Venous thromboembolism in women

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.