Review and Meta-Analysis. Semin Thromb Hemost 2013; 39: 913–27.
63. Tufano A, Guida A, Coppola A, Nardo A, Capua M Di, Quintavalle G, Di Minno MND, Cerbone AM, Di Minno G. Risk factors and recurrent thrombotic episodes in patients with cerebral venous thrombosis. Blood Transfus 2014; 12.
64. Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood 2003; 102: 1363–6.
65. Wysokinska EM, Ii RDM. Thrombophilia differences in cerebral venous sinus and lower extremity deep venous thrombosis. Hematology 2008; 70: 627–33.
66. Bugnicourt J-M, Roussel B, Tramier B, Lamy C, Godefroy O. Cerebral venous thrombosis and plasma concentrations of factor VIII and von Willebrand factor: a case control study. J Neurol Neurosurg Psychiatry 2007; 78: 699–701.
67. Cantu C, Alonso E, Jara A, Martínez L, Ríos C, De Los Angeles Fernández M, Garcia I, Barinagarrementeria F. Hyperhomocysteinemia, low folate and vitamin B12 concentrations, and methylene tetrahydrofolate reductase mutation in cerebral venous thrombosis. Stroke 2004; 35: 1790–4.
68. Couturier M-A, Huguet F, Chevallier P, Suarez F, Thomas X, Escoffre-Barbe M, Cacheux V, Pignon J-M, Bonmati C, Sanhes L, Bories P, Daguindau E, Dorvaux V, Reman O, Frayfer J, Orvain C, Lhéritier V, Ifrah N, Dombret H, Hunault-Berger M, et al. Cerebral venous thrombosis in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma during induction chemotherapy with L-asparaginase: The GRAALL experience. Am J Hematol 2015; 90: 986–91.
69. Martinelli I, De Stefano V, Carobbio A, Randi ML, Santarossa C, Rambaldi A, Finazzi MC, Cervantes F, Arellano-Rodrigo E, Rupoli S, Canafoglia L, Tieghi A, Facchini L, Betti S, Vannucchi AM, Pieri L, Cacciola R, Cacciola E, Cortelezzi A, Iurlo A, et al. Cerebral vein thrombosis in patients with Philadelphia-negative myeloproliferative neoplasms An European Leukemia Net study. Am J Hematol 2014; 89: E200–5.
70. Dentali F, Ageno W, Rumi E, Casetti I, Poli D, Scoditti U, Maffioli M, Di Minno MND, Caramazza D, Pietra D, De Stefano V, Passamonti F. Cerebral venous thrombosis and myeloproliferative neoplasms: Results from two large databases. Thromb Res 2014; 134: 41–3.
71. Barbui T, De Stefano V. Management of venous thromboembolism in myeloproliferative neoplasms. Curr Opin Hematol 2017; 24: 108–14.

72. Katsanos AH, Katsanos KH, Kosmidou M, Giannopoulos S, Kyritsis AP, Tsianos E V. Cerebral sinus venous thrombosis in inflammatory bowel diseases. Qjm 2013; 106: 401–13.
73. Defilippis EM, Barfield E, Leifer D, Steinlauf A, Bosworth BP, Scherl EJ, Sockolow R. Cerebral venous thrombosis in inflammatory bowel disease. J Dig Dis 2015; 16: 104–8.
74. De Sousa DA, Mestre T, Ferro JM. Cerebral venous thrombosis in Behçet's disease: A systematic review. J Neurol 2011; 258: 719–27.
75. Silvis SM, De Sousa DA, Ferro JM, Coutinho JM. Cerebral venous thrombosis. Nat Rev Neurol 2017; 13: 555–65.
76. Cotlarciuc I, Marjot T, Malik R, Khan M, Pare G, Sharma P, on behalf of the BEAST Consortium. Exome array analysis on cerebral venous thrombosis:preliminary results. Int J Stroke 2015; 10: 219–219.
77. Cotlarciuc I, Marjot T, Khan MS, Hiltunen S, Haapaniemi E, Metso TM, Putaala J, Zuurbier SM, Brouwer MC, Passamonti SM, Bucciarelli P, Pappalardo E, Patel T, Costa P, Colombi M, Canhão P, Tkach A, Santacroce R, Margaglione M, Favuzzi G, et al. Towards the genetic basis of cerebral venous thrombosis—the BEAST Consortium: a study protocol: Table 1. BMJ Open 2016; 6: e012351.
78. Junker R, Nabavi DG, Wolff E, Lüdemann P, Nowak-Göttl U, Käse M, Bäumer R, Ringelstein EB, Assmann G. Plasminogen activator inhibitor-1 4G/4G-genotype is associated with cerebral sinus thrombosis in factor V Leiden carriers. Thromb Haemost 1998; 80: 706–7.
79. Le Cam-Duchez V, Bagan-Triquenot A, Barbay V, Mihout B, Borg JY. The G79A polymorphism of protein Z gene is an independent risk factor for cerebral venous thrombosis. J Neurol 2008; 255: 1521–5.
80. Passamonti SM, Biguzzi E, Cazzola M, Franchi F, Gianniello F, Bucciarelli P, Pietra D, Mannucci PM, Martinelli I. The JAK2 V617F mutation in patients with cerebral venous thrombosis. J Thromb Haemost 2012; 10: 998–1003.
81. Bellucci S, Cassinat B, Bonnin N, Marzac C, Crassard I. The V617F JAK 2 mutation is not a frequent event in patients with cerebral venous thrombosis without overt chronic myeloproliferative disorder. Thromb Haemost 2008; 99: 1119–20.
82. Andrew M, Paes B, Milner R, Johnstone M, Mitchell L, Tollefsen DM, Powers P. Development of the human coagulation system in the full-term infant. Blood 1987; 70: 165–72.
83. Van Ommen CH, Sol JJ. Developmental Hemostasis and Management of Central Venous Catheter Thrombosis in Neonates. Semin Thromb Hemost 2016; 42: 752–9.
84. Tan M, deVeber G, Shroff M, Moharir M, Pontigon A-M, Widjaja E, Kirton A. Sagittal Sinus Compression Is Associated With Neonatal Cerebral Sinovenous Thrombosis. Pediatrics 2011; 128: e429–35.
85. Hedlund GL. Cerebral sinovenous thrombosis in pediatric practice. Pediatr Radiol 2013; 43: 173–88.
86. Saracco P, Bagna R, Gentilomo C, Magarotto M, Viano A, Magnetti F, Giordano P, Luciani M, Molinari AC, Suppiej A, Ramenghi LA, Simioni P. Clinical Data of Neonatal Systemic Thrombosis. J Pediatr 2016; 171: 60–66e1.
87. Star M, Flaster M. Advances and Controversies in the Management of Cerebral Venous Thrombosis. Neurol Clin 2013; 31: 765–83.
88. Quesnel S, Nguyen M, Pierrot S, Contencin P, Manach Y, Couloigner V. Acute mastoiditis in children: A retrospective study of 188 patients. Int J Pediatr Otorhinolaryngol Elsevier Ireland Ltd; 2010; 74: 1388–92.
89. Fluss J, Geary D, DeVeber G. Cerebral sinovenous thrombosis and idiopathic nephrotic syndrome in childhood: Report of four new cases and review of the literature. Eur J Pediatr 2006; 165: 709–16.
90. Uziel Y, Laxer RM, Blaser S, Andrew M, Schneider R, Silverman ED. Cerebral vein thrombosis in childhood systemic lupus erythematosus. J Pediatr 1995; 126: 722–7.
91. Caruso V, Iacoviello L, Castelnuovo A Di, Storti S, Mariani G, Gaetano D, Donati MB, Dc W, Gaetano G De. Thrombotic complications in childhood acute lymphoblastic leukemia : a meta-analysis of 17 prospective studies comprising 1752 pediatric patients Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studie. 2014; 108: 2216–22.
92. Bonduel M, Sciuccati G, Hepner M, Pieroni G, Torres AF, Mardaraz C, Frontroth JP. Factor V Leiden and prothrombin gene G20210A mutation in children with cerebral thromboembolism. Am J Hematol 2003; 73: 81–6.
93. Stansfield FR. Puerperal cerebral thrombophlebitis treated by heparin. Br Med J 1942; 1: 436–8.
94. Einhäupl KM, Villringer A, Mehraein S, Garner C, Pellkofer M, Haberl RL, Pfister H-W, Schmiedek P, Meister W. Heparin treatment in sinus venous thrombosis. Lancet 1991; 338: 597–600.
95. de Bruijn SFTM, Stam J. Randomized, Placebo-Controlled Trial of Anticoagulant Treatment With Low-Molecular-Weight Heparin for Cerebral Sinus Thrombosis. Stroke 1999; 30: 484–8.
96. Coutinho J, de Bruijn SF, DeVeber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. Cochrane Database Syst Rev 2011; .
97. Ghandehari K, Riasi HR, Noureddine A, Masoudinezhad S, Yazdani S, Mirzae MM, Razavi AS, Ghandehari K. Safety assessment of anticoagulation therapy in patients with hemorrhagic cerebral venous thrombosis. Iran J Neurol 2013; 12: 87–91.

98. Coutinho JM, Ferro JM, Canhão P, Barinagarrementeria F, Bousser MG, Stam J. Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. Stroke 2010; 41: 2575–80.
99. Misra UK, Kalita J, Chandra S, Kumar B, Bansal V. Low molecular weight heparin versus unfractionated heparin in cerebral venous sinus thrombosis: A randomized controlled trial. Eur J Neurol 2012; 19: 1030–6.
100. Afshari D, Moradian N, Nasiri F, Razazian N, Bostani A, Sariaslani P. The efficacy and safety of low-molecular-weight heparin and unfractionated heparin in the treatment of cerebral venous sinus thrombosis. Neurosciences 2015; 20: 357–61.
101. Viegas LD, Stolz E, Canhão P, Ferro JM. Systemic thrombolysis for cerebral venous and dural sinus thrombosis: a systematic review. Cerebrovasc Dis 2014; 37: 43–50. Dentali F, Squizzato A, Gianni M, De Lodovici ML, Venco A, Paciaroni M, Crowther M,
102. Ageno W. Safety of thrombolysis in cerebral venous thrombosis: A systematic review of the literature. Thromb Haemost 2010; 104: 1055–62.
103. Coutinho JM, Ferro JM, Zuurbier SM, Mink MS, Canhão P, Crassard I, Majoie CB, Reekers JA, Houdart E, de Haan RJ, Bousser M-G, Stam J. Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis: Rationale and Design of the TO-ACT Trial. Int J Stroke 2013; 8: 135–40.
104. Théaudin M, Crassard I, Bresson D, Saliou G, Favrole P, Vahedi K, Denier C, Bousser MG. Should decompressive surgery be performed in malignant cerebral venous thrombosis?: A series of 12 patients. Stroke 2010; 41: 727–31.
105. Canhão P, Cortesão A, Cabral M, Ferro JM, Stam J, Bousser MG, Barinagarrementeria F. Are steroids useful to treat cerebral venous thrombosis? Stroke 2008; 39: 105–10.
106. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck D V., Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014.
107. Miranda B, Aaron S, Arauz A, Barinagarrementeria F, Borhani-haghighi A, Carvalho M, Conforto AB. The benefit of EXtending oral antiCOAgulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. 2018; 0: 1–4.
108. Geisbüsch C, Richter D, Herweh C, Ringleb PA, Nagel S. Novel factor Xa inhibitor for the treatment of cerebral venous and sinus thrombosis: First experience in 7 patients. Stroke 2014; 45: 2469–71.
109. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, Vesely SK. Antithrombotic therapy in neonates and children: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012; 141.
110. von Vajna E, Alam R, So T-Y. Current Clinical Trials on the Use of Direct Oral Anticoagulants in the Pediatric Population. Cardiol Ther Springer Healthcare; 2016; 5: 19–41.
111. Lebas A, Chabrier S, Fluss J, Gordon K, Kossorotoff M, Nowak-Göttl U, De Vries LS, Tardieu M. EPNS/SFNP guideline on the anticoagulant treatment of cerebral sinovenous thrombosis in children and neonates. Eur J Paediatr Neurol 2012; 16: 219–28.

Chapter 4

Duration of oral contraceptive use and the risk of venous thromboembolism. A case-control study

---

Ida Martinelli, Alberto Maino, Maria Abbattista, Paolo Bucciarelli, Serena M. Passamonti, Andrea Artoni, Francesca Gianniello, Flora Peyvandi

Thromb Res. 2016 May; 141:153-7. doi: 10.1016/j.thromres.2016.03.025. Epub 2016 Mar 23. PMID: 27043069.

Summary

Introduction: Oral contraceptive (OC) use increases the risk of venous thromboembolism (VTE), but the effect of duration of use remains to be elucidated.
Patients and methods: This case-control study was aimed to investigate the duration of OC use on the risk of VTE according to women age, periods of use, prevalence of other risk factors and the role of thrombophilia abnormalities. Seven-hundred patients and 209 controls who used OC were stratified into short users (≤1 year), long users (1 to 5 years), and very long users (>5 years).
Results and conclusions: Compared to non-users, the odds ratio (OR) for VTE was 9.0 (95% CI 6.9–12.2) in short, 6.5 (95% CI 4.8–83.7) in long and 5.9 (95% CI 4.4–8.1) in very long users. The risk of VTE in short users was highest in women ≤30 years and in the first year of use (OR 13.1, 95% CI 7.7–22.4) and decreased afterward (OR 7.7, 95% CI 5.0–11.9). This trend was not observed in women >30 years. Compared to non-carriers and non-users, a joint effect of thrombophilia abnormalities and OC use on VTE risk was observed particularly in short users (OR 62.2, 95% CI 29.8–129.6), but also afterward (OR 25.4, 95% CI 16.5–39.2). Other transient risk factors for VTE were present in 25% of very long and 16% of short users.
In conclusion, the risk of VTE in OC users decreases over time only before 30 years and in first users. Thrombophilia abnormalities strongly interact with the duration of OC use in determining VTE.

Introduction

Oral contraceptives (OC) are the most popular and efficacious contraception method worldwide. However, their use is associated with an increased risk of venous thromboembolism (VTE), that is attributable either to the dose of estrogen and the type of progestogen.[1] The use of OC increases the 0.5 to 1.0 per 10,000 person-years baseline incidence rate of VTE in women in childbearing age by a factor of approximately 6 or even more for preparations containing >30 μg of estrogen and progestogens other than levonorgestrel.[2,3] Although the incidence of VTE remains low, OC use has a strong impact on the thrombotic risk, being >100 million women who use OC worldwide.[4] The OC related risk of VTE is particularly high in women with a baseline increased risk, e.g. carriers of thrombophilia abnormalities, and the two risk factors interact synergistically on the thrombotic risk.[5–7] Among women with VTE during childbearing age, the most common transient risk factor is OC use, recognized in approximately 60% of patients and inherited or acquired thrombophilia abnormalities are also frequently detected.[8,9] Being VTE a multifactorial disease, more than one risk factor is frequently recognized and it is important to weight each of them on an individual basis. Indeed, it is known that the risk of thrombosis in OC users is higher in the first 6–12 months of use and in those using OC for the first time, but whether this difference is present at any age and is mediated by the presence of thrombophilia abnormalities has not been elucidated yet.[1,2,5]

Aims of this case-control study were to investigate the association between the duration of OC use and the risk of VTE according to the age and the periods of OC use, the prevalence of other risk factors for VTE in OC users and the role of thrombophilia abnormalities according to the duration of use.

Patients and methods

In this case-control study women of childbearing age (defined as the period of life between puberty and menopause when it is physically possible to conceive) referred to our Thrombosis Center for thrombophilia screening after a first episode of objectively confirmed VTE between January 1994 and December 2014 formed the initial patients population. VTE included deep vein thrombosis of the lower limbs (diagnosed by compression ultrasound or venography), pulmonary embolism (V/Q lung scan, CT scan or pulmonary

angiography) and cerebral vein thrombosis (cerebral digital angiography, CT angiography, magnetic resonance or magnetic resonance angiography). Women with pregnancy- or cancer-related VTE were excluded because pregnancy mutually excludes OC use and cancer is a strong independent risk factor for VTE.[10] Women with liver or renal diseases are not represented in our patients' population as their diseases affect most of the thrombophilia tests performed in plasma. The definition of liver and kidney disease was based on an existing diagnosis made by a specialist or abnormal liver or renal function tests. Healthy women of childbearing age, friends or partners of the whole population of the patients referred to our Center in the same study period, who voluntarily agreed to undergo thrombophilia testing, were selected as control group. Exclusion criteria for controls were pregnancy, overt neoplastic, autoimmune, liver or renal diseases at the time of blood sampling. Previous episodes of thrombosis were excluded by means of a validated questionnaire.[11] Information on OC use at the time of VTE for patients or blood sampling for controls, duration of use and previous periods of use were carefully collected, as well as the type of compound. OC were classified as first generation, containing lynestrenol or norethindrone/ norethindrone acetate; second generation, containing levonorgestrel or norgestrel; third generation, containing desogestrel or gestodene; fourth generation containing the antimineralocorticoid drospirenone; those containing cyproterone acetate; others, containing dienogest or transdermal patches or hormone releasing intrauterine devices. Surgery, trauma and immobilization (plaster casts or prolonged bed rest >1week) within a month preceding the eventwere considered transient risk factors for VTE. Events that occurred in the absence of the aforementioned risk factors were considered unprovoked. The study was approved by the Hospital Institutional Review Board and all patients and controls gave written informed consent to participate to the study.

Laboratory tests

Blood samples for thrombophilia testing were anticoagulated with sodium citrate (3.8% wt/vol) and taken after at least one month from VTE in patients and at the time of the visit in controls. Thrombophilia screening included: DNA analysis for the 1691 guanine to adenine substitution in coagulation factor V gene (factor V Leiden)[12] and for the 20210 guanine to adenine substitution in the 3'-untranslated region of the prothrombin gene[13] that are both gain-of-function mutations associated with hypercoagulability;

functional and antigenic (when required) assays for plasma fibrinogen, antithrombin, protein C and protein S,[14] antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein IgG and IgM antibodies),[15] plasma factor VIII, measured with one-stage coagulation bioassay using factor VIII-deficient plasma as substrate and the activated partial thromboplastin time as reagent.[16] High factor VIII plasma levels were defined when exceeding the 95th percentile of the distribution among controls (158 IU/dL). Plasma homocysteine was measured both at fasting and after a methionine load of 3.8 g per square-meter of body surface area, and HHcy was defined when levels exceeded the 95th percentile of the homocysteine distribution among controls (17 and 22 μmol/L fasting levels and 28 and 29 μmol/L the difference between post-methionine load and fasting levels, for women and men, respectively).[17] Patients who were taking vitamin K-antagonists at the time of the first visit were asked to provide a second blood sample after discontinuation of oral anticoagulant therapy, because it affects measurements of protein C and protein S. The inheritance of antithrombin, protein C and protein S deficiency was confirmed on a second blood sample and in at least one relative.

Statistical analysis

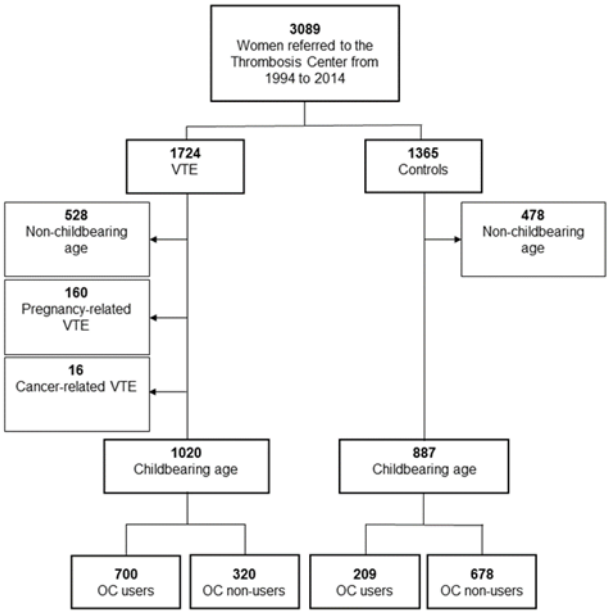
Duration of OC was calculated as the difference between the VTE index date for patients or blood sampling for controls and the beginning of OC use. If a women used more than one OC consecutively, or started a new OC within two months from the previous one, the time of OC use was considered uninterrupted. We chose three categories based on duration of OC use, grouping women into short users (≤1 year of uninterrupted OC use), long users (from 1 to 5 years), and very long users (>5 years). We analyzed the risk of VTE for short, long and very long OC users compared with non-users, by estimating the odds ratio (OR) with 95% confidence interval (CI), calculated by unconditional multivariable logistic regression adjusted for body mass index (BMI) and the presence of thrombophilia abnormalities. Because OC use is the most common risk factor for cerebral vein thrombosis, we performed a sensitivity analysis excluding patients with thrombosis at this site. The analysis was stratified for a predefined age cut-off of 30 years to account for the confounding effect of age, and for periods of OC use. Women who were taking OC for the first time in their life with no interruption or interruptions shorter than 2 months were considered first OC users.[18] Those who used OC

in other periods of life other than at the time of VTE for patients or blood sampling for controls were considered multiple users if the periods of use were interrupted by a time frame of at least 2 months. The joint effect of short (≤1 year of uninterrupted use) or long OC use (>1 year) with the presence of thrombophilia abnormalities was assessed comparing the risk of those with either one or both exposures with those with neither exposure (i.e., non OC users without thrombophilia). All analyses were performed with the statistical software SPSS (release 22.0, IBM Corp., Armonk, NY, USA).

Results

From January 1994 to December 2014, thrombophilia screening was performed in 3089 women, 1724 with VTE and 1365 controls. After exclusion of women in postmenopausal age and those with pregnancy- or cancer-related VTE, 1020 patients and 887 controls of childbearing age remained, of whom 700 (69%) and 209 (24%), respectively, were OC users (Fig. 1). Table 1 shows the general characteristics of the study population. Patients had mainly deep vein thrombosis of the lower limbs and/or pulmonary embolism (86%), were slightly younger and had a higher BMI and a higher prevalence of thrombophilia abnormalities than controls. Third generation preparations were the most widely used OC (66% of patients and 68% of controls), followed by fourth generation preparations (13% and 11%). In 560 patients (80%) OC use was the only transient risk factor for VTE, whereas in the remaining 140 (20%) at least one additional transient risk factor was present (Table 1).

Figure 1. Selection of the study population



VTE =venous thromboembolism
OC =oral contraceptive

Table 1 Demographic and clinical characteristics of oral contraceptive users.

	Patients	Controls
Oral contraceptive users, n	700	209
Age, years, median (range)	30 (15-53)	32 (16-54)
BMI, kg/m^2, median (range)	22.1 (15.4-42.5)	20.8 (17.2-33.7)
Months of use, median (range)	22.2 (0.2-371.1)	31.3 (0.2-333.4)
First users, n (%)	425 (60.7)	114 (54.5)
Type of VTE, n (%)		
DVT only	397 (56.7)	-
PE only	120 (17.1)	-
DVT and PE	82 (11.7)	-
CVT	101(14.4)	-
Type of oral contraceptive, n (%)*		
First generation	0	0
Second generation	24 (3.4)	12 (5.7)
Third generation	463 (66.2)	142 (67.9)
Fourth generation	88 (12.6)	16 (7.7)
Cyproterone acetate	67 (9.6)	10 (4.8)
Others†	29 (4.1)	20 (9.6)
Type of thrombophilia abnormalities, n (%)		
AT, PC or PS deficiency	37 (5.3)	3 (1.4)
Factor V Leiden	101 (14.4)	6 (2.9)
Prothrombin G20210A	93 (13.3)	7 (3.3)
Antiphospholipid antibodies	43 (6.1)	0
Hyperhomocysteinemia	94 (13.4)	14 (6.7)
High factor VIII	88 (12.6)	9 (4.3)
Other risk factors, n (%) ‡		
None	560 (80)	209 (100)
Surgery	39 (5.6)	-
Trauma	38 (5.4)	-
Immobilization	45 (6.4)	-
Others$	32 (5.6)	-

DVT = deep vein thrombosis, PE = pulmonary embolism, CVT = cerebral vein Thrombosis, AT= antithrombin, PC = protein C, PS = protein S

***** 29 (4.1%) types of OC in patients and 9 (4.3%) types in controls are missing.

† Containing dienogest or transdermal patches or hormone releasing intrauterine devices.

‡ Some patients had more than one transient risk factor other than OC use.

$ 11 autoimmune diseases, 18 infections, 3 inferior vena cava agenesia.

The overall OR for VTE in OC users was 7.5 (95% CI 6.1–9.3). Table 2 shows the risk of VTE in relation to duration of OC use.

Table 2. Risk of venous thromboembolism according to the duration of oral contraceptive use.

Duration of use	Patients, n.	Controls, n.	OR (95% CI)	Adj*OR (95%CI)
Non-users	320	678	Ref.	Ref.
Very long users	203	72	5.9 (4.4-8.1)	6.1 (4.5-8.5)
Long users	220	72	6.5 (4.8-8.7)	6.9 (5.0-9.4)
Short users	277	65	9.0 (6.9-12.2)	8.8 (6.4-12.1)

Ref.: reference group
* Adjusted for BMI and thrombophilia abnormalities

Compared to non-users, short OC users had a 9-fold, long users 6.5-fold and very long users 5.9-fold increased risk of VTE (Cochran-Armitage test for trend, p = 0.031). Adjustment for BMI and the presence of thrombophilia abnormalities did not affect the risk estimates. Sensitivity analysis limited to women taking third generation OC or excluding women with cerebral vein thrombosis gave similar results (data not shown). When we considered different categories of duration of OC use, i.e., ≤6 months, 6 months to 1 year, 1 to 5 years, 5 to 10 years and >10 years, the trend of the risk estimates did not substantially change, but results become more unstable because of the small number of users in the additional strata. When analyses were done stratifying women by age ≤ 30 years (median 24 years, range 15–30 in 365 patients and 25 years, range 16–30 in 91 controls) and >30 years (median 39 years, range 31–53 in 335 patients and 40 years, range 31–54 in 118 controls) the risk of VTE was higher in the youngest group in the first year of use (adj. OR 13.1, 95% CI 7.7–22.4), whereas among the oldest the risk of VTE was 6 to 7-fold increased and not influenced by the periods and duration of OC use (Table 3).

Very long OC users had at least another transient risk factor for VTE in 25% of cases compared to 16% in short OC users and at least two other risk factors were present in 10% and 5%, respectively. These figures were the same in women aged below or above 30 years. Thrombophilia abnormalities were slightly more prevalent in short OC users than in very long users, either as exclusive (48% and 39%) or non-exclusive (55% and 52%) risk factor for VTE.

Table 4 shows the joint effect of thrombophilia and OC use according to the duration of use. The risk of VTE was higher in women with thrombophilia abnormalities, particularly short OC users, than in those without thrombophilia and non-users (adj. OR 62.2, 95% CI 29.8– 129.6).

After the first year of OC use the relative risk in thrombophilia carriers decreased but remained still high (adj. OR 25.4, 95% CI 16.5– 39.2).

Table 3. Effect of age and period of OC use on the risk of venous thromboembolism according to the duration of OC use.

Age	Periods of use	Duration of use	Patient, n	Controls, n	OR (95% CI)	Adj*OR (95% CI)
≤30 years	First	Non-users	124	241	Ref.	Ref.
		Long users	139	37	7.3 (4.8-11.1)	7.7 (5.0-11.9)
		Short users	130	19	13.3 (7.8-22.5)	13.1 (7.7-22.4)
	Multiple	Non-users	124	241	Ref.	Ref.
		Long users	48	22	4.2 (2.4-7.3)	4.3 (2.5-7.5)
		Short users	48	13	7.2 (3.7-13.7)	7.0 (3.6-13.5)
>30 years	First	Non-users	196	437	Ref.	Ref.
		Long users	112	46	5.5 (3.7-7.9)	6.2 (4.1-9.1)
		Short users	44	12	8.2 (4.2-15.9)	7.7 (3.9—15.1)
	Multiple	Non-users	196	437	Ref.	Ref.
		Long users	124	39	7.1 (4.9-10.6)	7.4 (4.9-11.1)
		Short users	55	21	5.9 (3.5-9.9)	6.2 (3.6-10.6)

Ref.: reference group
* Adjusted for BMI.

Table 4. Joint effect of oral contraceptive use with thrombophilia abnormalities according to the duration of use.

	Patients	Controls	OR (95% CI)	Adj*OR (95% CI)
Non-users/thrombophilia-	170	577	Ref.	Ref.
Non-users/thrombophilia+	150	101	4.1 (3.0-5.5)	4.0 (2.9-5.4)
Long and very long users/thrombophilia-	213	120	6.1 (4.6-8.1)	6.6 (4.9-8.8)
Long and very long users/thrombophilia+	210	24	23.9 (15.6-36.5)	25.4 (16.5-39.2)
Short users/thrombophilia-	125	59	7.2 (5.1-10.3)	7.5 (5.3-10.8)
Short users/thrombophilia+	152	6	62.6 (30.1-130.1)	62.2 (29.8-129.6)

Ref.: reference group
* Adjusted for BMI.

These figures were higher in first OC users (adj. OR 158.2, 95% CI 38.6–648.5 for short users and 25.9, 95% CI 15.0–44.9 for long or very long users) than in multiple OC users (adj. OR 30.8, 95% CI 13.0– 72.6 for short users and 21.3, 95% CI 11.6–39.2 for long or very long users). Among women without thrombophilia abnormalities the risk of VTE was 7.5-fold increased in short OC users and 6.5-fold after the first year of use, compared to non-users without thrombophilia. Excluding women with CVT, the risk of VTE in carriers of thrombophilia slightly decreased both in short users (adj. OR 56.9, 95% CI 27.2–118.9) and after the first year of use (adj. OR 22.2, 95%CI 14.3–34.5). These estimates did not substantially change when considering among thrombophilia abnormalities only the most common factor V Leiden and prothrombin G20210A mutations.

Discussion

The first robust observation of a highest risk of VTE during the first 6-12 months of OC use and in carriers of thrombophilia was made in the frame of the population-based case-control Leiden Thombophilia Study, in 109 patients with VTE and 65 controls [5]. The large sample size of our study allowed us to estimate the risk of VTE according to three categories of duration of OC use (≤1 year, 1 to 5 years and >5 years), to perform subanalyses by strata of age (≤ or > 30 years) and periods of assumption (first and multiple OC users), and to evaluate the joint effect of OC use and thrombophilia abnormalities according to the duration of use. Our study shows that the increased risk of VTE in OC users decreases progressively over time. In women who use OC for more than 5 years, the risk of VTE halves that observed in the first year of use. However, this is valid only for women aged less than 30 years who are first users, i.e., those who used an OC at the time of VTE for the first time in their life with no other periods of assumption in the past. In addition, the longer the duration of OC use, the higher the prevalence of transient risk factors for VTE other than OC and the (slightly) lower the prevalence of thrombophilia abnormalities. In a pattern of causality, this means that after a certain period of OC use, other triggering factors become more important to develop the disease. The synergistic effect between OC use and the presence of thrombophilia abnormalities was highest in the first year of OC use and particularly in first users, but remained still high in the following years of use, being weakest in multiple users for more than one year. Our observation of a progressive decrease of the risk of VTE with the length

of OC use is in contrast with data stemming from a Danish population study that did not find a reduction of the risk in women who used OC for more than 4 years compared to those who used OC for one to 4 years, but the different design of the two studies makes them not comparable [2]. On one hand, among the strengths of our study other than the large sample size for a single-center case-control study, there is the accuracy of diagnosis of VTE and the expertise of our laboratory to perform thrombophilia screening, which was uniformly done in all patients and controls. On the other hand, our Thrombosis Center is a tertiary care center where patients are referred for thrombophilia screening after a first VTE and therefore our women are likely not representative of the VTE patients from the general population. Other limitations of this study need to be addressed. First, our results can not be generalized to all OC, as two thirds of women were taking third generation compounds that contain desogestrel or gestodene as progestogen, which is known to be associated with a higher risk of VTE than levonorgestrel [2,3]. This preference of prescription reflects the overall preference of prescription in the Italian population and the small proportion of users of OC other than the third generation ones did not allow separate analysis according to the type of compound [18]. Second, one may argue that we included among our patients also those with cerebral vein thrombosis, in whom the association between the disease and OC use is stronger than for other sites of VTE [19]. However, the risk estimates only slightly decreased when the analyses were performed only in women with lower-limb deep vein thrombosis and/or pulmonary embolism, and the differences found according to periods and duration of OC use, and presence or absence of thrombophilia abnormalities did not substantially change. Finally, due to the case-control design, information on OC use were collected after the occurrence of the disease and this may raise concern that the disease affected the OC duration (recall bias). However, it is likely that this bias was equally distributed between patients (more incline to remember the exposure but interviewed after VTE) and controls (less incline to remember the exposure but interviewed while taking OC). In conclusion, our study provides the new clinical information that the duration of OC use influences the risk of VTE in young women (median age 25 years) but not in older ones (median age 40 years), and that the risk of VTE associated with duration of OC use strongly interacts with the presence of thrombophilia abnormalities, particularly in the first year of OC use but, at a lesser extent, also later. Moreover, the longer the use of OC the higher the number of other transient

risk factors present at the time of VTE, independently of women age. These results are helpful in evaluating the individual profile of the risk of VTE and therefore in optimizing patients' management.

References

1. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. Bmj. 2009; 339: b2921.
2. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. Bmj. 2009; 339: b2890.
3. Stegeman BH, de Bastos M, Rosendaal FR, van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. Bmj. 2013; 347: f5298.
4. Christin-Maitre S. History of oral contraceptive drugs and their use worldwide. Best Pract Res Clin Endocrinol Metab. 2013; 27: 3-12.
5. Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. Arch Intern Med. 2000; 160: 49-52.
6. Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Buller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet. 1995; 346: 1593-6.
7. Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. Arterioscler Thromb Vasc Biol. 1999; 19: 700-3.
8. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet. 1994; 344: 1453-7.
9. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995; 346: 1575-82.
10. Khorana AA. Cancer-associated thrombosis: updates and controversies. Hematology Am Soc Hematol Educ Program. 2012; 2012: 626-30.
11. Frezzato M, Tosetto A, Rodeghiero F. Validated questionnaire for the identification of previous personal or familial venous thromboembolism. Am J Epidemiol. 1996; 143: 1257-65.
12. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994; 369: 64-7..
13. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996; 88: 3698-703.
14. Tripodi A. A review of the clinical and diagnostic utility of laboratory tests for the detection of congenital thrombophilia. Seminars in thrombosis and hemostasis. 2005; 31: 25-32.
15. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, De Groot PG, Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the S, Standardisation Committee of the International Society on T, Haemostasis. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Journal of thrombosis and haemostasis: JTH. 2009; 7: 1737-40.
16. Mannucci PM, Tripodi A. Factor VIII clotting activity. In Jaspersin J, Bertina RM, Haverkate F, Editors Laboratory Tecnics in Thrombosis A Manual Dordrecht: Kluwer Academic Publishers. 1999.
17. Zighetti ML, Cattaneo M, Falcon CR, Lombardi R, Harari S, Savoritto S, Mannucci PM. Absence of hyperhomocysteinemia in ten patients with primary pulmonary hypertension. Thrombosis research. 1997; 85: 279-82.
18. Spinelli A, Talamanca IF, Lauria L. Patterns of contraceptive use in 5 European countries. European Study Group on Infertility and Subfecundity. Am J Public Health. 2000; 90: 1403-8.

19. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. Journal of thrombosis and haemostasis: JTH. 2007; 5: 692-9.
20. Martinelli I. Cerebral vein thrombosis. Thrombosis research. 2013; 131 Suppl 1: S51-4.

Chapter 5

Pregnancy outcome after a first episode of cerebral vein thrombosis.

Martinelli I, Passamonti SM, Maino A, Abbattista M, Bucciarelli P, Somigliana E, Artoni A, Gianniello F, Peyvandi F.

J Thromb Haemost. 2016 Dec;14(12):2386-2393. doi: 10.1111/jth.13496. Epub 2016 Oct 12. PMID: 27598406.

Essentials

• Little is known about recurrences and pregnancy outcome after cerebral vein thrombosis (CVT).

• We studied a cohort of pregnant women with CVT.

• Women with CVT appear at increased risk of late obstetrical complications despite prophylaxis.

• Risks of recurrent thrombosis and bleeding in women on heparin prophylaxis while pregnant are low.

Summary

Background: The risk of recurrent thrombosis and bleeding episodes in women with previous cerebral vein thrombosis (CVT) on antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) during pregnancy is not established and little information is available on pregnancy outcome.
Objectives: The aims of this study were to evaluate the risk of obstetrical complications, recurrent venous thrombosis and bleeding in a cohort of pregnant women on LMWH after a first episode of CVT. In addition, to estimate the relative risk of obstetrical complications, patients were compared with healthy women without thrombosis and with at least one pregnancy in their life.
Patients: We studied a cohort of 52 patients and 204 healthy women.
Results: The risk of developing late obstetrical complications was 24% (95% CI, 18–38%), leading to a relative risk of 6.09 (95% CI, 2.46–15.05). The risk of miscarriage was not increased. The higher risk of late obstetrical complications in patients appeared unrelated to a previous history of obstetrical complications, to the carriership of thrombophilia abnormalities, or to the presence of co-morbidities. The incidence of termination observed in patients with thrombophilia was double that observed in those without. No recurrent thrombosis or bleeding episodes were observed.
Conclusions: Women with previous CVT on LMWH prophylaxis during pregnancy have a low risk of developing recurrent thrombosis or bleeding episodes, but seem to have an increased risk of late obstetrical complications.

Introduction

Cerebral vein thrombosis (CVT) is a rare life-threatening disease that occurs in three to four adult individuals per one million per year [1]. Because of a strong association between CVT and oral contraceptive use or pregnancy/puerperium, women of childbearing age account for twothirds of described cases [2]. The majority of patients with a first CVT receive anticoagulant treatment for a limited period that varies from 3 to 12 months, depending on the type and number of risk factors present at the time of the episode, although in the absence of controlled trials the optimal duration of anticoagulant treatment is based on experts' opinions [3-5]. The recurrence rate of thrombosis after oral anticoagulant withdrawal is low, ranging from 1.9% to 4.4% for CVT and from 3.7% to 12.9% for lower limb deep vein thrombosis and/or pulmonary embolism [3,4,6-9]. Similarly to patients with venous thrombosis at other sites, those who had a CVT and discontinued oral anticoagulant therapies receive secondary antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) during high-risk situations, such as surgical interventions, fractures, prolonged bed rest and pregnancy/puerperium [10].

Women with a predisposition to develop thrombosis may also develop obstetrical complications as a result of impaired placental circulation. Thrombophilia abnormalities are associated not only with an increased risk of thrombosis, but also of obstetrical complications, either miscarriages or late placenta-mediated complications [11,12]. Randomized controlled trials failed to show a benefit of LMWH prophylaxis in preventing recurrent miscarriages [13–15], but suggest, as confirmed by a summary-based meta-analysis, a positive treatment effect on late placenta-mediated complications in women with or without thrombophilia [16]. Because of the rarity of the disease, scarce and scattered information is available on the risk of recurrent venous thrombosis during pregnancy and on maternal and fetal outcome in women who remain pregnant after an episode of CVT [17,18]. A recent review of 13 studies reported an increased risk of pregnancy-related recurrent thrombosis and a low risk of spontaneous abortion with respect to the general population [18].

The aims of this study were to evaluate the obstetrical outcome in a cohort of women on antithrombotic prophylaxis with LMWH after a first episode of CVT, the risk of pregnancy-related recurrent venous thrombosis

and the safety of LMWH treatment. In addition, to estimate the relative risk of obstetrical complications, patients with previous CVT were compared with a cohort of healthy women without thrombosis and with at least one pregnancy in their life.

Patients and methods

Study population

All patients referred to our center from January 1995 for a thrombophilia work-up after a first episode of CVT (objectively documented with digital angiography, CT angiography, magnetic resonance or magnetic resonance angiography) were invited to contact the center in the case of symptoms of recurrent CVT or thrombosis at other sites, as well as in high-risk situations (i.e. surgery, trauma, need for hormone therapies and pregnancy). In particular, women of childbearing potential were counseled about a future pregnancy and invited to come back to the center as soon as possible after a positive pregnancy test to be prescribed antithrombotic prophylaxis with LMWH. A letter for the general practitioner and the gynecologist containing this information, our telephone contacts and the invitation to refer the patient to the center at the beginning of pregnancy was given to all women. Physicians from the center also contacted the women by telephone on a yearly basis. According to the national guidelines of the Italian Society for Haemostasis and Thrombosis [19], a dose of 4000 IU of sodium enoxaparin or 3800 IU of calcium nadroparin as a daily subcutaneous injection was prescribed to pregnant women for the whole gestational period and the puerperium (the 6-week period after delivery). One woman received fondaparinux 2.5 mg o.d. because of a previous heparin-induced thrombocytopenia. The comparison cohort comprised healthy women, who were partners or friends of the patient group, who agreed to be tested for thrombophilia in the same timeframe as patients. An ongoing pregnancy or puerperium and surgery or major trauma within the previous month were exclusion criteria. The inclusion criterion in this study was having had at least one pregnancy between the age of 22 and the age of 42 (minimum and maximum value at index pregnancy in patients). In addition, healthy women were matched with patients by gravidity at the index pregnancy. Four healthy women for each patient were randomly selected. The use of oral contraceptives at the time of blood sampling was recorded. Previous episodes

of thrombosis were excluded by means of a validated questionnaire [20]. The obstetrical history was recorded in the study population, including gravidity (number of times that a woman has been pregnant), parity (number of times that a woman has delivered a fetus with a gestational age of 24 weeks or more) and pregnancy outcome. The study was approved by the Hospital Institutional Review Board and all women gave written informed consent to participate in the study.

Definition of outcomes

As adverse obstetrical outcomes we considered miscarriage, defined as pregnancy loss occurring before the 20th gestational week [21], and late placenta-mediated complications that occurred beyond the 20th gestational week. Particular care was given to the collection of data on hypertensive disorders developing during pregnancy or the puerperium, placental disorders and neonatal health. The term 'termination' refers to an elective voluntary abortion. Preterm birth was defined as a delivery before 37 weeks gestation. The diagnosis of fetal growth restriction was based on the documentation of an abnormal fetal growth in utero confirmed by a newborn weight < 10th percentile, according to the local referral values [22]. Preeclampsia was defined as the concomitant presence of hypertension and a significant amount of protein in the urine [23]. Recurrent CVT or thrombosis at other sites was assessed by confirming the event with the same objective diagnostic methods described for the first CVT (see above) and other methods for thrombosis at other sites (e.g. compression ultrasound or venography for deep vein thrombosis of the limbs and lung V/Q scan for pulmonary embolism). The safety of LMWH was assessed in terms of major or minor bleeding according to the definition of the International Society of Thrombosis and Haemostasis [24], local (at the site of injection) or diffuse skin reactions, or development of heparin-induced thrombocytopenia.

Thrombophilia testing

Blood samples for thrombophilia testing were anticoagulated with sodium citrate (3.8% wt/vol) and taken at least 1 month after CVT in patients and at the time of the visit in the healthy-women group. Thrombophilia work-up included: DNA analysis for the 1691 guanine to adenine substitution in the coagulation factor (F) V gene (FV Leiden) [25] and for the 20210 guanine to

adenine substitution in the 30-untranslated region of the prothrombin gene [26], which are both gain-of-function mutations associated with hypercoagulability; functional and antigenic (when required) assays for plasma antithrombin, protein C and protein S [27]; antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-b2 glycoprotein I IgG and IgM antibodies) [28]; and plasma FVIII, measured with one-stage coagulation bioassay using FVIII-deficient plasma as substrate and the activated partial thromboplastin time as reagent [29]. High FVIII plasma levels were defined as exceeding the 95th percentile of the distribution among controls (158 IU dL 1). Fasting and/or postmethionine load hyperomocysteinemia [30], tested in patients after CVT, was considered among the causes of thrombophilia only for the risk of first CVT and not for thrombosis during pregnancy, because pregnant women are supplemented with folic acid (for the prevention of spina bifida in the fetus), which reduces plasma homocysteine levels. Patients who were taking vitamin K antagonists at the time of the first visit were asked to provide a second blood sample after discontinuation of oral anticoagulant therapy, because this therapy affects measurements of protein C and protein S. The inheritance of antithrombin, protein C and protein S deficiency was confirmed in a second blood sample and in at least one relative.

Statistical analysis

Median and minimum-maximum values were used for continuous variables, and count and percentage were used to describe demographic and obstetrical variables. Patients with CVT were followed from the time of thrombosis to the first occurring pregnancy within July 2015 (index pregnancy). We decided to stop the follow-up at the completion of the index pregnancy because this is the one on which the influence of CVT itself, if any, is greater. The risk of miscarriage, late obstetrical complications and terminations at the index pregnancy was calculated by dividing the number of pregnancy outcomes by the total number of pregnancies at risk, and the corresponding 95% confidence intervals (CI) were calculated [31]. We calculated that with a sample of 65 patients with CVT and an expected 30% risk of obstetrical complications, we would obtain an 11% (95% CI, 0.19–0.41) precision regarding the risk estimate. Outcomes of index pregnancies were compared with those of a healthy group of women in terms of risk ratios (RRs) and corresponding 95% CI. As the index pregnancy for the healthy-women group, we considered the last one before the visit to the center for

thrombophilia testing. Because thrombophilia may be associated with both CVT and adverse pregnancy outcome, and therefore might act as a confounder, the main analysis has been stratified for the presence of at least one marker of thrombophilia, and the RRs calculated for the subgroups that were thrombophilia positive or negative. Finally, to evaluate the risk of obstetrical complications we compared the pregnancy outcomes of women with pregnancies either before or after CVT in a case-crossover design (i.e. a model in which each case serves as its own control). We considered the 'control window' to be the pregnancy preceding CVT and the 'case window' to be the index pregnancy. The risk during the case window was compared with the risk during the control window and unadjusted odds ratios (ORs) with 95% CI were calculated as a surrogate for relative risks.

Results

In the 20-year study period 283 patients aged ≥ 15 years with a first objectively confirmed CVT were referred to the center, of whom 215 were women (median age at referral, 34 years [range 15–77]) and 192 of childbearing age (33 years [range 15–52]). Among the latter, 59 (31%) became pregnant after CVT. The last pregnancy included in the study started in July 2015 and ended in January 2016 with a late obstetrical complication (preeclampsia). All the women were Italian. Fifty-two women returned to the center, and we became aware of pregnancy in the seven remaining women through telephone calls. These seven women did not receive LMWH during pregnancy and were therefore excluded. Their pregnancies ended in miscarriage for four women, fetal growth restriction in one woman, termination in one and full-term delivery in one woman; no recurrent CVT or thrombosis at other sites was reported. Table 1 shows the general characteristics of the 52 women who received LMWH prophylaxis during pregnancy and those of the healthy-women group. In patients the most frequently involved sinuses were the lateral and the superior sagittal, and in 38% of patients CVT occurred in more than one sinus. The most common transient risk factor at the time of CVT was oral contraceptive use (81% vs. 17% in healthy women), followed by pregnancy or puerperium (17%). Only one woman had an idiopathic CVT. An inherited or acquired thrombophilia abnormality, mainly heterozygous prothrombin G20210A mutation, was found in 24 patients (54%) and 31 healthy women (15%).

Table 1 General characteristics of patients who remained pregnant after CVT (only the first pregnancy after CVT was considered as index pregnancy) and of a comparison group of healthy women who had at least one pregnancy (only the last pregnancy before blood sampling was considered as the index pregnancy)

	Patients	Healthy women
No.	52	204
Age at thrombosis, y, median (range)	26 (16-40)	-
Age at first referral to the Center, y, median (range)	29 (18-41)	47 (26-63)
Age at index pregnancy, y, median (range)	32 (22-42)	30 (22-42)
Body Mass Index, kg/m^2, median (range)	21 (17-36)	23 (16-41)
Involved sinuses/veins, n (%)		
superior sagittal sinus	24 (47)	
lateral sinus	35 (67)	
straight sinus	8 (15)	
cavernous sinus	0	
inferior sagittal sinus	3 (6)	
cortical veins	1 (2)	
jugular veins	5 (10)	
combined	20 (38)	
Transient risk factors, n (%)*		
none	1 (2)	169 (83)
surgery	4 (8)	0
major trauma	0	0
oral contraceptive use	42 (81)	35 (17)
pregnancy/puerperium	9 (17)	0
Type of thrombophilia abnormalities, n (%)*		
none	24 (46)	173 (85)
factor V Leiden	5 (10)	6 (3)
prothrombin G20210A	13 (25)	5 (2)
AT, PC or PS deficiency	5 (10)	2 (1)
antiphospholipid antibodies†	2 (4)	2 (1)
high factor VIII	2 (4)	2 (1)
hyperhomocysteinemia†	12 (23)	15 (7)

AT, antithrombin; PC , protein C; PS, protein S.* Some patients had more than one transient risk factor at the time of thrombosis or thrombophilia abnormality. † No more present in patients at the time of index pregnancy

At the conceiving of the index pregnancy five women (10%) were taking vitamin K antagonists (three were within the therapeutic period and two continued for longer than needed because of their own preferences) and 47 (90%) had already discontinued this therapy. All women received LMWH prophylaxis for the whole gestational period. In 17 women, antithrombotic prophylaxis with LMWH had already been started by the gynecologist or the

general practitioner, and in the remaining 35 it was started by one of us. No woman took aspirin as an additional medication. The median gestational age at which women started LMWH prophylaxis was 7 weeks (interquartile range, 6–9). No recurrent CVT, thrombosis at other sites, major or minor bleeding or heparin-induced thrombocytopenia was observed during the index pregnancy. One woman had a transient local skin reaction at the beginning of treatment that recovered promptly with an antihistaminic cream. Table 2 shows the outcome of the index pregnancy in the study population. The proportion of term pregnancies was 74% in patients and 86% in the healthy-women group. Patients and healthy women were similar for the risk of miscarriage (2% and 9%), but differed for the risk of late obstetrical complications, which were observed in 24% and 4% of women, respectively, for a relative risk of 6.09 (95% CI, 2.46–15.05). None of the women with late obstetrical complications had pre-existing diabetes mellitus, arterial hypertension, renal diseases or other comorbidities predisposing to an adverse pregnancy outcome. The slightly higher incidence of terminations in patients than in healthy women (19% and 12%) was likely to be attributable to the high parity (n = 4) in two patients and a previous termination in another patient. High parity and previous terminations were present in two healthy women, and the incidence of termination in the two groups not considering these women was 13% and 11%, respectively. Overall, gravidity and parity among patients and healthy women were 82 and 68, and 344 and 253, respectively. These figures remained similar in the group of women with term pregnancies and in those with late obstetrical complications. Among the 31 patients with a term index pregnancy, 25 were primigravidae and six had at least one previous pregnancy before CVT, all at term but one termination. The only patient who ended the index pregnancy with a miscarriage was in her first pregnancy. Of the 10 women who had a late obstetrical complication, six were primigravidae, three had previous term pregnancies and one had a previous placental abruption. Among the 10 patients who terminated their index pregnancy, three were primigravidae, six had at least one previous term pregnancy and one had a previous termination. Table 3 shows the relative risk of pregnancy complications according to the presence or absence of thrombophilia abnormalities. Among patients with thrombophilia, 12 (80%; seven heterozygous prothrombin G20210A mutation, one FV Leiden, two antithrombin deficiency, one protein C deficiency and one combined FV Leiden and protein C deficiency) had a term index pregnancy and three (20%;

one homozygous prothrombin G20210A mutation, one double heterozygous FV Leiden and prothrombin G20210A and one high FVIII) had obstetrical complications. The relative risk of obstetrical complications was similar in women with or without thrombophilia, whereas carriership of thrombophilia was associated with a 2-fold probability of termination. When excluding two women with thrombophilia who had four pregnancies and one termination before CVT, the rate of termination was 22.7% in patients and 12.5% in healthy women, for a relative risk of 1.82 (95% CI, 0.35–9.37). Seventeen of the 52 women with pregnancy after CVT had had at least one pregnancy before CVT. As shown in Table 4, comparing the last 17 pregnancies before (median age 27.5 years, range 20–34) with the first 17 pregnancies after (median age, 32 years; range, 25–42) CVT, the rate of late obstetrical complications was 13% and 40% (none of these women had thrombophilia) and that of termination was 6% and 41%. Excluding two women who terminated the index pregnancy because it was the fifth and one who had a previous termination, the rate of terminations after CVT was 24%, still four times higher than before CVT.

Table 2 Outcome of the index pregnancy in patients (the first after CVT) and healthy women (the last before blood sampling)

	Patients		**Healthy women**	
	n=52	**Risk (95%CI)**	***n*=204**	**Relative Risk (95%CI)**
Pregnancy outcome, n.(%)				
Term*	31 (74)	0.74 (0.59-0.85)	155 (86)	0.85 (0.71-1.03)
Miscarriage	1 (2)	0.02 (0.00-0.11)	18 (9)	0.24 (0.03-1.72)
Late obstetrical complications*†	10 (24)	0.24 (0.18-0.38)	7 (4)	6.09 (2.46-15.05)
Terminations	10 (19)	0.19 (0.10-0.32)	24 (12)	1.78 (0.92-3.42)

* Percentage calculated excluding terminations. † Preeclampsia/eclampsia/HELLP in four patients and five healthy women; stillbirth in one patient and one healthy woman; fetal growth restriction in four patients and 1 healthy woman; placental abruption in one patient.

Table 3 Relative risk of pregnancy complications in women with or without thrombophilia abnormalities

	Thrombophilia positive			**Thrombophilia negative**		
	Patients n=22	Healthy women n=16	Relative Risk (95%CI)	Patients n=30	Healthy women n=188	Relative Risk (95%CI)
Pregnancy outcome, n (%)						
Term*	12 (80)	13 (92.9)	0.86 (0.39-1.89)	19 (70)	142 (85.5)	0.82 (0.51-1.33)
Miscarriage/ late obstetrical complications*†	3 (20)	1 (7)	2.80 (0.29-26.9)	8 (29.6)	24 (14.5)	2.04 (0.92-4.56)
Terminations	7 (31.8)	2 (12.5)	2.55 (0.53-12.3)	3 (10)	22 (11.7)	0.85 (0.26-2.86)

* percentage calculated excluding terminations †among thrombophilia positive, 1 miscarriage and 2 late obstetrical complications in patients and 1 miscarriage in healthy women; among thrombophilia negative, 0 miscarriage and 8 late obstetrical complications in patients and 17 miscarriages and 7 late obstetrical complications in healthy women.

Table 4 Pregnancy outcome of the 17 patients with pregnancies either before or after CVT

	Last pregnancy before CVT	First pregnancy after CVT	Odds Ratio (95%CI)
Pregnancy outcome, n.(%)			
term*	14 (88)	6 (60)	0.21 (0.03-1.50)
miscarriage	0	0	-
late obstetrical complications*†	2 (13)	4 (40)	4.67 (0.67-32.74)
terminations	1 (6)	7 (41)	11.2 (1.19-105.13)

*Percentage calculated excluding terminations.†Among pregnancies before CVT , one placental abruption and one preeclampsia; among pregnancies after CVT, one stillbirth, two fetal grow restrictions and one placental abruption.

Discussion

This is the first observational study designed to investigate the obstetrical outcome of women on antithrombotic prophylaxis with LMWH because of a previous episode of CVT, the recurrence rate of thrombosis and the safety of prophylaxis during pregnancy. Our cohort of women who became pregnant after CVT was compared with a population of healthy women who had at least one previous pregnancy and were similar to patients in age at the index pregnancy and gravidity. With an intermediate dose of LMWH prophylaxis we did not observe pregnancy- related recurrent thrombosis or bleeding episodes, and only one woman developed a transient skin reaction. We also observed that patients with previous CVT had a 24% probability of developing a late obstetrical complication and a 6-fold increased risk compared with healthy women without previous CVT. We looked at the possibility that this figure was influenced by the obstetrical history (women with obstetrical complications are more prone to have recurrent complications in a future pregnancy) [32] or by the presence of thrombophilia abnormalities (which may increase the risk of obstetrical complications) [11,33]. Our study shows that the high rate of late obstetrical complications was not associated with a previous history of obstetrical complications, because only one woman had a recurrent placental abruption and gravidity and parity were similar in women with term pregnancies and those with complications. This observation was confirmed by the case-crossover analysis, which showed an increased risk of late obstetrical complications in pregnancies after CVT, apparently not justified by the increased mean age of pregnant women (27 vs. 32 years). Moreover, co-morbidities potentially affecting pregnancy outcome were absent in our women and also carriership of thrombophilia abnormalities did not

influence the obstetrical outcome, because only two women out of 10 with late obstetrical complications had FV Leiden and antithrombin deficiency, respectively. Hence, the high risk of obstetrical complications seems to be correlated with the previous CVT itself, but because of the limited sample size this observation remains to be confirmed, and also the mechanisms underlying the possible tendency to develop late obstetrical complications after CVT and despite LMWH prophylaxis remain to be elucidated. In general, the risk of recurrent venous thromboembolis (i.e. deep vein thrombosis of the lower limbs or pulmonary embolism) is higher than that of recurrent CVT [3,4,6–9,18]. In pregnancy, LMWH prophylaxis lowers the risk of recurrent thrombosis in women with previous venous thromboembolism, but not that of late obstetrical complications [34,35]. Whether or not this is true also for pregnant women with previous CVT is not known, because owing to the rarity of the disease there is a paucity of studies on the efficacy and safety of heparin prophylaxis and few data on obstetrical outcomes are available [17,18]. Indeed, women at increased risk of venous thrombosis have also an increased risk of obstetrical complications, particularly in the late period where a normal placental circulation is needed to sustain fetal growth and the woman's health [34]. A common denominator between the two risks is carriership of thrombophilia abnormalities [11,33]. Whether or not women with thrombophilia may benefit from prophylaxis with LMWH during pregnancy, with the aim of preventing obstetrical complications, is debatable [36]. Our study does not support the effectiveness of this approach in women with previous CVT, with or without thrombophilia. Moreover, although the proportion of terminations was similar between patients and healthy women, particularly when those with high parity or previous terminations were excluded, we observed a 2.5-fold increased risk of terminations in patients with thrombophilia compared with those without. A 1.8-fold increased risk remained after exclusion of women with high parity or previous terminations, probably reflecting the fear of women having a recurrent pregnancy-related thrombosis because of the carriership of thrombophilia abnormalities. To support this hypothesis there is also the fact that the two women who arbitrarily continued vitamin K antagonist therapy had thrombophilia (double heterozygous FV Leiden plus prothrombin G20210A mutation and antithrombin deficiency, respectively). Again, a confirmation of this finding is desirable, because the point estimates of the risks of termination did not reach statistical significance, possibly because of the small sample of women

stratified for the presence of thrombophilia. Finally, our data are apparently in contrast with a recent observation of an increased risk of miscarriage in women with previous CVT [17], but the lack of definition of miscarriage, the retrospective design and the absence of a standardized antithrombotic prophylaxis make that study and our study not comparable. Among the strengths of this study are the careful assessment of patients, the possibility to compare the obstetrical outcome with a selected group of healthy women, the relatively high number of pregnancies after CVT and the choice of a strict methodology. However, there are some limitations. We had no control group of patients who did not receive prophylaxis with LMWH during pregnancy. Actually, such a randomized controlled trial is not feasible for obvious ethical issues. Hence, we can only report the observation of no recurrent thrombosis or bleeding or other significant side-effects of heparin. This may seem in contrast with a recent review of 13 studies, but the retrospective design, the small series of patients and the lack of information on heparin prophylaxis in the vast majority of them make the results of such review quite uncertain [18]. Concerning the obstetrical outcome, for the design of our study we cannot conclude that there is not a favorable effect of heparin in the prevention of miscarriage or late obstetrical complications. However, the effect of heparin on pregnancy outcome seems to be independent of the presence of thrombophilia, always considering the limitation of the small number of women when divided into thrombophilia positive and negative. Finally, because of the retrospective nature of the information regarding the outcome of the last pregnancy in the group of healthy women and the lack of obstetric records review, the possibility of a recall bias should be taken into account. However, it is unlikely that a woman does not remember the outcome of her pregnancies, particularly if adverse. In conclusion, despite antithrombotic prophylaxis, women with previous CVT appear at increased risk of developing late obstetrical complications. The possibility that the diagnosis of thrombophilia abnormalities made after CVT would influence the decision to voluntarily terminate a subsequent pregnancy should be taken into account when counseling these patients. Pregnant women who receive an intermediate dose of LMWH for thromboprophylaxis have a low risk of developing recurrent thrombosis, bleeding episodes or other heparin-related side-effects.

References

1. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005; 352: 1791–8.
2. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a metaanalysis. Blood 2006; 107: 2766–73.
3. Dentali F, Gianni M, Crowther MA, Ageno W. Review article Natural history of cerebral vein thrombosis: a systematic review. Nat Hist 2006; 108: 1129–34.
4. Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannucci PM. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. Circulation 2010; 121: 2740–6.
5. Martinelli I, Passamonti SM, Rossi E, de Stefano V. Cerebral sinus-venous thrombosis. Intern Emerg Med 2012; 7: 221–5.
6. Ferro JM, Canh~ao P, Stam J, Bousser M-G, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004; 35: 664–70.
7. Dentali F, Poli D, Scoditti U, di Minno MND, Stefano VD, Siragusa S, Kostal M, Palareti G, Sartori MT, Grandone E, Vedovati MC, Ageno W, Falanga A, Lerede T, Bianchi M, Testa S, Witt D, McCool K, Bucherini E, Grifoni E, et al. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. J Thromb Haemost 2012; 10: 1297–302.
8. Maqueda VM, Thijs V. Risk of thromboembolism after cerebral venous thrombosis. Eur J Neurol 2006; 13: 302–5.
9. Miranda B, Ferro JM, Canh~ao P, Stam J, Bousser MG, Barinagarrementeria F, Scoditti U. Venous thromboembolic events after cerebral vein thrombosis. Stroke 2010; 41: 1901–6.
10. Martinelli I, De Stefano V. Rare thromboses of cerebral splanchnic and upper-extremity veins. A narrative review. Thromb Haemost 2010; 103: 1136–44.
11. Rodger MA, Betancourt MT, Clark P, Lindqvist PG, Dizon- Townson D, Said J, Seligsohn U, Carrier M, Salomon O, Greer IA. The association of factor V leiden and prothrombin gene mutation and placenta-mediated pregnancy complications: a systematic review and meta-analysis of prospective cohort studies. Fisk NM, editor. PLoS Med 2010; 7: e1000292.
12. Simcox LE, Ormesher L, Tower C, Greer IA. Thrombophilia and pregnancy complications. Int J Mol Sci 2015; 16: 28418–28.
13. Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, Whyte S. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular- weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood 2010; 115: 4162–7.
14. Kaandorp SP, Goddijn M, van der Post JAM, Hutten BA, Verhoeve HR, Hamulyak K, Mol BW, Folkeringa N, Nahuis M, Papatsonis DNM, B€uller HR, van der Veen F, Middeldorp S. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med 2010; 362: 1586–96.
15. Visser J, Ulander VM, Helmerhorst FM, Lampinen K, Morin-Papunen L, Bloemenkamp KWM, Kaaja RJ. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia - HABENOX: a randomised multicentre trial. Thromb Haemost 2011; 105: 295–301.
16. Rodger MA, Carrier M, Le Gal G, Martinelli I, Perna A, Rey E, Vries D, Gris J, Dc W. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. Blood 2014; 123: 822–8.
17. Ciron J, Godeneche G, Vandamme X, Rosier MP, Sharov I, Mathis S, Larrieu D, Neau JP. Obstetrical outcome of young women with a past history of cerebral venous thrombosis. Cerebrovasc Dis 2013; 36: 55–61.
18. Aguiar de Sousa D, Canh~ao P, Ferro JM. Safety of pregnancyafter cerebral venous thrombosis. Stroke 2016; 47: 713–8.
19. Lussana F, Dentali F, Abbate R, d'Aloja E, D'Angelo A, De Stefano V, Faioni EM, Grandone E, Legnani C, Martinelli I, Simioni P, Tormene D. Screening for thrombophilia and

antithrombotic prophylaxis in pregnancy: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res 2009; 124: e19–25.
20. Frezzato M, Tosetto A, Rodeghiero F. Validated questionnaire for the identification of previous personal or familial venous thromboembolism. Am J Epidemiol 1996; 143: 1257–65.
21. Parazzini F, Cortinovis I, Bortolus R, Fedele L. Standards of birth weight in Italy. Ann Ostet Ginecol Med Perinat 1991; 112: 203–46.
22. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012; 379: 2162–72.
23. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet 2015; 387: 999–1011.
24. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692–4.
25. Bertina R, Koeleman B, Koster T, Rosendaal F, Dirven R, de Ronde H, van der Velden P, Reitsma P. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994; 369: 64–7.
26. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 30-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996; 88: 3698–703.
27. Tripodi A. A review of the clinical and diagnostic utility of laboratory tests for the detection of congenital thrombophilia. Semin Thromb Hemost 2005; 31: 25–32.
28. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost 1995; 74: 1185–90.
29. Mannucci PM, Tripodi A. Factor VIII clotting activity. In: Jespersen J, Bertina RM, Haverkate F, eds. Laboratory Techniques in Thrombosis- A Manual Dordrecht: Kluwer Academic Publishers, 1999; 107–13.
30. Zighetti ML, Cattaneo M, Falcon CR, Lombardi R, Harari S, Savoritto S, Mannucci PM. Absence of hyperhomocysteinemia in ten patients with primary pulmonary hypertension. Thromb Res 1997; 85: 279–82.
31. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2008. 32 van Rijn BB, Hoeks LB, Bots ML, Franx A, Bruinse HW. Outcomes of subsequent pregnancy after first pregnancy with early onset preeclampsia. Am J Obstet Gynecol 2006; 195: 723–8.

Chapter 6

Pregnancy after cerebral venous thrombosis.

Abbattista M, Capecchi M, Martinelli I.

Thromb Res. 2019 Sep;181 Suppl 1:S15-S18. doi: 10.1016/S0049-3848(19)30360-3. PMID: 31477221.

Abstract

Pregnancy outcome in women with previous cerebral vein thrombosis (CVT) on antithrombotic prophylaxis with low-molecular weight heparin (LMWH) is largely unknown. Aims of this study were to evaluate the risk of recurrent VTE, bleeding and pregnancy outcome in a cohort of pregnant women on LMWH after a first episode of CVT. To estimate the efficacy of LMWH in the prevention of obstetrical complications we compared pregnancies before (without LMWH) with pregnancies after (with LMWH) CVT in 25 women. Two recurrent thrombosis (3.2%, 95%CI 0.9-10.9%) and no bleeding episodes were observed in 63 pregnant women on LMWH. The risk of miscarriage was 13.5% (95%CI 6.1-24.8%) and that of late obstetrical complications 19.2% (95%CI 10.2-31.6%), independently of previous history of obstetrical complications and carriership of thrombophilia abnormalities. A double prevalence of terminations was observed in patients with thrombophilia than in those without. In conclusion, women with previous CVT on LMWH prophylaxis during pregnancy have a low risk of recurrent thrombosis and bleeding, but an increased risk of obstetrical complications.

Introduction

Cerebral vein thrombosis (CVT) is a rare manifestation of thrombosis with an annual incidence in adults of 2 to 16 cases per million individuals.[1-3] CVT is more common in women of childbearing age, because of the use of oral contraceptives (80% of cases)[4] and pregnancy/puerperium (5-20% of cases).[5] Patients with a first episode of CVT receive anticoagulant treatment for a period that varies from 3 months to lifelong, depending on the type and number of risk factors present at the time of the episode, although in the absence of controlled trials the optimal duration of anticoagulant therapy is currently based on experts' opinions.[6] The recurrence rate of venous thrombosis within the first year after a first episode of CVT is approximately 4% patient-year (p-y), lower for recurrent CVT (0.5% to 2.2% p-y) than for venous thrombosis in most common sites as lower limbs or pulmonary circulation (1.1% to 5.0% p-y).[7-11] After a first episode of CVT, patients receive antithrombotic prophylaxis with low molecular weight heparin (LMWH) in high-risk situations, including pregnancy/puerperium, according to the recommendations reported in guidelines on extracranial venous thrombosis.[6]

Women who develop thrombosis may also develop obstetrical complications as a result of impaired intrauterine mucosae or placental circulation.[12] Other than with an increased risk of thrombosis, thrombophilia abnormalities are associated with an increased risk of obstetrical complications, either miscarriages or late placenta-mediated complications.[13,14] Thrombophilia abnormalities are found in up to 40% of women with CVT.[11] The efficacy of LMWH prophylaxis in preventing obstetrical complications in women with thrombophilia abnormalities is uncertain. Although a randomized controlled trial failed to show a benefit in the prevention of recurrent miscarriages,[15] data from a meta-analysis are in favor of LMWH in the prevention of recurrent placenta-mediated pregnancy complications.[16] Because of the rarity of the disease, scarce data are available on the risk of recurrent venous thrombosis during pregnancy after CVT, on maternal and fetal outcome and on the efficacy of LMWH prophylaxis. A recent review of four studies reported a trend towards lower rates of recurrent CVT and extra-cerebral thrombosis and a significantly low rate of miscarriages in patients on LMWH prophylaxis.[17]

Aims of this study were to evaluate the risk of pregnancy-related recurrent venous thrombosis, the risk of bleeding and the obstetrical outcome

in a cohort of pregnant women on antithrombotic prophylaxis with LMWH after a first episode of CVT.

Patients and methods

Study population

All patients referred to our Center from January 1995 to June 2018 for a thrombophilia work-up after a first episode of CVT (objectively documented with digital subtraction angiography, CT angiography, magnetic resonance or magnetic resonance angiography) were invited to contact the Center in case of symptoms of recurrent CVT or thrombosis at other sites, as well as in case of high risk situations, i.e., surgery, trauma, need of hormone therapies and pregnancies. A letter for the general practitioner and the gynecologist containing contact information on the Center and the invitation to refer the patient to the Center at the beginning of pregnancy was given to all women in childbearing age. Thrombophilia testing included DNA analysis for factor V Leiden and for the G20210A mutation of the prothrombin gene; functional and antigenic (when required) assays for plasma antithrombin, protein C, protein S and factor VIII; antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin and anti-β2 glycoprotein I IgG and IgM antibodies). Fasting and/or post-methionine load hyperomocysteinemia was considered among the thrombophilia abnormalities only for the risk of first CVT and not for the risk of thrombosis during pregnancy, because it was no longer present after vitamin supplementation. Women of childbearing potential who came back to the Center after a positive pregnancy test for the prescription of LMWH prophylaxis were included in the study. Women were also contacted by telephone calls by the physicians of the Center annually. The last follow-up visit or call was in November 2018. According to the national guidelines of the Italian Society for the Study of Haemostasis and Thrombosis [31], a dose of 4000 IU of sodium enoxaparin or 3800 IU of calcium nadroparin as daily subcutaneous injection was prescribed to pregnant women for the whole gestational period and the puerperium (six weeks after delivery). A therapeutic dose (bid injections) was prescribed to women who remained pregnant while receiving oral anticoagulant therapy. One woman received fondaparinux 2.5 mg od because of a previous heparin-induced thrombocytopenia.

The obstetrical history was recorded, including gravidity (number of pregnancies), parity (number of deliveries at 24 weeks or more) and pregnancy

outcome. The study was approved by the Hospital Institutional Review Board and all women gave written informed consent to participate to the study.

Definition of outcomes

Recurrent CVT or thrombosis at other sites was assessed by confirming the event with objective diagnostic methods. Safety of LMWH was assessed in terms of major or minor bleeding according to the definition of the International Society of Thrombosis and Haemostasis, [19] local (at the site of injection) or diffuse skin reactions or development of heparin-induced thrombocytopenia. As adverse obstetrical outcomes we considered miscarriage, defined as a pregnancy loss occurred before the 20th gestational week and late placenta-mediated complications occurred beyond the 20th gestational week. Among the latter we considered small-for-gestational-age (SGA) newborn (weight < 10th percentile, according to the local referral values)[20]; preeclampsia/eclampsia/HELLP syndrome (preeclampsia defined as the concomitant presence of hypertension and significant amount of urine proteins;[21] eclampsia, by the occurrence of new onset seizures in a preeclamptic woman; HELLP syndrome, by the concomitant presence of hemolysis, elevated liver enzymes and thrombocytopenia); placental abruption (vaginal bleeding with or without uterine tenderness and fetal distress followed by emergency delivery after 24 gestational weeks) and stillbirth (fetal loss occurred beyond the 20th gestational week). Termination indicates an elective voluntary abortion. Full-term birth was defined as a delivery after 37th weeks gestation.

Statistical analysis

Median and interquartile values were used for continuous variables, counts and percentages for demographic and obstetrical variables. Patients with CVT were followed from the time of thrombosis to the first occurring pregnancy within June 2018 (index pregnancy). The risk of miscarriages, late obstetrical complications and terminations at the index pregnancy was calculated as risk proportion with the corresponding 95% confidence intervals (CI).[22] Because of the association of thrombophilia abnormalities with both CVT and adverse pregnancy outcome, the main analysis was stratified for the presence of at least one marker of thrombophilia that might act as a confounder. Finally, to evaluate the effect of CVT on the risk of obstetrical complications we compared pregnancy outcomes of women with pregnancies

before (without LMWH prophylaxis) and after CVT (with LMWH prophylaxis) in a case-crossover design, in which each case serves as its own control. We considered as 'control window' the pregnancy preceding CVT, and as 'case window' the index pregnancy. The risk during the case window was compared with the risk during the control window and unadjusted odds ratios (OR) with 95% CI were calculated as a surrogate of relative risks.

Results

Study population

In the 23-year study period, 271 women aged ≥ 15 years with a first objectively confirmed CVT were referred to the Center, of whom 241 of childbearing age at the time of CVT. Among them, 70 (29%) women remained pregnant after CVT. Two pregnancies included in the study are still ongoing. Sixty-three women returned to the Center while the remaining 7 did not and we became aware of their pregnancy through telephone calls. These 7 women did not receive LMWH during pregnancy and were therefore excluded. Four of them had a miscarriage, one a SGA newborn , one a pregnancy at term and one a termination; no recurrent CVT nor thrombosis at other sites were reported. Table 1 shows the general characteristics of the 63 women who received LMWH prophylaxis during pregnancy. The most frequently involved sinuses were the lateral and the superior sagittal and in 41% of patients CVT occurred in more than one sinus. The most common transient risk factor at the time of CVT was oral contraceptive use (74.6%), followed by pregnancy or puerperium (15.6%). Only two women had an idiopathic CVT. An inherited or acquired thrombophilia abnormality, mainly heterozygous prothrombin G20210A mutation, was found in 31 patients (49.2%).

Risk of recurrent thrombosis and bleeding

At the conceiving of the index pregnancy 9 women were on vitamin K antagonists, 2 were on aspirin and 54 were off-therapy. All women received LMWH for the whole gestational period, starting at a median gestational age of 7 weeks (IQR 6-9). Two women on LMWH prophylaxis developed thrombosis at other sites (both a deep vein thrombosis of the leg, complicated by pulmonary embolism in one woman). No recurrent CVT, major or minor bleeding nor heparin-induced thrombocytopenia were observed during the

index pregnancy. A woman had a transient local skin reaction at the beginning of treatment that recovered promptly with topic antihistaminic.

Table 1. General characteristics of women who remained pregnant after CVT.

	Patients
No.	63
Age at CVT, y, median (range)	26 (23-31)
Age at first referral to the Center, y, median (range)	30 (26-34)
Age at index pregnancy, y, median (range)	32 (28-36)
Gravidity, n	107
Parity, n	72
Body Mass Index, kg/m^2, median (range)	21 (20-24)
Involved sinuses/veins, n (%)	
Superior sagittal sinus	10 (15.9)
Lateral sinus	20 (31.7)
Straight sinus	3 (4.8)
Cavernous sinus	0
Inferior sagittal sinus	1 (1.6)
Cortical veins	1 (1.6)
Jugular veins	0
More than one sinus involved	26 (41)
Transient risk factors, n (%)*	
None	2 (3.2)
Infection	4 (6.3)
Surgery	4 (6.3)
Major trauma	1 (1.6)
Autoimmune disease	1 (1.6)
Hypertension	1 (1.6)
Oral contraceptive use	47 (74.6)
Pregnancy/puerperium	10 (15.9)
Type of thrombophilia abnormalities, n (%)*	
None	32 (50.8)
Factor V Leiden	5 (7.8)
Prothrombin G20210A	13 (20.6)
AT, PC or PS deficiency	5 (7.8)
Antiphospholipid antibodies	4 (6.3)
High factor VIII	5 (7.8)
Hyperhomocysteinemia	12 (19)

AT, antithrombin; CVT, cerebral vein thrombosis; PC, protein C; PS, protein S

* Some patients had more than one transient risk factor or thrombophilia abnormality at the time of thrombosis

Table 2. Obstetrical outcome of the index pregnancy (the first after CVT) on LMWH prophylaxis.

Outcome*	Patients N=63		With thrombophilia N=31	Without thrombophilia N=32
	N	% (95%CI)	N (%)	N (%)
At term	33	63.5 (50-76)	16 (72.7)	17 (56.7)
Ongoing	2	3.8 (0.6-12)	-	2 (6.7)
Miscarriage	7	13.5 (6.1-24.8)	3 (13.6)	4 (13.3)
Late obstetrical complications†	10	19.2 (10.2-31.6)	3 (13.6)	7 (23.3)
Terminations	11	17.4 (9.5-28.3)	9 (29)	2 (6.3)

* Percentage calculated excluding terminations

† Four women had an SGA newborn; four had pre-eclampsia/eclampsia/HELLP; one had a placental abruption; and one had a stillbirth

Obstetrical outcome

Table 2 shows the outcome of the index pregnancy, that was adverse in 17 women (27%) for a risk of miscarriage of 13.5% (95%CI 6.1-24.8%) and late complications of 19.2% (95%CI 10.2-31.6%). None of the women with late obstetrical complications had pre-existing diabetes mellitus, arterial hypertension, renal diseases or other comorbidities predisposing to an adverse pregnancy outcome. Of the 7 women with miscarriages one was primigravid and 6 had at least a previous pregnancy (two of them had a miscarriage, one had a late complication and three had full-term pregnancies). Of the 10 women with late obstetrical complications, 6 were primigravid, 3 had previous full-term pregnancies and one had a previous placental abruption. Among the 33 women (52.4%) who ended the index pregnancy at term, 25 were primigravid and 8 had at least one pregnancy before CVT, all at term but one termination. Among the 11 women (17.5%) who terminated their index pregnancy, 4 were primigravid, 6 had at least one previous pregnancy at term and one had a previous termination. Patients with or without thrombophilia were similar for the risk of miscarriage but differed for the risk of late complications that occurred in 23.3% and 13.6%, and for the rate of terminations that were 29% and 6.3%, respectively (Table 2).

Twenty-five of the 63 women with pregnancy after CVT had had at least one pregnancy before CVT. Table 3 compares the outcome of their index pregnancies after (median age 32 years, range 28-36) with their last pregnancies before (median age 26 years, range 24-32) CVT. The overall risk of miscarriage

or late complications was 4.8 (95%CI 1.2-18.4). Thrombophilia abnormalities were found in 15 of these 25 women. The proportion of obstetrical complications before CVT (without LMWH) was 21% in women with and 30% in those without thrombophilia whereas after CVT (with LMWH) complications occurred in 25% with and 80% without thrombophilia. The odds ratio for terminations was 9 times higher after CVT than before. The reason for termination was clearly declared as the unwillingness to have children by only two women; the remaining declared that previous CVT was a concern for the index pregnancy outcome.

Table 3. Comparison of obstetrical outcome of the 25 women with pregnancies before (without LMWH) and after (with LMWH) CVT.

Pregnancy outcome*	First pregnancy after CVT	Last pregnancy before CVT	OR (95%CI)
at term	8 (44.4)	19 (79)	0.2 (0.1-1.0)
miscarriage	6 (33.3)	2 (8.3)	5.5 (1.0-31.6)
late obstetrical complications	4 (22.2)	3 (12.5)	2.0 (0.4-10.3)
terminations	7 (28)	1 (4)	9.3 (1.1-82.8)

* Percentage calculated excluding terminations

Discussion

In this study of pregnant women on LMWH prophylaxis because of a previous episode of CVT, the recurrence rate of thrombosis, the safety profile of LMWH and the obstetrical outcome were investigated. Two pregnancy-related recurrent thrombosis (3.2%) and no bleeding episodes were observed. The probability to have a miscarriage or a late obstetrical complication was high (13.5% and 19.2%, respectively) and not justified by comorbidities (absent in our women) nor by previous adverse obstetrical outcome (women with obstetrical complications are more prone to have recurrent complications). [23] Indeed, only one woman had a recurrent placental abruption and gravidity and parity were similar in women with and without obstetrical complications. The case-crossover analysis confirmed a 5-fold increased risk of late obstetrical complications or miscarriages in pregnancies after CVT compared to those before, apparently not justified by the increased mean age of the women (32 versus 27 years) but to CVT itself. Other than CVT, the second new variable in the index-pregnancy was LMWH prophylaxis, but its association with adverse obstetrical outcome is likely excluded by the high rate of complications (5 out of 6) in women who did not receive prophylaxis. Hence, the risk of recurrent thrombosis in pregnant women on LMWH was low but that of obstetrical complications was not negligible. Another important finding of our study was the association between thrombophilia abnormalities and late obstetrical complications, that were doubled in carriers (23.3%) than in non-carriers (13.6%), supporting the hypothesis of a higher placental dysfunction in women with than in those without thrombophilia. Additionally, having had a CVT and being carrier of a thrombophilia marker greatly influenced the decision to terminate pregnancy and terminations accounted for 29% of index pregnancies in women with and 6.3% in those without thrombophilia. These figures reflect the fear of women to develop a recurrent pregnancy-related thrombosis, in particular if they are predisposed because of a coagulation abnormality, despite physicians reassurance. [24]

Our study adds information on management of pregnant women after a venous thrombotic episode. It is known that LMWH prophylaxis lowers the risk of recurrent thrombosis in women with previous venous thromboembolism, but not that of late obstetrical complications.[25,26] Whether or not this is valid also for women with previous CVT was not known, because the rarity of the disease justifies the paucity of data not only on

efficacy and safety of LMWH during pregnancy but even more on obstetrical outcome.[27,28] Our results support, as common denominator between the risk of thrombosis and that of obstetrical complications (particularly in the late period when a normal placental circulation is needed to sustain fetal growth and woman's health)[25], the carriership of thrombophilia abnormalities.[29,30] Whether or not women with thrombophilia may benefit from LMWH prophylaxis during pregnancy with the aim to prevent obstetrical complications is debated.[31] Our data raise the question of whether higher doses of LMWH in carriers than in non-carriers of thrombophilia would result in a more favourable pregnancy outcome. Finally, our data differ from a recent observation of a low risk of late obstetrical complications in women with previous CVT [27], but the absence of a standardized antithrombotic prophylaxis make that and our study not comparable.

Among the strengths of this study there are the careful assessment of patients, the relatively high number of pregnancies after CVT and the choice of a strict methodology. However, some limitations need to be discussed. Firstly, since a controlled trial with a control group of pregnant women who did not receive LMWH prophylaxis is not ethical, we can only report the observation of no recurrent thrombosis nor bleeding or other significant side effects of LMWH. Secondly, data on the obstetrical outcome and the role of thrombophilia are based on small numbers and an adjusted analysis for possible confounders is unfeasible. The design of our study does not allow to conclude against a favourable effect of LMWH in the prevention of miscarriage or late obstetrical complications, but the proportion of adverse outcomes in our cohort was not negligible. Thirdly, due to the retrospective nature of the information collected on the outcome of the last pregnancy before CVT and the lack of the corresponding obstetric records, the possibility of a recall bias should be considered. However, it is unlikely that a woman does not remember the outcome of her pregnancies, particularly if adverse.

In conclusion, antithrombotic prophylaxis with LMWH in pregnant women with previous CVT seems to be effective in preventing recurrent thrombosis and safe. Women with previous CVT appear at increased risk to develop obstetrical complications, particularly in the late period and in the presence of thrombophilia abnormalities, despite LMWH prophylaxis. The pathophysiological mechanisms underlying this association remain to be elucidated to tailor the best preventive measures in women at risk of pregnancy complications.

References

1. Stam J. Thrombosis of the Cerebral Veins and Sinuses. N Engl J Med. 2005;352(17):1791-1798. doi:10.1056/NEJMra042354
2. Bousser M-G, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2):162-170. doi:10.1016/S1474-4422(07)70029-7
3. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral Venous Sinus Thrombosis Incidence is Higher Than Previously Thought: A Retrospective Population-Based Study. *Stroke*. 2016;47(9):2180-2182.
4. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: A meta-analysis. Blood. 2006;107(7):2766-2773.
5. Bousser M-G, Crassard I. Cerebral venous thrombosis, pregnancy and oral contraceptives. *Thromb Res*. 2012;130(SUPPL.1):S19-S22.
6. Saposnik G, Barinagarrementeria F, Brown RD, et al. Diagnosis and management of cerebral venous thrombosis: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(4):1158-1192.
7. Ferro JM, Canhão P, Stam J, Bousser M-G, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664-670.
8. Miranda B, Ferro JM, Canhão P, et al. Venous thromboembolic events after cerebral vein thrombosis. *Stroke*. 2010;41(9):1901-1906.
9. Gosk-Bierska I, Wysokinski W, Brown RD, et al. Cerebral venous sinus thrombosis: Incidence of venous thrombosis recurrence and survival. *Neurology*. 2006;67(5):814-819.
10. Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannuccio Mannucci P. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. *Circulation*. 2010;121(25):2740-2746.
11. Dentali F, Poli D, Scoditti U, et al. Long-term outcomes of patients with cerebral vein thrombosis: A multicenter study. *J Thromb Haemost*. 2012;10(7):1297-1302.
12. Pabinger I, Grafenhofer H, Kaider a, et al. Preeclampsia and fetal loss in women with a history of venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 2001;21(5):874-879.
13. Greer IA. Thrombosis in pregnancy: Maternal and fetal issues. *Lancet*. 1999;353(9160):1258-1265.
14. Walker ID. Thrombophilia in pregnancy. *J Clin Pathol*. 2000;53(8):573-580.
15. Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. *Lancet*. 2014;384(9955):1673-1683.
16. Rodger MA, Carrier M, Gal G Le, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. *Blood*. 2014;123(6):822-828.
17. Aguiar de Sousa D, Canhão P, Ferro JM. Safety of pregnancy after cerebral venous thrombosis: systematic review update. *J Neurol*. 2018;265(1):211-212.
18. Lussana F, Dentali F, Abbate R, et al. Screening for thrombophilia and antithrombotic prophylaxis in pregnancy: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). *Thromb Res*. 2009;124(5):e19-e25.
19. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
20. Parazzini F, Cortinovis I, Bortolus R, Fedele L. Standards of birth weight in Italy. *Ann Ostet Ginecol Med Perinat*. 1991;112(4):203-246.
21. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet*. 2016;387(10022):999-1011
22. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Third edit. (Lippincott Williams & Wilkins, ed.); Oxford University Press (2008).
23. van Rijn BB, Hoeks LB, Bots ML, Franx A, Bruinse HW. Outcomes of subsequent

pregnancy after first pregnancy with early-onset preeclampsia. *Am J Obstet Gynecol*. 2006;195(3):723-728.
24. Poli D, Cenci C, Testa S, Paoletti O, Silvestri E, Antonucci E. Obstetrical history of women with cerebral vein thrombosis: outcome of the pregnancies before and after the thrombotic event. *Intern Emerg Med*. 2017;12(7):941-945.
25. Pabinger I, Grafenhofer H, Kaider A, et al. Preeclampsia and fetal loss in women with a history of venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 2001;21(5):874-879.
26. Alguel G, Vormittag R, Simanek R, et al. Preeclampsia and pregnancy loss in women with a history of venous thromboembolism and prophylactic low-molecular-weight heparin (LMWH) during pregnancy. *Thromb Haemost*. 2006;96(09):285-289.
27. Ciron J, Godenèche G, Vandamme X, et al. Obstetrical outcome of young women with a past history of cerebral venous thrombosis. *Cerebrovasc Dis*. 2013;36(1):55-61.
28. Aguiar de Sousa D, Canhão P, Crassard I, et al. Safety of Pregnancy After Cerebral Venous Thrombosis: Results of the ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis)-2 PREGNANCY Study. *Stroke*. 2017;48(11):3130-3133.
29. Rodger MA, Betancourt MT, Clark P, et al. The Association of Factor V Leiden and Prothrombin Gene Mutation and Placenta-Mediated Pregnancy Complications: A Systematic Review and Meta-analysis of Prospective Cohort Studies. Fisk NM, ed. *PLoS Med*. 2010;7(6):e1000292.
30. Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: A systematic review. *Br J Haematol*. 2006;132(2):171-196.
31. Bates SM. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy. *CHEST J*. 2012;141(2_suppl):e691S.

Chapter 7

Risk of pregnancy-related venous thromboembolism and obstetrical complications in women with inherited type I antithrombin deficiency: a retrospective, single-center, cohort study

---

Abbattista M, Gianniello F, Novembrino C, Clerici M, Artoni A, Bucciarelli P, Capecchi M, Peyvandi F, Martinelli I.

Lancet Haematol. 2020 Apr;7(4):e320-e328. doi: 10.1016/S2352-3026(20)30007-7. Epub 2020 Feb 26. PMID: 32112716.

Abstract

Background: inherited quantitative (type I) deficiency of plasma antithrombin (AT) is associated with a high risk of venous thromboembolism (VTE), that further increases in pregnancy. Inherited thrombophilia increases also the risk of obstetrical complications, but data on maternal and fetal outcomes in women with AT deficiency are poor. Aim of this study was to evaluate the risk of pregnancy-related VTE and obstetrical complications in women with type I AT deficiency.

Methods: in this single-center retrospective cohort study we identified 126 women diagnosed from Jan 1, 1980 to Jan 1, 2018 with type I AT deficiency and included in the analysis 88 women who had at least one pregnancy, women with type II AT were excluded. Data on pregnancy-related VTE, pregnancy outcomes, and the use of low-molecular-weight heparin (LMWH) were collected to evaluate the risk of pregnancy-related VTE and obstetrical complications with or without LMWH.

Findings: eighty women were evaluated for the risk of VTE. We observed three VTE out of 43 pregnancies conducted with LMWH and 17 VTE out of 146 pregnancies without for a risk of VTE of 7.0% (1.8-17.8%) and 11.6% (7.2-17.6%), respectively (RR 0.6; 95%CI 0.2-1.9, p=0.57). The risk of first VTE without LMWH was 5.4% (0.9-16.7%) in women with negative and 11.8% (6.4-19.6%) in those with a positive family history of VTE. Eighty-seven women evaluated for the risk of obstetrical complications had 48 pregnancies conducted with LMWH and 170 without. Miscarriages occurred in 6(13.3%) and 32(19.9%) pregnancies, late complications in 11(24.4%) and 9(5.6%) (RR 4.4, 95%CI 1.9-9.9, p<0.01), respectively.

Interpretation: women with type I AT deficiency have a high risk of first or recurrent VTE during pregnancy. The risk of VTE is highest in women with positive family history of VTE but still relevant in those with negative, suggesting that LMWH prophylaxis may also be considered in the latter.

Funding:none.

Research in context

Evidence before this study

Quantitative antithrombin deficiency is a rare coagulation abnormality associated with a high risk of venous thromboembolism, which further increases at certain stages of life, including during pregnancy. Low molecular weight heparin (LMWH) is the anticoagulant of choice for the prevention and treatment of pregnancy-associated venous thromboembolism and is also considered (with less robust evidence) to be effective in preventing obstetrical complications. We searched PubMed on May 3, 2019, for existing guidelines published by various scientific societies and screened their relative references. Additionally, we
searched PubMed on Aug 20, 2019, for relevant scientific literature using the search terms "anthithrombin deficiency" OR "antithrombin" OR "thrombophilia" OR "inherited thrombophilia" AND "pregnancy" OR "puerperium" OR "postpartum" AND "antithrombotic treatment" OR "prophylaxis" OR "antithrombotic treatment" in all fields without restricting the search by date. The searches were restricted to publications in the English language. Because of the rarity of antithrombin deficiency, robust observational studies and randomised trials are scarce, and guidance on the management of antithrombin deficiency in pregnant women is limited. On the basis of this gap in knowledge, current guidelines of the American College of Obstetricians, the Society of Obstetricians and Gynecologists, and the American College of Chest Physicians offer recommendations based on low-grade evidence, which are sometimes controversial. The most recent guidelines of the American Society of Hematology (2018) suggest (with a very low certainty of evidence) primary LMWH prophylaxis in pregnant women with antithrombin deficiency only if they have a positive family history
of venous thromboembolism.

Added value of this study

To our knowledge, this is the largest cohort of pregnant women with antithrombin deficiency that has been reported to date, and adds information to the already available evidence on pregnancy-associated risk of venous thromboembolism. Our data suggest that women with antithrombin deficiency have a high risk of venous thromboembolism during pregnancy and

puerperium, which is highest in those with a positive family history of the condition but, in contrast to the information reported in some guidelines, is still relevant in those with a negative family history. Additionally, we observed for the first time that antithrombin-deficient women have an increased risk of late placenta-mediated obstetrical complications, despite the use of LMWH prophylaxis.

Implications of all the available evidence

LMWH nearly halved the risk of pregnancy-associated venous thromboembolism in women with antithrombin deficiency, but a third of those receiving therapeutic doses had a recurrence. Alternative approaches, such as higher LMWH doses, monitoring anti-factor Xa activity, or the use of antithrombin concentrates should be considered in future studies. Our results support routine primary LMWH prophylaxis for prevention of pregnancy-associated venous thromboembolism, not only in women with a positive family history of venous thromboembolism, but also in those with a negative family history of the condition. If the increased risk of late obstetrical complications in women receiving LMWH is confirmed, it should be taken into account when prescribing antithrombotic prophylaxis in women with an antithrombin deficiency. Future studies are warranted to elucidate the pathogenesis of late obstetrical complications to identify women who could benefit from LMWH without harm.

Introduction

Antithrombin (AT) is a natural anticoagulant protein, being a serine protease inhibitor that inactivates thrombin, the activated forms of factors VII, X, IX, XI and XII. Its enzymatic activity is enhanced by heparin.[1] AT deficiency is a rare but severe cause of inherited thrombophilia, with a prevalence in the general population ranging from 1:500 to 1:5000. Quantitative (type I) deficiency is characterized by low functional and antigenic plasma levels of AT and is associated with a 20-fold increased risk of venous thromboembolism (VTE).[2] The qualitative (type II) deficiency, characterized by low functional and normal antigenic AT levels, is rarer than type I and its heterozygous form, is usually associated with a smaller risk of VTE.[3,4] During pregnancy, procoagulant changes in the hemostatic balance are likely to further increase the risk of VTE in women with inherited thrombophilia. Family studies of women with AT deficiency showed an overall absolute risk of pregnancy-related VTE of 16.6% (95% CI 0.0-45.1%), varying between 7.3% (95% CI 1.8-15.6%) antepartum and 11.1% (95% CI 3.7-21.0%) post-partum.[5] Women with thrombophilia may also have an increased risk of obstetrical complications (OC) owing to the impairment of the placental circulation.[6-9]

Low molecular weight heparin (LMWH) is the anticoagulant of choice in pregnancy for the prevention and treatment of VTE and is also thought, with less robust evidence, to be useful in preventing obstetrical complications.[10,11] Although several studies have assessed the risk of pregnancy-related VTE and the OC in women with the most common thrombophilia abnormalities, i.e., the G1691A substitution in the factor V gene (factor V Leiden) and the G20210A substitution in the prothrombin gene,[12] data on women with such a severe thrombophilia as inherited AT deficiency are scanty. Different guidelines offer controversial recommendations for the management with a low grade of evidence.[11,13-15] For instance, the guidelines of the American Society of Hematology suggest primary antepartum LMWH prophylaxis, but only when a positive family history of VTE is present.[16] Moreover, the optimal dosing of LMWH prophylaxis in pregnancy is not established and this is particularly relevant for AT deficient women, being AT the heparin's cofactor for the inhibition of activated coagulation factors X and II.

With this background and gaps of knowledge, aims of this study were to evaluate the risk of pregnancy-related VTE, obstetrical outcomes and the efficacy of LMWH in a large cohort of women diagnosed with inherited type I AT deficiency.

Methods

Study design and participants

This is a single-center, retrospective cohort study that included women with the following inclusion criteria: referred to our Center from Jan 1, 1980 to Jan 1, 2018 for a thrombophilia work-up, diagnosed with type I AT deficiency and who had remained pregnant at least once in their life. First and second degree relatives of patients diagnosed with AT deficiency were invited to the Center for AT testing and women with type I AT deficiency who met the inclusion criteria were also included. Women with type II AT deficiency were excluded to reduce the heterogeneity of the cohort and also because we do not perform molecular characterization routinely. At the time of the first referral, data on previous thrombotic events, family history of VTE, obstetrical history, and therapies during pregnancy and puerperium (defined as the 6 weeks after delivery) were collected from medical records. All women were invited to contact us for symptoms suggestive of thrombosis at any site and women of childbearing age were also invited to come back at the beginning of a new pregnancy to be prescribed LMWH since the first gestational weeks. A letter for the general practitioner and the gynecologist containing contact information of the Center and the invitation to refer the patient to the Center at the beginning of a future pregnancy, was given to all women of childbearing age. In addition, women who were not regularly visited at the Centre were contacted by yearly telephone calls. Finally, all the women included in this study were invited to the Center between July and October 2018 if their last visit or contact was before January 2018 in order to update their clinical records. Pregnancies that had occurred before the diagnosis of AT deficiency were conducted without antithrombotic prophylaxis, whereas those occurring after this diagnosis were conducted with LMWH started at the time of the first obstetric ultrasound at 7-10 gestational weeks. Women without a personal history of VTE (asymptomatic) or those with previous VTE (symptomatic) who had discontinued anticoagulant therapy before pregnancy onset received

intermediate prophylactic doses of LMWH (40 mg od or 60 mg od if body weight over 60 kg). Women on oral anticoagulant therapy or those asymptomatic but considered at particularly high thrombotic risk (e.g. with other thrombophilia abnormalities beside AT deficiency) received therapeutic doses of LMWH (body weight-adjusted dose bid). All women had the indication to continue LMWH prophylaxis in the puerperium and, if on anticoagulant therapy, to resume it soon after delivery at obstetrician discretion. There is limited guidance on the use of AT concentrates in pregnancy,[17]at delivery and in puerperium. There is also great uncertainty on which women may benefit from AT concentrate and even more, on when to administer the concentrate. For these reasons, and also considering the uncertainty of the cost-benefit ratio, we do not routinely give AT concentrate, as stated in a consensus paper of experts of the Italian Society for Haemostasis and Thrombosis.[18]

The study was approved by the Ethics Committee of our Hospital (Milano Area 2) and the written informed consent was obtained by study participants.

Procedures

Blood samples for thrombophilia testing were collected and tested according to laboratory methods listed in the appendix (p.1)

We considered among VTE proximal deep vein thrombosis (DVT) of the limbs, pulmonary embolism (PE) and thrombosis of the cerebral, splanchnic and superficial veins (SVT) of the lower limbs (any extension). Only objectively diagnosed VTE events occurred during pregnancy or puerperium were recorded (e.g. compression ultrasound or venography for DVT or SVT, lung V/Q scan or CT angiography for PE, CT angiography or MRI for cerebral or abdominal vein thrombosis). A positive family history of VTE was defined when at least one first- or second-degree relative had had VTE. Pregnancy outcomes included full term pregnancies, miscarriages, late OC (preterm delivery, small for gestational age (SGA) newborns, preeclampsia/eclampsia/HELLP syndrome, placental abruption, stillbirth), and terminations (voluntary abortions) according to their definitions (appendix p.2).

Women were encouraged to come to our Hospital at the time of delivery, but they were free to choose obstetrician and hospital. We provided a letter with

suggestions on antepartum, peripartum and postpartum management and also offer a 24/24 h x 365 on call assistance.

Statistical analysis

Median and inter-quartile ranges described continuous variables. Counts and percentages were used for demographic and discrete variables. Each pregnancy was considered a separate episode, as the same woman may have had more than one pregnancy with or without VTE. The risk of VTE during pregnancy or puerperium and pregnancy outcomes was expressed as risk proportions with 95% confidence intervals (CI). To evaluate the effect of LMWH in puerperium, the risk of VTE was calculated excluding women who had pregnancy-related VTE and those who resumed oral anticoagulant therapy after delivery. Comparisons between pregnancies with or without LMWH and between pregnancies in symptomatic or asymptomatic women were performed, both for VTE and OC, calculating relative risks (RR) with their 95% CI. Pregnancies initiated without LMWH, then complicated by VTE and treated with LMWH were included in the analysis of both pregnancies with and without LMWH. Women referred for thrombosis during pregnancy were excluded from the analysis of the risk of pregnancy-related VTE and women referred for OC from the analysis of the risk of OC. Stratification analysis considered the personal history of VTE and the use of LMWH during pregnancy. Sensitivity analysis on probands only (to avoid possible distortions from a mixed cohort), women with AT levels below 60IU/Dl[17], and women without additional thrombophilia abnormalities were performed. An additional sensitivity analysis of the risk of OC was done in pregnancies that had occurred after the year 2000 (when the association between thrombophilia and OC started to be addressed). A mixed-effects logistic regression was performed on probands only to take into account the within-patient correlation in the frame of observations within cluster (repeated measures). We applied a model considering treatment as fixed effect and controlling for woman and pregnancies in the same woman variability. The results are reported in term of odds ratio (OR) and 95% CI. We used Fisher's exact test to compare groups on binary variables.
All analyses were performed with SPSS (release 25.0, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA) and R (lmer in the lme4 package, version 3.6.1, R Foundation for Statistical Computing, Wien, Austria).

Role of the funding source

This study has no source of funding. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

One hundred and twenty-six women referred for a thrombophilia work-up had type I AT deficiency. Thirty-five of them were never pregnant and three were lost to follow-up. Eight women were referred to the Center for VTE occurring during pregnancy or puerperium and one for OC. Thus, 80 women were included in the analysis of the risk of pregnancy-related VTE and 87 in that of the risk of OC (Figure 1). General characteristics of the study population are in Table 1. No woman had comorbidities predisposing to obstetrical complications. The 88 women included in the study belonged to 70 different families. Fifty-seven were probands, of which 45 without and 12 with 16 relatives included in the study. In addition, 15 female relatives of 13 male probands were included. Eighty women had 189 pregnancies, 43 conducted with LMWH (32 prophylactic and 11 full therapeutic doses) and 146 without.

Figure 1: Trial profile

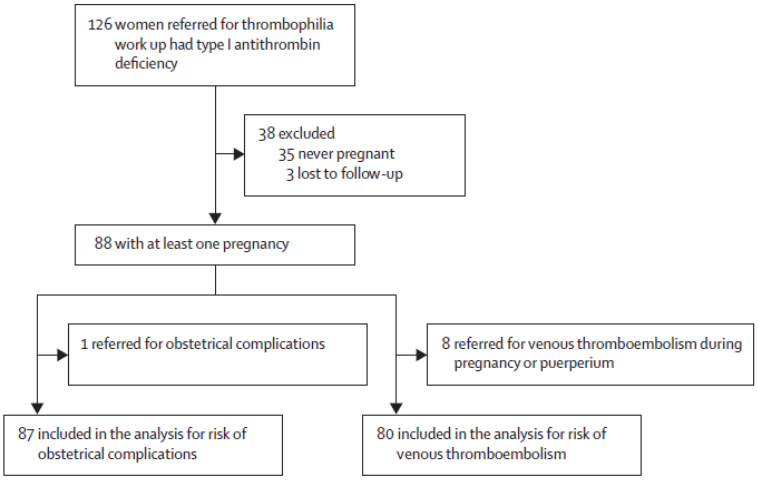


Table 1. Baseline characteristics

	Women with type I antithrombin deficiency with at least one pregnancy (n=88)
Probands	57
Relatives	31
Number of families	70
Number of relatives per probands	0·28*
Pregnancies	219
Age at diagnosis of antithrombin deficiency, years	40 (30–50)
Age at first thrombosis, years	29 (22–40)
Age at first pregnancy, years	26 (22–31)
Body-mass index, kg/m²	23 (20–26)
Antithrombin activity, %	61 (50–71)
Antithrombin antigen, %	65 (48–73)
Index venous thromboembolism†	
None	16 (28%)
Cerebral vein thrombosis	5 (9%)
Retinal vein thrombosis	2 (4%)
Deep vein thrombosis	24 (42%)
Pulmonary embolism	2 (4%)
Pulmonary embolism and deep vein thrombosis	3 (5%)
Superficial vein thrombosis	4 (7%)
Ischaemic stroke	1 (2%)
Other thrombophilia abnormalities	
Heterozygous FVL	6 (7%)
Heterozygous prothrombin G20210A mutation	2 (2%)
Homozygous prothrombin G20210A mutation	1 (1%)
Heterozygous FVL and heterozygous prothrombin G20210A mutation	1 (1%)
Heterozygous FVL and lupus anticoagulant at low titre in one test	1 (1%)
Lupus anticoagulant at low titre in two tests	1 (1%)

Data are median (IQR) or n (%), unless otherwise specified. FVL=factor V Leiden. *Number of relatives of probands included in the study (n=16) divided by the number of probands (n=57). †Percentages calculated from number of probands.

Overall, 20 new VTE events occurred during pregnancy (n=12) or puerperium (n=8), for a risk proportion of 10.6% (95%CI 6.8-15.6%). During pregnancy five VTE occurred in the first trimester (four DVT and one SVT), four in the second (three DVT and one SVT) and three in the third trimester (all SVT). During puerperium six DVT, one cerebral and one SVT, were observed. Two events (cerebral and SVT) happened on the second day after delivery and the remaining ones after the tenth. Two women with DVT delivered by cesarean section. Considering only DVT, the VTE risk proportion was 4.1% (95%CI 0.9-8.7%) in pregnancies without (six out of 146) and 2.3% (95%CI 0.4-12.1%) in pregnancies with LMWH (one out of 43); 4.3% (95%CI 1.8-8.7%) in puerperia without (six out of 140) and 3.1% (95%CI 0.6-15.7) in puerperia with LMWH (one out of 32). Two DVT of the lower limbs occurred with LMWH (one in pregnancy and one in puerperium), 11 DVT plus one cerebral vein thrombosis occurred without LMWH (six in pregnancy and five DVT plus one cerebral in puerperium) for a RR of 0.6 (95%CI 0.1-2.4, p=0.74) (Table 2). Including also the SVT, three events (7.0%) occurred in pregnancies conducted with LMWH and 17 (11.6%) in those without, for a similar RR of 0.6 (95%CI 0.2-1.9; p=0.57) (Table 2). Those three events had occurred during treatment with therapeutic doses of LMWH and were

recurrences. No VTE was observed in pregnancies conducted with prophylactic doses of LMWH.

Overall, the incidence of pregnancy-related VTE was higher in symptomatic (seven out of 32, 21.9%) than in asymptomatic women (13 out of 157, 8.3%) with a RR of 2.6 (95%CI, 1.1-6.1; p=0.05). Among the former, there were three VTE (two DVT and one SVT) in 16 pregnancies conducted with LMWH (18.8%) and four (one DVT and three SVT) in 16 pregnancies without (25%). Among asymptomatic women there were no VTE events in 27 pregnancies conducted with LMWH and 13 events (ten DVT, two SVT and one cerebral vein thrombosis) in 130 pregnancies conducted without (10%). Considering pregnancies without LMWH, the risk of VTE was higher in symptomatic than asymptomatic women (RR 2.5, 95%CI 0.9-6.7; p=0.09). Family history of VTE in asymptomatic women was positive in 48 and negative in 20. In women with a positive family history, no VTE was observed in 16 pregnancies with LMWH and 11 events (eight DVT, one cerebral vein and two SVT) in 93 pregnancies without (11.8%). In women with a negative family history, no VTE was observed in 11 pregnancies with LMWH and two DVT in 37 pregnancies without (5.4%). Neither arterial thrombosis nor bleeding was observed in all 189 pregnancies. Considering only asymptomatic probands 24 had a positive family history and 14 a negative one. Among the former, no event was observed in five pregnancies with LMWH and four DVT plus one cerebral vein thrombosis in 36 pregnancies without LMWH (13.9%). Among the latter, no VTE was observed in 11 pregnancies with LMWH and one DVT in 21 pregnancies without LMWH (4.8%).

Pregnancy outcome was evaluated in 87 women with 218 pregnancies (all spontaneous conceptions), the prevalence of outcomes being calculated on the total number of pregnancies excluding terminations. A mean of 0.29 OC per woman (0.14 for late OC) was observed. Overall, there were 58 (28.2%) OC (18.4% miscarriages and 9.7% late OC) and 148 (71.8 %) full term out of 206 pregnancies. Seventeen complications (29.4%) occurred in 45 pregnancies conducted with LMWH (35 prophylactic and 13 therapeutic doses) and 41 (25.5%) in 161 conducted without. Full term pregnancies and terminations had similar risk proportions in the two groups, but miscarriages were slightly less frequent and late OC more frequent in pregnancies with LMWH than in those without (RR 4.4, 95%CI 1.9-9.9; p<0.01) (Table 3). These differences were observed only in asymptomatic women but disappeared in those symptomatic (Table 4). Terminations were more frequent in women with previous VTE

than in those without (nine on 45 *vs* two on 157; RR 17.3, 95%CI 3.9-77.3; p<0.01). The two women with low-titre lupus anticoagulant were maintained in the analyses and both had two full term pregnancies (only one with LMWH). A family history of VTE did not influence the obstetrical outcome. Same data were obtained from the main analysis performed on the 79 women included (appendix p.3).

Considering only probands, two events (one DVT and one SVT) occurred in 31 pregnancy with LMWH and 10 events (seven DVT and three SVT) in 67 pregnancies without. The RR of pregnancy related DVT was 0.4 (95%CI 0.1-1.9; p=0.32). Late OC occurred in nine out of 36 pregnancies with LMWH and in eight out of 91 without, for a RR of 2.8 (95%CI 1.2-6.8; p=0.02). The mixed-effects logistic regression showed an OR for DVT of 0.3 (95% CI 0.0-2.4, p=0.25) and for late OC of 5.9 (95%CI 0.9-39.2, p=0.06) associated with LMWH use.

Considering only women at particularly high risk because of AT levels below 60IU/dL, three events (two DVT and one SVT) occurred in 27 pregnancies with LMWH and 11 (eight DVT and three SVT) in 68 pregnancies without, for a RR of DVT of 0.7 (95%CI 0.2-2.3; p=0.75). Eight pregnancies of 35 with LMWH and six of 86 without LMWH were complicated, for a RR of 3.2 (95%CI 1.2-8.6; p=0.02).

Considering only women with AT deficiency and no additional thrombophilia abnormalities, 68 women were analyzed for the risk of VTE and 75 for that of OC. Two DVT occurred in 40 pregnancies with LMWH and eight (eight DVT plus one SVT) in 119 without, for a RR of DVT of 0.7 (95%CI 0.2-3.4; p=1.0). Late OC occurred in 11 pregnancies of 45 with LMWH and in seven of 143 without, for a RR of 4.9 (95%CI 2.0-11.9; p<0.01).

Considering only pregnancies after the year 2000, the risk of late OC was 2.9 (95%CI 0.7-11.0; p=0.14) with three complications in 23 pregnancies with LMWH and five in 108 without.

Tabel 2. Risk of thrombosis during pregnancy and puerperium with ir without LMWH

	Pregnancies in women treated with LMWH (n=43)		Pregnancies in women who did not receive LMWH (n= 146)		RR (95%CI)	p value
	N	Risk proportion (95%CI)	N	Risk proportion (95%CI)		
Deep vein thrombosis	2	4.7% (1.3-15.5)	12	8.2% (4.8-13.8)	0.6 (0.1-2.4)	0.74
Deep and superficial vein thrombosis	3*	7.0% (1.8-17.8)	17†	11.6% (7.2-17.6)	0.6 (0.2-1.9)	0.57

LMWH, low molecular weight heparin; RR, relative risk; CI, confidence interval ***** All were recurrences that occurred with therapeutic doses of LMWH: one deep vein thrombosis in the puerperium (after a previous deep vein thrombosis in the first trimester of the same pregnancy); one deep vein thrombosis in the first trimester (after a previous deep vein thrombosis during oral contraceptive use and a previous spontaneous cerebral vein thrombosis); one superficial vein thrombosis in the second trimester (after a previous pregnancy-related deep vein thrombosis). **†** Four events were recurrences: three in the same woman (two superficial and one deep vein thrombosis in three different pregnancies) and one deep vein thrombosis after two previous spontaneous deep vein thrombosis in another woman. The remaining were all first events: three deep vein thrombosis in the first trimester, one deep vein thrombosis in the second trimester, two superficial vein in the third trimester and five deep vein thrombosis, one cerebral and one superficial vein thrombosis in the puerperium.

Table 3. Pregnancy outcomes with or without LMWH

	Pregnancies in women treated with LMWH (n= 48)		Pregnancies in women who did not receive LMWH (n= 170)		RR (95%CI)	p value
	N	Risk proportion (95%CI)	N	Risk proportion (95%CI)		
Full term	28	62.2% (47.5-75.4)	120	74.5% (67.4-80.8)	0.8 (0.7-1.1)	0.13
Miscarriage	6	13.3% (5.6-25.7)	32	19.9% (14.3-26.6)	0.7 (0.3-1.5)	0.39
Late obstetrical complications	11	24.4 % (13.6-38.5)	9	5.6% (2.8-10.0)	4.4 (1.9-9.9)	0.0006
Terminations	3	6.3% (1.6-16.1)	9	5.3% (2.6-9.5)	1.2 (0.3-4.2)	0.73

LMWH, low molecular weight heparin; RR, relative risk; CI, confidence interval

Table 4. Pregnancy outcomes in women receiving or not receiving antithrombotic prophylaxis stratified by personal history of venous thrombosis

	Pregnancies in women with previous venous thromboembolism (n=45)				Pregnancies in women without previous venous thromboembolism (n=173)			
	Treated with LMWH (n= 21)	Did not receive LMWH (n= 24)	RR (95%CI)	p value	Treated with LMWH (n= 27)	Did not receive LMWH (n=146)	RR (95%CI)	p value
Full term	11 (61.1%)	13 (72.2%)	0.8 (0.5-1.3)	0.72	17 (63%)	107 (74.8%)	0.8 (0.6-1.1)	0.24
Miscarriage	4 (22.2%)	3 (16.7%)	1.3 (0.3-5.1)	1.0	2 (7.4%)	29 (20.3%)	0.4 (0.1-1.4)	0.17
Late obstetrical complications	3 (16.7%)*	2 (11.1%)†	1.5 (0.3-7.9)	1.0	8 (29.6%)‡	7 (4.9%)§	6.1 (2.4-15.3)	0.0004
Terminations	3 (14.3%)	6 (25%)	0.6 (0.2-2.0)	0.47	0	3 (2.1%)	-	-

LMWH, low molecular weight heparin; RR, relative risk; CI, confidence interval ***** One stillbirth, one SGA newborn and one preeclampsia **†** One stillbirth and one preterm delivery **‡** Two SGA newborns (one with preterm delivery), four preterm deliveries (two with premature rupture of membrane) and two placental abruption **§** Three stillbirth (two with preeclampsia), two preeclampsia (with preterm deliveries) and two SGA newborns (one with preterm delivery)

Discussion

To our knowledge, this is the largest cohort study conducted in women with type I AT deficiency with the aim to investigate the risk of pregnancy- or puerperium-related VTE and the risk of OC. Pregnancies conducted on LMWH at prophylactic or therapeutic doses (after the diagnosis of AT deficiency) were compared to those conducted without LMWH (before the diagnosis of AT deficiency). We observed a moderate risk reduction (40%) of VTE with LMWH. The three events observed in pregnancies with LMWH were recurrences of previous VTE that had occurred during a previous pregnancy in two women and during the intake of an oral contraceptive in another, thus confirming the increased risk of recurrent VTE during pregnancy after a previous hormone-related event.[19-21] Moreover, there was a 10% risk of VTE in pregnancies of asymptomatic women without LMWH prophylaxis. Among them, the risk of VTE was doubled in women with positive family history of VTE, but was still relevant in those with negative history (5.4%), as shown in unselected women with severe thrombophilia.[22] Furthermore, pregnancies conducted with LMWH had a 4.4-fold increased risk of late placenta-mediated OC than those conducted without, a risk that increased up to 6-fold in asymptomatic women. Finally, the prevalence of terminations was 10-times higher in women with previous VTE than in those without, notwithstanding that our women were informed on the potential benefits and safety of LMWH treatment during pregnancy. Sensitivity analyses and the mixed-effects logistic regression performed to control for possible confounders and distortion showed similar risk estimates of the main analysis.
Due to the rarity of AT deficiency, controlled trials on the use of LMWH in pregnancy are lacking and data on antithrombotic prophylaxis in asymptomatic women are limited to a few retrospective cohort or case-control studies. A recent review of those studies reported a 11.6% incidence of VTE without LMWH prophylaxis (similar to our estimate) pooling together three cohort studies, and a 6-fold increased risk of first VTE pooling together four case-control studies.[23] A family study including a small sample of women with AT deficiency who did not receive LMWH during pregnancy showed a 14.8% incidence of VTE in asymptomatic women and a 60% incidence of recurrence.[24] These frequencies in our study were lower (10% and 25%, respectively), but still high. The difference can be attributed to the clustering effect of the family study and to our three-times larger sample size. Women

with a previous VTE and those with thrombophilia also have an increased risk of obstetrical complications, in particular late fetal loss, but data on AT deficient women are scanty.[8,9,21,25,26] A high risk of pregnancy loss was reported in homozygous carriers of type II AT deficiency (mutation p.Leu131Phe) who, despite antithrombotic prophylaxis, ended only one third of their pregnancies with a live infant.[27] In our study, the incidence of late obstetrical complications and miscarriage in asymptomatic women without LMWH was similar to that of the general population.[28] However, LMWH appears associated with a reduced risk of miscarriage but with an increased risk of late complications. These figures did not change after controlling the analysis for women and pregnancies variability. These findings are difficult to explain and should be interpreted with caution because of the relatively small number of patients. Heparin influences all stages of implantation through several mechanisms that are not fully understood. For example, it prevents hypoxic-induced apoptosis modulating the expression of the heparin binding epidermal-growth factor, that has a fundamental role in the early stages of placentation. Perhaps AT deficient women, having less AT-heparin complexes, have more circulating heparin available to induce the expression of the growth factor, with the result of preventing miscarriage.[29] This theoretical benefit is lost after the first trimester, when the prevention of apoptosis is no longer important. The efficacy of LMWH prophylaxis in preventing pregnancy-related VTE but not OC suggests that the two diseases have different pathological mechanisms, particularly in AT deficient women, and more studies are warranted to elucidate their molecular pathways. Alternative approaches, such as adjusted LMWH doses or the use of AT concentrates should be considered in the frame of future studies.[17,30]

Beside the large sample size, strengths of our study are the homogenous prophylactic regimen, as LMWH was started at predetermined doses since the first gestational weeks, and the collection of objective documentation of VTE. However, some limitations need to be discussed. Firstly, the lack of a control arm (women without thrombophilia) does not allow to calculate the absolute risk difference of VTE and obstetrical complications. Secondly, data concerning pregnancies that had occurred before the diagnosis of AT deficiency, and particularly when the association between thrombophilia and OC was not yet established, may have been collected less consistently. This may have led to an underestimation of the risk of OC in pregnancies conducted without LMWH prophylaxis, but the sensitivity analysis performed

on pregnancies that had occurred after the year 2000 (when thrombophilia screening was largely implemented) showed results similar to those of the whole cohort. Thirdly, because the VTE events observed in pregnancies conducted with LMWH were all recurrences, the poor preventive efficacy of LMWH may particularly apply to the therapeutic doses.

In conclusion, women with type I AT deficiency have not only a high risk of VTE during pregnancy and puerperium, but also a high risk of late placenta-mediated OC. Intermediate doses of LMWH prophylaxis reduced the risk of VTE by 40%, but the full therapeutic doses used in women with previous VTE were not sufficient to prevent recurrences. Our results support routine LMWH prophylaxis for prevention of VTE in pregnant women with AT deficiency also when their family history of VTE is negative, at variance with other recommendations.[16]

References

1 Olson ST, Bjork I, Sheffers R, Craig PA, Shore JD, Choay J. Role of the Antithrombin-binding Pentasaccharide in Heparin Acceleration of Antithrombin-Proteinase Reactions. J Biol Chem 1992; 267: 12528–38.

2 Buchanan GS, Rodgers GM, Ware Branch D. The inherited thrombophilias: genetics, epidemiology, and laboratory evaluation. Best Pract Res Clin Obstet Gynaecol 2003; 17: 397–411.

3 Luxembourg B, Pavlova A, Geisen C, et al. Impact of the type of SERPINC1 mutation and subtype of antithrombin deficiency on the thrombotic phenotype in hereditary antithrombin deficiency. Thromb Haemost 2014; 111: 249–57.

4 Kovac M, Mitic G, Mikovic Z, et al. The influence of specific mutations in the AT gene (SERPINC1) on the type of pregnancy related complications. Thromb Res 2019; 173: 12–9.

5 Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. BMJ 2017; 359: j4452.

6 Ferrazzi E, Bulfamante G, Mezzopane R, Barbera A, Ghidini A, Pardi G. Uterine Doppler velocimetry and placental hypoxic-ischemic lesion in pregnancies with fetal intrauterine growth restriction. Placenta 1999; 20: 389–94.

7 Many A, Schreiber L, Rosner S, Lessing JB, Eldor A, Kupferminc MJ. Pathologic features of the placenta in women with severe pregnancy complications and thrombophilia. Obstet Gynecol 2001; 98: 1041–4.

8 Kupferminc MJ, Eldor A, Steinman N, et al. Increased Frequency of Genetic Thrombophilia in Women with Complications of Pregnancy. N Engl J Med 1999; 340: 9–13.

9 Walker ID. Thrombophilia in pregnancy. J Clin Pathol 2000; 53: 573–80.

10 Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis 2016; 41: 92–128.

11 Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy. Chest 2012; 141: e691S–e736S.

12 Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: A systematic review. Br J Haematol 2006; 132: 171–96.

13 James A, Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 123: thromboembolism in pregnancy. Obstet Gynecol 2011; 118: 718–29.

14 Chan W-S, Rey E, Kent NE, et al. Venous Thromboembolism and Antithrombotic Therapy in Pregnancy. J Obstet Gynaecol Canada 2014; 36: 527–53.

15 Royal College Obstetricians and Gynaecologists. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium. RCOG Press 2015; 37a: 1–40.

16 Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv 2018; 2: 3317–59.

17 James AH, Bates SM, Bauer KA, et al. Management of hereditary antithrombin deficiency in pregnancy. Thromb Res 2017; 157: 41–5.

18 Lussana F, Dentali F, Abbate R, et al. Screening for thrombophilia and antithrombotic prophylaxis in pregnancy: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res 2009; 124: e19–25.

19 Pabinger I, Grafenhofer H, Kaider A, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J Thromb Haemost 2005; 3: 949–54.

20 Stefano V De, Martinelli I, Rossi E, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br J Haematol 2006; 135: 386–91.

21 White RH, Chan WS, Zhou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy-associated versus unprovoked thromboembolism. Thromb Haemost 2008; 100: 246–52.

22 Gerhardt A, Scharf RE, Greer IA, Zotz RB. Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium. Blood 2016; 128: 2343–9.
23 Rhéaume M, Weber F, Durand M, Mahone M. Pregnancy-Related Venous Thromboembolism Risk in Asymptomatic Women With Antithrombin Deficiency. Obstet Gynecol 2016; 127: 649–56.
24 van Boven HH, Vandenbroucke JP, Briët E, Rosendaal FR. Gene-gene and gene-environment interactions determine risk of thrombosis in families with inherited antithrombin deficiency. Blood 1999; 94: 2590–4.
25 Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia. Lancet 1996; 348: 913–6.
26 Greer IA. Thrombosis in pregnancy: Maternal and fetal issues. Lancet 1999; 353: 1258–65.
27 Kraft J, Sunder-Plassmann R, Mannhalter C, et al. Women with homozygous AT deficiency type II heparin-binding site (HBS) are at high risk of pregnancy loss and pregnancy complications. Ann Hematol 2017; 96: 1023–31.
28 Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol 2018; 132: e197–207.
29 Quaranta M, Erez O, Mastrolia SA, et al. The physiologic and therapeutic role of heparin in implantation and placentation. PeerJ 2015; 3: e691.
30 James AH, Konkle BA, Bauer KA. Prevention and treatment of venous thromboembolism in pregnancy in patients with hereditary antithrombin deficiency. Int J Womens Health 2013; 5: 233–41.

Chapter 8

Low-molecular-weight heparin for the prevention of pregnancy-related recurrent venous thromboembolism and obstetrical complications.

Abbattista M., Gianniello F., Artoni A., Capecchi M., Bucciarelli P., Ciavarella A., Peyvandi F., Martinelli I.

submitted

Summary

Background: Pregnancy and inherited thrombophilia increase the risk of venous thromboembolism (VTE) and thrombophilia also that of obstetrical complications. Data on the use of low-molecular-weight heparin (LMWH) for the prevention of such conditions are poor.
Objective: To evaluate the risk of pregnancy-related recurrent VTE and obstetrical complications in women with or without LMWH prophylaxis.
Patients and Methods: This retrospective cohort study includes fertile women referred to the Thrombosis Center from Jan 2000 to Sep 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 treated with LMWH, whereas 10 VTE (14%) were recorded in 70 non-treated. Nine women (90%) with recurrent VTE had had a previous hormone-related event. The incidence of miscarriage was lower in pregnancies treated with LMWH than in those without (11% *vs* 26%, relative risk 0.4, 95%CI: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 miscarriage, but not late obstetrical complications. Women with thrombophilia decided for terminations twice more than those without.

Introduction

Venous thromboembolism (VTE) is an important cause of maternal morbidity and mortality.[1,2] The estimated incidence of maternal VTE is 1 case every 1000 pregnancies per year.[3–5] During pregnancy, physiological changes in the hemostatic balance occur, such as the increase of some procoagulant factors, decrease of the natural anticoagulant proteins and hypofibrinolysis. An additional important mechanistic role is played by stasis caused by pressure of the uterus on the inferior vena cava and iliac veins. Tissue damage at the time of delivery also contributes to increase the risk of postpartum VTE. This risk is likely to be further increased by inherited thrombophilia.[6] Furthermore, after a first episode of VTE, the risk of recurrence during pregnancy changes according to the presence or absence of other risk factors and is influenced by those risk factors that triggered the first VTE episode.[7] In particular, women who experienced a first VTE associated with a transient non hormone-related risk factor seem at lower risk of recurrence than those who had a first hormone-related VTE, i.e. during pregnancy or oral contraceptive use. [8,9]

The use of low-molecular-weight heparin (LMWH) prophylaxis during pregnancy should be considered after a careful evaluation of the woman's risk profile, as suggested by several guidelines. [10–13] However, data on the use of LMWH during pregnancy for the prevention of recurrent VTE and obstetrical complications, particularly during the first pregnancy after VTE are still to be confirmed. [14,15]

Women with thrombophilia abnormalities also have an increased risk of miscarriage and late obstetrical complications owing to the impairment of the circulation in the uterine mucosa and placenta. [16–21] LMWH is the anticoagulant of choice for the prevention and treatment of VTE during pregnancy and it is also thought to be useful to prevent obstetrical complications. [12,22–24] There is evidence on the efficacy of LMWH in the prevention of VTE and recurrent miscarriages in women with the acquired thrombophilia due to antiphospholipid antibodies, [25,26] but there are less robust data on the use of LMWH for the prevention of obstetrical complications in women with inherited thrombophilia. With this background and gaps of knowledge 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-centre cohort study on women referred to our Centre from Jan 1st, 2000 to Sep 30th, 2018 for a thrombophilia work-up after a previous episode of VTE. Young women who were between 15 and 40 years old at the time of first VTE and between 18 and 40 years old 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 during pediatric or non-childbearing age, a VTE event other than deep vein thrombosis (DVT) of the lower limbs or pulmonary embolism (PE), infertility and the antiphospholipid syndrome.

Our common 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 at any site, as well as in high-risk situations such as pregnancy. Women of childbearing age were invited to come back at the beginning of pregnancy for the prescription of LMWH prophylaxis. In addition, women who were not seen by us in the past year were contacted by phone to update their clinical records for the purpose of this study up to Sep 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, were prescribed prophylactic intermediate doses of enoxaparin (40 mg daily or 60 mg daily if body weight > 60 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 non-hormone 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)[27] and the G20210A substitution in the 30-untranslated region of the prothrombin gene; [28] functional and immunoassays (when required) for plasma antithrombin, protein C and protein S; [29] functional assay for factor VIII; antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein I IgG and IgM antibodies); [30] fasting and post-methionine load homocysteine.[31] Patients still taking 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,[32] preeclampsia as the concomitant presence of arterial hypertension and a significant amount of proteins in the urine [33], and stillbirth as a pregnancy loss that occurred beyond the 20th gestational week.

Statistical analysis

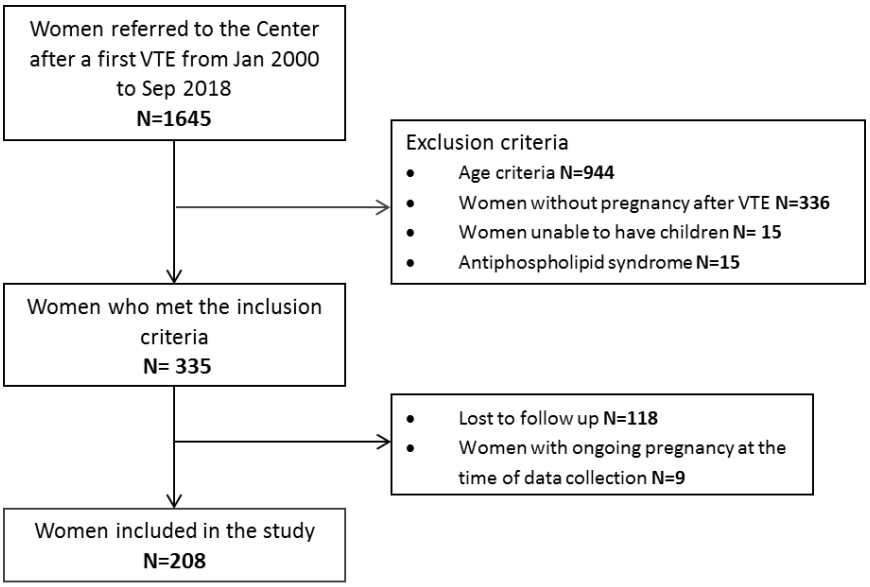
Continuous variables are presented as median and inter-quartile range (IQR), and categorical variables as counts and percentages. Comparisons between pregnancies with and without LMWH were performed for the risks of VTE and obstetrical complications, calculating the relative risks and their 95% confidence intervals (CI). 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). Hyperhomocysteinemia and high FVIII are thrombophilia abnormalities of little clinical relevance. In addition, hyperhomocysteinemia is normalized in pregnant women by folic acid supplementation. Hence, these two abnormalities are only reported in table 1, but not in other analyses. The relative risks of pregnancy outcomes for full term, miscarriage and late obstetrical complications were calculated as the number of pregnancy outcomes on the total number of pregnancies excluding terminations. All analyses were performed using the statistical software SPSS (release 26.0, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA).

Results

Patients characteristics

In the inclusion period considered for this study, 1645 women were referred to our Center, of whom 1310 were excluded for age criteria, not having become pregnant after VTE, infertility or having the antiphospholipid antibody syndrome (Figure 1). Among 335 women who met the inclusion criteria, 118 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.

Figure 1. Flow chart of the 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 and the prevalence of hormone-related risk factors, i.e. oral contraceptive use, pregnancy and puerperium 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. 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 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, 12 had miscarriages, 3 terminated voluntarily, 3 developed VTE at a very early gestational week and 6 did not come back to the Center when pregnant.

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)
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)
Hyperhomocysteinemia	8 (6)	10 (14)
High factor FVIII	8 (6)	4 (6)
Number of thrombophilia abnormalities*, n (%)		
None	71 (51)	52 (74)
Single	56 (41)	9 (13)
Multiple	11 (8)	9 (13)
Severity of thrombophilia abnormalities*†, 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)	-

LMWH, low-molecular-weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism; SVT, superficial vein thrombosis

*excluding hyperhomocysteinemia and high Factor VIII

†Severe thrombophilia includes: antithrombin (AT), protein (PC), protein S (PS)deficiencies; homozygous factor V Leiden (FVL) or prothrombin (PT) and combined abnormalities.

Pregnancy-related recurrent VTE

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 (3 DVT, one cerebral vein thrombosis and one PE) occurred in women referred to us after the index pregnancy, 3 DVT occurred in women at the 7th, 9th and 10th gestational week before the start of LMWH prophylaxis and the remaining 2 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 6 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. Nine of the 10 women who experienced a recurrent pregnancy-related VTE had had a previous hormone-related event, 7 during oral contraceptive intake and two during pregnancy. Among women who received LMWH during pregnancy one episode of minor bleeding during delivery and one mild thrombocytopenia after delivery were observed.

Table 2. Prevalence of recurrent venous thromboembolism during pregnancy

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

No superficial vein thrombosis was observed.

VTE, venous thromboembolism; LMWH, low-molecular-weight heparin.

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 3). 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), 2 had small for gestational age newborns, 2 preeclampsia and 2 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.

Table 3. Risk of obstetrical complications

Pregnancy outcome, n (%)	Pregnancies LMWH + N= 138	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) *	8 (13) †	1.3 (0.6-2.8)
Termination	10 (7)	7 (10)	0.7 (0.3-1.8)

LMWH, low-molecular-weight heparin; RR, relative risk; CI, confidence interval.
* 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. † 2 stillbirth, 3 small for gestational age, 2 preterm (one with SGA), 1 preeclampsia, 1 placental abruption

Thrombophilia

Table 4 shows the risk proportions of pregnancy-related VTE and obstetrical complications stratified by the presence of thrombophilia abnormalities. The risk 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 (12%) compared to 7 of 123 without (6%) chose to terminate their pregnancy. Further distinction when these women were stratified 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.

Table 4. 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 (%)	-	3 (17)	-	-	7 (13)	-
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.

Discussion

This retrospective cohort study evaluated the risk of recurrent pregnancy-related VTE and the risk of obstetrical complications in the 208 first pregnancies that occurred following an episode of VTE and were 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 complicated the 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,[34] at variance with our findings (14.3% vs 0%). Moreover, we found slightly higher prevalence in the antepartum period than previously reported. [8,35,36] This might be due 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, 5 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 rate of pregnancy-related VTE remained the same.

Concerning thrombophilia as an additional risk factor, the prevalence of pregnancy-related recurrent VTE was similar in women with or without abnormalities (17% vs 13%), in broad agreement with other studies.[8,9,37] 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 VTE episode during pregnancy, puerperium or oral contraceptive intake are at increased risk of recurrence during pregnancy.[8,9,38] Notwithstanding the fact that the absolute risk of antepartum recurrent VTE remains controversial,[24] 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.[13] Some findings support the views that a history of VTE is associated with an increased risk of obstetrical complications,[39,40] but the evidence to support the use of LMWH for the prevention of those complications are still poor, with inconsistent results and weak recommendations. [2,41] 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, in our cohort we observed that women with thrombophilia chose termination twice more frequently than women without, suggesting that women with thrombophilia should receive careful counselling for the available options in order to give birth safely. 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 and the possibility to incur into referral bias. 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 to draw 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 that the use of prophylactic doses of LMWH during pregnancy and puerperium lowers the risk of pregnancy-related recurrent VTE, particularly in women who previously had hormone-related VTE, a condition associated with an increased risk of pregnancy-related recurrent VTE. LMWH prophylaxis during pregnancy may be effective also for the prevention 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 counselling regarding future pregnancies in women diagnosed as having thrombophilia. They should be reasonably reassured on the safety and efficacy of LMWH prophylaxis in preventing VTE and perhaps miscarriage.

References

1 Parunov LA, Soshitova NP, Ovanesov M V., Panteleev MA, Serebriyskiy II. Epidemiology of venous thromboembolism (VTE) associated with pregnancy. Birth Defects Res Part C Embryo Today Rev 2015; 105: 167–84.

2 Brenner B, Arya R, Beyer-Westendorf J, Douketis J, Hull R, Elalamy I, Imberti D, Zhai Z. Evaluation of unmet clinical needs in prophylaxis and treatment of venous thromboembolism in at-risk patient groups: pregnancy, elderly and obese patients. Thromb J Thrombosis Journal; 2019; 17: 24.

3 Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the Incidence of Venous Thromboembolism During Pregnancy or Postpartum: A 30-Year Population-Based Study. Obstet Gynecol Surv 2006; 61: 220–1.

4 James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: Incidence, risk factors, and mortality. Am J Obstet Gynecol 2006; 194: 1311–5.

5 Kane E V., Calderwood C, Dobbie R, Morris C, Roman E, Greer IA. A population-based study of venous thrombosis in pregnancy in Scotland 1980–2005. Eur J Obstet Gynecol Reprod Biol 2013; 169: 223–9.

6 Gerhardt A, Scharf RE, Greer IA, Zotz RB. Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium. Blood 2016; 128: 2343–9.

7 Bistervels IM, Scheres LJJ, Hamulyák EN, Middeldorp S. Sex matters: Practice 5P's when treating young women with venous thromboembolism. J Thromb Haemost 2019; 17: 1417–29.

8 Pabinger I, Grafenhofer H, Kaider A, Kyrle PA, Quehenberger P, Mannhalter C, Lechner K. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J Thromb Haemost 2005; 3: 949–54.

9 Stefano V De, Martinelli I, Rossi E, Battaglioli T, Za T, Mannuccio Mannucci P, Leone G. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br J Haematol 2006; 135: 386–91.

10 The american college of obstetricians and gynecologists women's health care physicians. Practice Bulletin No. 123. Obstet Gynecol 2011; 118: 718–29.

11 Royal College of Obstetricians & Gynaecologists. Green-top Guideline No.37a. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. 2015; .

12 Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy. Chest The American College of Chest Physicians; 2012; 141: e691S-e736S.

13 Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, Vazquez SR, Greer IA, Riva JJ, Bhatt M, Schwab N, Barrett D, LaHaye A, Rochwerg B. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv 2018; 2: 3317–59.

14 Rodger M a., Langlois NJ, de Vries JI, Rey E, Gris J-C, Martinelli I, Schleussner E, Ramsay T, Mallick R, Skidmore B, Middeldorp S, Bates S, Petroff D, Bezemer D, van Hoorn ME, Abheiden CN, Perna A, de Jong P, Kaaja R. Low-molecular-weight heparin for prevention of placenta-mediated pregnancy complications: protocol for a systematic review and individual patient data meta-analysis (AFFIRM). Syst Rev 2014; 3: 69.

15 Rodger MA, Gris JC, de Vries JIP, Martinelli I, Rey É, Schleussner E, Middeldorp S, Kaaja R, Langlois NJ, Ramsay T, Mallick R, Bates SM, Abheiden CNH, Perna A, Petroff D, de Jong P, van Hoorn ME, Bezemer PD, Mayhew AD. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet 2016; 388: 2629–41.

16 Ferrazzi E, Bulfamante G, Mezzopane R, Barbera A, Ghidini A, Pardi G. Uterine Doppler velocimetry and placental hypoxic-ischemic lesion in pregnancies with fetal intrauterine growth restriction. Placenta 1999; 20: 389–94.

17 Many A, Schreiber L, Rosner S, Lessing JB, Eldor A, Kupferminc MJ. Pathologic Features of the Placenta in Women With Severe Pregnancy Complications and Thrombophilia. 2001.
18 Preston FE, Rosendaal FR, Walker ID, Briët E, Berntorp E, Conard J, Fontcuberta J, Makris M, Mariani G, Noteboom W, Pabinger I, Legnani C, Scharrer I, Schulman S, Van Der Meer FJM. Increased fetal loss in women with heritable thrombophilia. Lancet 1996; 348: 913–6.
19 Greer IA. Thrombosis in pregnancy: Maternal and fetal issues. Lancet 1999; 353: 1258–65.
20 Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, Fait G, Lessing JB. Increased Frequency of Genetic Thrombophilia in Women with Complications of Pregnancy. N Engl J Med 1999; 340: 9–13.
21 Walker ID. Thrombophilia in pregnancy. Journal of Clinical Pathology. 2000. p. 573–80.
22 Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, Whyte S. SPIN (Scottish Pregnancy Intervention) study: a multicenter , randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood 2010; 115: 4162–7.
23 Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: A systematic review of safety and efficacy. Blood. 2005. p. 401–7.
24 Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis Springer US; 2016; 41: 92–128.
25 Opatrny L, David M, Kahn SR, Shrier I, Rey E. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: A metaanalysis. J Rheumatol 2006; 33: 2214–21.
26 Abou-Nassar K, Carrier M, Ramsay T, Rodger MA. The association between antiphospholipid antibodies and placenta mediated complications: A systematic review and meta-analysis. Thromb Res Elsevier Ltd; 2011; 128: 77–85.
27 Bertina RM, Koeleman BPC, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden, Pieter A. Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994; 369: 64–7.
28 Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood American Society of Hematology; 1996; 88: 3698–703.
29 Tripodi A. A Review of the Clinical and Diagnostic Utility of Laboratory Tests for the Detection of Congenital Thrombophilia. Semin Thromb Hemost United States; 2005; 31: 25–32.
30 Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, De groot PG. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009; 7: 1737–40.
31 Zighetti ML, Cattaneo M, Falcon CR, Lombardi R, Harari S, Savoritto S, Mannucci PM. Absence of hyperhomocysteinemia in ten patients with primary pulmonary hypertension. Thromb Res 1997; 85: 279–82.
32 Parazzini F, Cortinovis I, Bortolus R, Fedele L, Decarli A. Weight at birth by gestational age in Italy. Hum Reprod 1995; 10: 1862–3.
33 Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet 2016; 387: 999–1011.
34 Lindqvist Pg, Bremme K, Hellgren M. Efficacy of obstetric thromboprophylaxis and long-term risk of recurrence of venous thromboembolism. Acta Obstet Gynecol Scand 2011; 90: 648–53.
35 Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, Geerts W, Kovacs M, Weitz JI, Robinson KS, Whittom R, Couture G. Safety of Withholding Heparin in Pregnant Women with a History of Venous Thromboembolism. N Engl J Med 2000; 343: 1439–44.
36 Lazo-Langner A, Al-Ani F, Weisz S, Rozanski C, Louzada M, Kovacs J, Kovacs MJ. Prevention of venous thromboembolism in pregnant patients with a history of venous thromboembolic disease: A retrospective cohort study. Thromb Res Elsevier; 2018; 167: 20–5.

37 Simioni P, Tormene D, Prandoni P, Girolami A. Pregnancy-related recurrent events in thrombophilic women with previous venous thromboembolism. Thromb Haemost 2001; 86: 929.
38 White RH, Chan WS, Zhou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy-associated versus unprovoked thromboembolism. Thromb Haemost 2008; 100: 246–52.
39 Pabinger I, Grafenhofer H, Kaider A, Ilic A, Eichinger S, Quehenberger P, Husslein P, Mannhalter C, Lechner K. Preeclampsia and fetal loss in women with a history of venous thromboembolism. Arterioscler Thromb Vasc Biol 2001; 21: 874–9.
40 Hansen AT, Schmidt M, Horváth-Puhó E, Pedersen L, Rothman KJ, Hvas AM, Sørensen HT. Preconception venous thromboembolism and placenta-mediated pregnancy complications. J Thromb Haemost 2015; 13: 1635–41.
41 Rodger MA, Langlois NJ, Ip De Vries J, Rey É, Gris J-C, Martinelli I, Schleussner E, Ramsay T, Mallick R, Skidmore B, Middeldorp S, Bates S, Petroff D, Bezemer D, Van Hoorn ME, Abheiden CN, Perna A, De Jong P, Kaaja R. Low-molecular-weight heparin for prevention of placenta-mediated pregnancy complications: protocol for a systematic review and individual patient data meta-analysis (AFFIRM). 2014.

Chapter 9

Summary and general discussion

Summary and general discussion

VTE is a serious and life-threatening situation with an incidence of 1-2 per 1000 person-years. These figures are doubled for women exposed to reproductive risk factors, such as hormonal intake (oral contraception or hormonal replacement therapy), pregnancy and puerperium, compared to men of similar age. [1] There are also evidences on the different clinical presentation and location of VTE between men and women. Hence, when it comes to women, reproductive risk factors, presence of thrombophilia abnormalities, unusual location of VTE, and their possible interactions, must be considered to evaluate and stratify the risk of VTE for primary or secondary prevention and treatment of VTE, accordingly.

In **Chapter 2** we reviewed the literature to provide an update summary of the available recommendations for the treatment of VTE at unusual sites, since it could vary widely according to the affected site. Among others, the therapeutic approach for CVT and for the ovarian vein thrombosis, as female-related unusual sites, were described. For the first one a therapeutic algorithm was provided, while for the latter, it is worth considering that it is mostly reported during pregnancy or post-partum and therapeutic recommendation from international scientific societies are lacking. Treatment of ovarian vein thrombosis is only mentioned by the Canadian Society of Obstetricians and Gynecologists.

Furthermore, we tried to address the issue of the usefulness of performing thrombophilia screening in patients who experienced VTE at unusual site, although recommendations from the guidelines are lacking. When a local or systemic condition triggers the event, thrombophilia screening seems worthless, whereas it can be useful for those selected patients with idiopathic events, young age, or positive family history of VTE. However, caution should be used in interpreting the results of thrombophilia screening for various reasons, among them their possible psychological implications. This issue should be carefully evaluated, particularly for fertile women.

CVT has a skewed sex ratio, being more frequent in women than in men, as described in **Chapter 3**. Although the incidence of this rare manifestation remains uncertain, it has increased over the last decade up to 15 annual cases per million individuals, possibly for the amelioration of objective techniques.[2,3] CVT occurs more often in young women because it is particularly associated with oral contraceptive use and pregnancy, other than

with certain infection or inflammatory states (sinusitis, meningitis, vasculitis, etc.), local trauma or lumbar puncture. Indeed, oral contraceptive use was reported in more than 80% of women with CVT and pregnancy and puerperium account for 5-20% of cases, with an annual incidence of 12 cases per 100000 deliveries. [4,5]

The mainstay of treatment for CVT, regardless of presence of intracranial haemorrhage, is anticoagulation. To date, anticoagulant therapy for CVT, as well as for other VTE at unusual sites, is generally accepted, but the optimal therapeutic approach remains challenging, particularly when an intracranial hemorrhage occurs (approximately 40% of cases).[6] Moreover, the optimal duration is still debated. The ongoing study EXCOA-CVT has the aim to evaluate the benefit of extended anticoagulant therapy after CVT, comparing short-(3-6 months) versus long-term (12 months) anticoagulation. [7] Also, the use of direct oral anticoagulants is still under investigation. The RE-SPECT CVT trial comparing dabigatran to warfarin was recently concluded, showing that the majority of patients with CVT anticoagulated with either dabigatran or warfarin reached a partial or complete recanalization after six months.[8]

The extended use of oral contraceptives for medical reasons and for birth control, has allowed to highlight their role as risk factor for VTE (Roach 2014).1 It has been showed that the risk varies widely according to dose, type, administration route [9,10] and is highest in the first 6-12 months of use.[11] The large case-control study on 1020 fertile women with previous VTE and 887 controls presented in **Chapter 4** aimed to address the unanswered specific question of whether or not oral contraceptive use should be considered the same risk factor in women who develop VTE within few months or after many years of use. The association between the duration of oral contraceptive use and risk of VTE according to the women's age and periods of use, as well as the prevalence of thrombophilia and other risk factors, were investigated. Our study confirms that women on oral contraceptive are at higher risk in the first year of use than beyond.[12] We stratify our population in short (<1 year), who had the highest risk, long (1 to 5 years) and very long users (>5 years) whose risk was not established. The risk of VTE decrease progressively over time, in contrast to what showed from a large population-based study.[9] Then, thrombophilia and body mass index were included as variables in the adjusted model, while age and the categories first/multiple user were considered as mediators. Stratifying the analyses by age, we considered the possible

confounding effect of age and showed that the association between the duration of oral contraceptive use and VTE was valid only for women aged 30 years or less and first users. We also showed the joint effect of thrombophilia on the risk of VTE in the short users. Separate analysis for women with CVT showed similar results of the main analysis on common sites, with slightly decreased estimate for the latter, as expected. [13]

Also, pregnancy, as a hormonal-related condition at risk of VTE, contribute to the majority of the first thrombotic manifestations among women during reproductive age. In particular, the safety of a pregnancy in women who had had a previous CVT need to be established in terms of thrombotic recurrences and pregnancy outcomes. In **Chapter 5** we aimed to address specifically this question evaluating the risk of obstetrical complications, recurrent thrombosis and bleeding complications in a cohort of pregnant women on LMWH prophylaxis after a first episode of CVT. In **Chapter 6** we extended the same questions to a wider study period, up to 23 years. A previous systematic review, with limited data on antithrombotic prophylaxis, showed a low absolute risk of pregnancy-related recurrence (9 per 1000, 95%CI 12-61) although the relative risk is 80-fold higher compared to general population.[14] Among 52 women on intermediate dose of LMWH prophylaxis included in the study presented in Chapter 5, neither recurrent event nor minor or major bleeding were observed. The relative risk of developing obstetrical complications was 6-fold increase compared to healthy controls and it was not associated to an adverse obstetrical history. The intra-women case-cross over analysis among 17 women with pregnancies either before and after CVT confirmed the main observation of increased risk of late obstetrical complication after CVT. Therefore, our study did not support the hypothesis that LMWH prophylaxis could prevent obstetrical complication, [15] either in women with or without thrombophilia. These figures did not substantially change in the wider sample presented in Chapter 6. Moreover, having had a CVT and being a carrier of thrombophilia abnormalities seemed to influence the decision to terminate, reflecting the fear of the women to perpetrate a situation at risk.

Data from a meta-analysis are in favor of LMWH in the prevention of recurrent placenta-mediated pregnancy complications.[16] On the other hand, the evidence about the risks and benefits of antithrombotic prophylaxis in women at risk of VTE is uncertain [17] because definitive trials are difficult to set up, particularly for rare condition such as severe thrombophilia. In

Chapter 7 was reported a single-centre cohort study aimed to evaluate the risk of pregnancy-related VTE and obstetrical complications in 88 women with type I antithrombin deficiency, the most severe thrombophilia abnormality. These women were referred to our Center over a 38 years period. Due to the rarity of the condition, similar studies are lacking. The most recent guidelines of the American Society of Hematology [18] suggest with low certainty of evidence the use of LMWH prophylaxis in pregnant women with antithrombin deficiency only if they had had previous VTE or a positive family history for VTE. Our data suggest that women with antithrombin deficiency have a high risk of VTE during pregnancy and puerperium and this risk is still relevant in those with a negative family history for VTE. Moreover, an increased risk of late placenta-mediated obstetrical complications, despite the use of LMWH prophylaxis, was observed. Finally, the prevalence of terminations was 10-times higher in women with previous VTE than in those without. The efficacy of LMWH prophylaxis in preventing pregnancy-related VTE but not obstetrical complications, suggests that the two diseases could have different pathological mechanisms, particularly in antithrombin deficient women, and more basic research on molecular pathways are warranted. In **Chapter 8** we evaluated the use of LMWH in the first pregnancy following a previous episode of VTE. The majority of the investigated events (n=158), contrary to what is mainly reported in the literature, occurred in primigravidae women. Once more, antithrombotic prophylaxis has proven effective and safe in preventing the risk of recurrent VTE and perhaps miscarriage, but not that of late obstetrical complications.

In conclusion, this work provides some lights on the use of anticoagulant treatment for VTE at unusual sites and on the use of LMWH in pregnant women at risk of VTE. In the era of precision medicine, it is important to measure and understand inter-personal differences to better define the individual risk of VTE, particularly in such high-risk situations as oral contraceptive use, pregnancy and puerperium. As randomized controlled trials are unlikely to be done in these settings, due to the large sample size needed and the rarity of the disease, this work provides data that will be useful for future secondary data analysis, particularly for pregnant women with thrombosis at unusual sites or women with rare thrombophilia abnormalities. Future studies will elucidate whether or not some women receiving LMWH have an increased risk of late obstetrical complications. Data on the interaction between thrombophilia and LMWH prophylaxis during pregnancy indicate

that uncertainty remains on the pathophysiology of obstetrical complications. There are some risk factors, such as thrombophilia abnormalities, that are shared between the risk of VTE and that of obstetrical complications, but the underlying molecular pathways could be different and need to be elucidated to tailor preventive strategies. Additionally, some alternative approaches, such as higher doses of LMWH, monitoring anti-factor Xa activity, or using of antithrombin concentrate, should be considered in future studies on pregnant women, due to their high risk of developing pregnancy-related VTE. Furthermore, these data underscore the need to 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.

References

1 Roach REJ, Lijfering WM, Rosendaal FR, Cannegieter SC, Le Cessie S. Sex difference in risk of second but not of first venous thrombosis: Paradox explained. Circulation 2014; 129: 51–6.

2 Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: A cross-sectional study. Stroke 2012; 43: 3375–7.

3 Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral Venous Sinus Thrombosis Incidence is Higher Than Previously Thought: A Retrospective Population-Based Study. Stroke 2016; 47: 2180–2.

4 Coutinho JM, Ferro JM, Canhão P, et al. Cerebral venous and sinus thrombosis in women. Stroke 2009; 40: 2356–61.

5 Bousser M-G, Crassard I. Cerebral venous thrombosis, pregnancy and oral contraceptives. Thromb Res 2012; 130: S19–22.

6 Afifi K, Bellanger G, Buyck PJ, et al. Features of intracranial hemorrhage in cerebral venous thrombosis. J Neurol 2020; 267: 3292–8.

7 Miranda B, Aaron S, Arauz A, et al. The benefit of EXtending oral antiCOAgulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. Int J Stroke 2018; 13: 771–4.

8 Ferro JM, Bendszus M, Jansen O, et al. Recanalization after cerebral venous thrombosis. A randomized controlled trial of the safety and efficacy of dabigatran etexilate versus dose-adjusted warfarin in patients with cerebral venous and dural sinus thrombosis. Int J Stroke 2021; 0: 1–9.

9 Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009; 339: b2890.

10 Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011; 343: 1–15.

11 Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP, Investigation O. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. Arch Intern Med 2000; 160: 49–52.

12 van Hylckama VA, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009; 339: b2921.

13 Martinelli I. Cerebral vein thrombosis. Thromb Res 2013; 131: S51–4.

14 Aguiar de Sousa D, Canhão P, Ferro JM. Safety of Pregnancy After Cerebral Venous Thrombosis. Stroke 2016; : STROKEAHA.115.011955.

15 Bates SM. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy. CHEST J 2012; 141: e691S.

16 Rodger MA, Carrier M, Le Gal G, *et al.* Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. *Blood* 2014; **123**: 822–8.

17 Middleton P, Shepherd E, Gomersall JC. Venous thromboembolism prophylaxis for women at risk during pregnancy and the early postnatal period. Cochrane Database Syst Rev 2021; published online March 29. DOI:10.1002/14651858.CD001689.pub4.

18 Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv 2018; 2: 3317–59.

Impact Paragraph

Impact paragraph

Venous thromboembolism is a life-threating condition and the leading cause of maternal mortality in developed countries. In many cases it can be prevented and adequately treated, but some areas of uncertainty remain. The contents of this thesis contribute to summarize the available evidences on the risk factors, clinical aspects, prevention and treatment of venous thromboembolism in women, particularly when it occurs at such unusual sites as cerebral veins and sinuses. This work also contributes to the knowledge on oral contraceptive use and pregnancy as risk factors for venous thrombosis and pregnancy outcomes with or without antithrombotic prophylaxis with low molecular weight heparin.

These data further strengthen the knowledge on how the duration of oral contraceptive use influences the risk of venous thromboembolism. The period within one year of use is associated with a higher risk of venous thromboembolism in women aged less than 30 years than in those over 30, particularly in the first-time users. Additionaly, the risk of venous thromboembolism associated with the short duration of oral contraceptive use strongly interacts with the presence of thrombophilia abnormalities. The longer the use of hormonal contraception, the higher the number of transient risk factors other than oral contraceptive that act as main triggers of venous thrombosis, independently of women's age. The studies on cerebral venous thrombosis and pregnancy contribute to improve the knowledge on a poorly investigated topic, showing that women with previous cerebral vein thrombosis appear at increased risk of late obstetrical complications despite antithrombotic prophylaxis, however the risk of recurrent thrombosis and bleeding during pregnancy is low. Additionally, having had a cerebral vein thrombosis and being carrier of a thrombophilia abnormality greatly influenced the decision to terminate pregnancy. Although on one hand women with previous cerebral vein thrombosis should not be discouraged to become pregnant, on the other hand they should be informed and reassured on the possible risks. Investigating a large sample of women with the rare and severe thrombophilia abnormalities antithrombin deficiency, we observed a high risk of venous thromboembolism during pregnancy and puerperium both in those with positive and negative family history, and also an increased risk of late obstetrical complications. The efficacy of antithrombotic prophilaxis for the prevention of pregnancy-related venous thromboembolism but not obstetrical complications suggests that the causes underlying the two complications could be different. Finally, in women with or without thrombophilia abnormalities with the exception of antiphopsholipid antibodies, antithrombotic prophylaxis is effective and safe in preventing recurrent thrombosis and miscarriage in the first pregnancy after venous thrombosis, but it does not prevent late obstetrical complications.

The provided data are added to the scarce available evidence, particularly in rare settings such as pregnant women after thrombosis at unusual sites or women with severe thrombophilia at risk of pregnancy-related venous thromboembolism. All the results included in this thesis have been submitted to peer-reviewed scientific journals in the area of Thrombosis and Haemostasis, and all but one have already been published online or printed. In the absence of randomized clinical trials in the setting of rare thrombosis and pregnancy, our data provide evidence in favor of the use of low molecular weight heparin prophylaxis to lower the risk of pregnancy-related recurrent thrombosis in women with previous cerebral vein thrombosis. We would also encourage international scientific societies to share therapeutic recommendation for rare thromboses that are often neglected by the guidelines. The increased risk of recurrent thrombosis during pregnancy in women who had had a previous thrombotic event during oral contraceptive use should motivate physicians to carefully evaluate pregnant women for the thrombotic history and the risk factors present at the time of previous event. These data highlight the importance of the assessment of an individual risk profile, as well as of the treatment-associated risks and benefits (i.e. risk of placenta-mediated obstetrical complications despite antithrombotic prophylaxis in women with previous cerebral vein thrombosis or carrier of antithrombin deficiency), suggesting a personalized approach. In addition, these data underline how having experienced a thrombotic event and being carrier of a thrombophilia abnormality can negatively affect the choice to carry a pregnancy to term. This should prompt awareness on a balanced counselling for women with a personal history of thrombosis taking into account psychological aspects. Pregnancy is a complex phenomenon which includes psychological changes and could be a stressful event, particularly for women who experienced a previous pregnancy-related thrombosis. In light of these findings, the scientific and social challenge should be directed towards new preventive measures, including adequate psychological support strategy for women who might get pregnant after a thrombotic event.

First and foremost, prompt recognition investing in communication campaigns and adequate treatment, which in the near future could include direct oral anticoagulants, will allow to reduce mortality. As well, any progress in the knowledge of risk factors for venous thromboembolism will ameliorate the risk stratification and optimize preventive strategies, increasing the benefits and limiting the harms of anticoagulant therapy. Observational and epidemiological studies, like those proposed in this thesis, fit into this framework adding evidence on the management of such unusual situations as rare thrombosis and pregnancy, and increasing the awareness of the gaps of knowledge. The pathophysiology of obstetrical complications, either in women who experience a previous cerebral vein thrombosis or women with antithrombin type I deficiency, should be elucidated. If the occurrence of

obstetrical complications in these settings will be confirmed, future studies should identify those women who could benefit from antithrombotic prophylaxis without harm.

Curriculum vitae

Maria Abbattista was born on May 14th, 1988 in Foggia, Italy. She received her Bachelor's degree in Biotechnology in July 2010 at the Tor Vergata University of Rome. Then, she started her Master of Science in Molecular Biotechnology and Bioinformatics at Università degli Studi di Milano, where she graduated in 2013 with honours with an experimental thesis conducted at the Firc Institute of Molecular Oncology (IFOM-IEO campus), Milan, Italy. The curiosity for clinical research led her to persue a post-lauream Master Degree in Clinical Research in 2014 at Università degli Studi di Milano in collaboration with the Istituto di Ricerche Farmacologiche "Mario Negri". This master gave her the opportunity to start working as a clinical reaserch coordinator at Haemophilia and Thrombosis Center "A. B. Bonomi", Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, in the non-tumoral hematological therapeutic area. She also gained interest in data analysis and epidemiology having attended several courses promoted by the Hospital and the University of Milan. In 2019 she received a Research fellowship from University of Milan. She acquired knowledge and expertise in clinical research in the field of venous thrombosis, both in coordination of pharmacological studies (phase I, II and III) and in development of observational study protocols and data analysis. She also tutored students from Master in Clinical Research.

The results of her research presented in this thesis have been published in renowned international medical journals and have also been presented at various national and international conferences (posters ISTH, oral presentations SISET, best abstract – oral presentation Non-tumoral hematology congress). The review on Cerebral vein thrombosis received the mention from JTH journal of the top downloaded paper of 2019. She also received a prize for the best scientific production of the year 2020 from "Angelo Bianchi Bonomi" Foundation.

List of publications

1. **Abbattista M**, Martinelli I, Peyvandi F. Comparison of adverse drug reactions among four COVID-19 vaccines in Europe using the EudraVigilance database: Thrombosis at unusual sites. J Thromb Haemost. 2021 Oct;19(10):2554-2558
2. Ken-Dror G, Cotlarciuc I, Martinelli I, Grandone E, Hiltunen S, Lindgren E, Margaglione M, Duchez VLC, Triquenot AB, Zedde M, Mancuso M, Ruigrok YM, Marjot T, Worrall B, Majersik JJ, Metso TM, Putaala J, Haapaniemi E, Zuurbier SM, Brouwer MC, Passamonti SM, **Abbattista M**, Bucciarelli P, Mitchell BD, Kittner SJ, Lemmens R, Jern C, Pappalardo E, Costa P, Colombi M, de Sousa DA, Rodrigues S, Canhão P, Tkach A, Santacroce R, Favuzzi G, Arauz A, Colaizzo D, Spengos K, Hodge A, Ditta R, Pezzini A, Debette S, Coutinho JM, Thijs V, Jood K, Pare G, Tatlisumak T, Ferro JM, Sharma P. Genome-Wide Association Study Identifies First Locus Associated with Susceptibility to Cerebral Venous Thrombosis. Ann Neurol. 2021 Nov;90(5):777-788.
3. Capecchi M, Ciavarella A, Artoni A, **Abbattista M**, Martinelli I. Thrombotic Complications in Patients with Immune-Mediated Hemolysis. J Clin Med. 2021 Apr 18;10(8):1764.
4. Passamonti SM, Artoni A, Carrabba G, Merati G, **Abbattista M**, Capecchi M, Castellani M, Marenghi C, Trombetta E, Giammattei L, Caroli M, Bucciarelli P, Scalambrino E, Peyvandi F, Martinelli I. Plasma levels of extracellular vesicles and the risk of post-operative pulmonary embolism in patients with primary brain tumors: a prospective study. J Thromb Thrombolysis. 2021 Jul;52(1):224-231.
5. Martinelli I, Ciavarella A, **Abbattista M**, Aliberti S, De Zan V, Folli C, Panigada M, Gori A, Artoni A, Ierardi AM, Carrafiello G, Monzani V, Grasselli G, Blasi F, Peyvandi F. Increasing dosages of low-molecular-weight heparin in hospitalized patients with Covid-19. Intern Emerg Med. 2021 Aug;16(5):1223-1229.
6. **Abbattista M**, Ciavarella A, Capecchi M, Tantardini F, Gramegna A, Lombardi R, Scaramellini N, Peyvandi F, Martinelli I. Risk factors for mortality in hospitalized patients with COVID-19: a study in Milan, Italy. Infect Dis (Lond). 2021 Mar;53(3):226-229.
7. Ciavarella A, Erra R, **Abbattista M**, Iurlaro E, Boscolo-Anzoletti M, Ossola MW, Mosca F, Ferrazzi E, Peyvandi F, Martinelli I. Hemostasis in pregnant women with COVID-19. Int J Gynaecol Obstet. 2021 Feb;152(2):268-269.
8. Antonucci E, Migliaccio L, **Abbattista M**, Caronna A, De Marchi S, Di Giorgio A, Di Giulio R, Lerede T, Garzia MG, Martinelli I, Mastroiacovo D, Marzolo M, Montevecchi E, Pastori D, Pignatelli P, Poli D, Ria L, Santoliquido A, Testa S, Palareti G; START POST VTE Investigators. Treatment Decision-Making of Secondary Prevention After Venous Thromboembolism: Data From the Real-Life START2-POST-VTE Register. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620945792.
9. **Abbattista M**, Gianniello F, Novembrino C, Clerici M, Artoni A, Bucciarelli P, Capecchi M, Peyvandi F, Martinelli I. Risk of pregnancy-related venous thromboembolism and obstetrical complications in women with inherited type I antithrombin deficiency: a retrospective, single-centre, cohort study. Lancet Haematol. 2020 Apr;7(4):e320-e328.
10. **Abbattista M**, Capecchi M, Martinelli I. Treatment of unusual thrombotic manifestations. Blood. 2020 Jan 30;135(5):326-334.
11. Papareddy P, Rossnagel M, Doreen Hollwedel F, Kilic G, Veerla S, Naudin C, Smeds E, Westman J, Martinez-Martinez I, Egesten A, de la Morena-Barrio ME, Corral J, Linder A, Artoni A, **Abbattista M**, Novembrino C, Herbert Brakebusch C, Martinelli I, Kasetty G, Herwald H. A human antithrombin isoform dampens inflammatory responses and protects from organ damage during bacterial infection. Nat Microbiol. 2019 Dec;4(12):2442-2455.
12. **Abbattista M**, Capecchi M, Martinelli I. Pregnancy after cerebral venous thrombosis. Thromb Res. 2019 Sep;181 Suppl 1:S15-S18.
13. Artoni A, Bassotti A, **Abbattista M**, Marinelli B, Lecchi A, Gianniello F, Clerici M, Bucciarelli P, La Marca S, Peyvandi F, Martinelli I. Hemostatic abnormalities in patients with Ehlers-Danlos syndrome. J Thromb Haemost. 2018 Dec;16(12):2425-2431.
14. Capecchi M, **Abbattista M**, Martinelli I. Cerebral venous sinus thrombosis. J Thromb Haemost. 2018 Oct;16(10):1918-1931.
15. Martinelli I, **Abbattista M**, Bucciarelli P, Tripodi A, Artoni A, Gianniello F, Novembrino C, Peyvandi F. Recurrent thrombosis in patients with antiphospholipid antibodies treated with vitamin K antagonists or rivaroxaban. Haematologica. 2018 Jul;103(7):e315-e317.
16. Artoni A, **Abbattista M**, Bucciarelli P, Gianniello F, Scalambrino E, Pappalardo E, Peyvandi F, Martinelli I. Platelet to Lymphocyte Ratio and Neutrophil to Lymphocyte Ratio as Risk Factors for Venous Thrombosis. Clin Appl Thromb Hemost. 2018 Jul;24(5):808-814.
17. Martinelli I, Ponziani FR, Maino A, Bhoori S, **Abbattista M**, Maggi U, De Feo TM, Bucciarelli P, Artoni A, Longhi E, Serafini M, Rossi G, Mazzaferro V. Thrombosis after liver transplantation for hepatocellular carcinoma. PLoS One. 2017 Oct 26;12(10):e0186699.

18. Fasulo MR, Biguzzi E, **Abbattista M**, Stufano F, Pagliari MT, Mancini I, Gorski MM, Cannavò A, Corgiolu M, Peyvandi F, Rosendaal FR. The ISTH Bleeding Assessment Tool and the risk of future bleeding. J Thromb Haemost. 2018 Jan;16(1):125-130.
19. Martinelli I, **Abbattista M**, Somigliana E, Gianniello F, Peyvandi F. Pregnancy outcome after a first episode of cerebral vein thrombosis: reply. J Thromb Haemost. 2017 Jul;15(7):1526.
20. Maino A, **Abbattista M**, Bucciarelli P, Artoni A, Passamonti SM, Lanfranconi S, Martinelli I. Red cell distribution width and the risk of cerebral vein thrombosis: A case-control study. Eur J Intern Med. 2017 Mar;38:46-51.
21. Martinelli I, Passamonti SM, Maino A, **Abbattista M**, Bucciarelli P, Somigliana E, Artoni A, Gianniello F, Peyvandi F. Pregnancy outcome after a first episode of cerebral vein thrombosis. J Thromb Haemost. 2016 Dec;14(12):2386-2393.
22. Martinelli I, Maino A, **Abbattista M**, Bucciarelli P, Passamonti SM, Artoni A, Gianniello F, Peyvandi F. Duration of oral contraceptive use and the risk of venous thromboembolism. A case-control study. Thromb Res. 2016 May;141:153-7.
23. Bucciarelli P, Maino A, Felicetta I, **Abbattista M**, Passamonti SM, Artoni A, Martinelli I. Association between red cell distribution width and risk of venous thromboembolism. Thromb Res. 2015 Sep;136(3):590-4.

Listed as collaborator in

1. Monagle P, Lensing AWA, Thelen K, Martinelli I, Male C, Santamaría A, Samochatova E, Kumar R, Holzhauer S, Saracco P, Simioni P, Robertson J, Grangl G, Halton J, Connor P, Young G, Molinari AC, Nowak-Göttl U, Kenet G, Kapsa S, Willmann S, Pap AF, Becka M, Twomey T, Beyer-Westendorf J, Prins MH, Kubitza D; EINSTEIN-Jr Phase 2 Investigators. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies. Lancet Haematol. 2019 Oct;6(10):e500-e509. doi: 10.1016/S2352-3026(19)30161-9. Epub 2019 Aug 13. PMID: 31420317.
2. Male C, Lensing AWA, Palumbo JS, Kumar R, Nurmeev I, Hege K, Bonnet D, Connor P, Hooimeijer HL, Torres M, Chan AKC, Kenet G, Holzhauer S, Santamaría A, Amedro P, Chalmers E, Simioni P, Bhat RV, Yee DL, Lvova O, Beyer-Westendorf J, Biss TT, Martinelli I, Saracco P, Peters M, Kállay K, Gauger CA, Massicotte MP, Young G, Pap AF, Majumder M, Smith WT, Heubach JF, Berkowitz SD, Thelen K, Kubitza D, Crowther M, Prins MH, Monagle P; EINSTEIN-Jr Phase 3 Investigators. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol. 2020 Jan;7(1):e18-e27. doi: 10.1016/S2352-3026(19)30219-4. Epub 2019 Nov 5. PMID: 31699660.