Long-term consequences of pregnancy-related venous thrombosis

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SUMMARY

Background: Venous thrombosis (VT) is among the leading causes of maternal mortality in countries with high standards of perinatal care; however the long-term outcomes of pregnancy-related VT are unknown.

Aims: To assess the long-term prevalence of post-thrombotic syndrome (PTS), a frequently occurring chronic complication after deep vein thrombosis (DVT), to identify possible predictors for PTS, and to evaluate disease specific quality of life (QOL) after pregnancy-related DVT compared with a control group. We also aimed to assess the mortality and incidence of cancer after VT in this population.

Materials and Methods: The Norwegian Patient Register and the Medical Birth Registry of Norway were used to identify cases of women with a first-ever pregnancy-related VT during 1990-2003 from 18 Norwegian hospitals. Women without VT matched for time of delivery were selected by the Medical Birth Registry as controls. All VTs were validated using the hospital medical records. Total 559 women with pregnancy-related VT and 1229 controls were identified and were invited to answer a comprehensive questionnaire. 313 cases and 353 controls met to participate in 2006. The questionnaire included self-reported Villalta score for the assessment of PTS and the disease specific QOL instrument VEINES-QOL/Sym. In 2012, the original study population of 1788 women was linked to the Norwegian Cause of Death Registry and the Cancer Registry of Norway.

Results: PTS was found in 42% of 204 women 3-16 years after a lower limb pregnancy-related DVT. Proximal DVT when occurring postnatal was the most important predictor for PTS. Higher age and smoking were also independently associated with PTS. Women with DVT reported reduced disease specific QOL compared to controls. Ten cases (1.8%) and 7 controls (0.6%) died during 13 years of follow-up. Mortality was 3.0 times higher among cases compared to controls (hazard ratio 3.0, 95% confidence interval 1.1-7.9, P=0.024). The mortality among cases was also 19 times higher than among the age-adjusted Norwegian female population the first year after VT (standardized mortality ratio (SMR) 18.8, 95% confidence interval 7.8-45.3), but thereafter the mortality was similar (SMR 0.9, 95% confidence interval 0.4-2.0). Fifteen cases (2.7%) and 13 controls (1.1%) were diagnosed with cancer after index pregnancy and subsequent cancer was 2.5 times more frequent among cases (hazard ratio 2.5, 95% confidence interval 1.2-5.2, P=0.017). Cases did not have higher incidence of cancer when comparing with the age-

and sex-adjusted general population (standardized incidence ratio 1.0, 95% confidence interval 0.6-1.7).

Conclusions: PTS was a common long-term complication after pregnancy-related DVT affecting almost half of the women and disease specific QOL in this population was reduced compared to a control group. Cases had significantly higher mortality and incidence of cancer than controls during 13 years of follow-up. When comparing with the age-adjusted Norwegian female population, mortality was increased only the first year after VT and incidence of cancer was similar.

ABBREVIATIONS

ACCP	American College of Chest Physician
BMI	Body mass index (kg/m2)
CaVenT study	Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis study
CDT	Catheter-directed thrombolysis
CI	Confidence interval
COC	Combined oral contraceptives
CTEPH	Chronic thromboembolic pulmonary hypertension
DVT	Deep vein thrombosis
ECS	Elastic compression stockings
HR(QOL)	(Health-related) quality of life
HUNT study	Helseundersøkelsen i Nord-Trøndelag (The Nord-Trøndelag health study)
INR	International normalized ratio
ISTH	International Society of Thrombosis and Haemostasis
LMWH	Low molecular weight heparin
NOAC	New oral anticoagulants
OR	Odds ratio
PE	Pulmonary embolism
PRO	Patient reported outcome
PTS	Post-thrombotic syndrome
SD	Standard deviation
SF-36	Short form 36 (a generic quality of life questionnaire)
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
VEINES	The VEnous INsufficiency Epidemiological and economic Study
VKA	Vitamin K antagonists
VIP study	Venous thrombembolism In Pregnancy study
VT	Venous thrombosis
WHO	World Health Organization

LIST OF PAPERS

The thesis is based on the following papers, referred to in the text by their Roman numerals:

PAPER I

Wik HS, Jacobsen AF, Sandvik L, Sandset PM.

Prevalence and predictors for post-thrombotic syndrome three to 16 years after pregnancy-related venous thrombosis: a population-based, cross-sectional, case-control study.

Journal of Thrombosis and Haemostasis 2012 May; **10**:840-7.

PAPER II

Wik HS, Enden TR, Jacobsen AF, Sandset PM.

Long-term quality of life after pregnancy-related deep vein thrombosis and the influence of socioeconomic factors and comorbidity.

Journal of Thrombosis and Haemostasis 2011; **9**: 1931–6.

PAPER III

Wik HS, Jacobsen AF, Fagerland MW, Sandvik L, Sandset PM.

Long-term mortality and incidence of cancer after pregnancy-related venous thrombosis: results of a population-based cohort study.

Submitted for publication.

1. INTRODUCTION

Venous thrombosis (VT) is an abnormal blood clot that forms within a vein and may obstruct normal flow of venous blood and destruct vein valves. The blood clot or fragments of the clot can break off and follow the blood stream to the pulmonary circulation, which is commonly known as pulmonary embolism (PE) and which is sometimes fatal. Approximately two-thirds of symptomatic VTs present as deep vein thrombosis (DVT) in the lower limbs and one-third as PE, most often thought to originate from the lower limbs, including about 5% presenting with a concurrent DVT.[1–3] Occasionally VT occur in other veins, such as the veins of the upper limbs, mesenterial veins, or cerebral sinus veins. The risk of VT during pregnancy is approximately 10-fold the risk of non-pregnant women of the same age.[4] Despite increasing awareness and prophylactic measures, VT continues to be one of the leading causes of maternal mortality in countries with high standards of perinatal care,[5] but little is known about the long-term outcomes after pregnancy-related VT and this is the main topic of this thesis.

1.1. EPIDEMIOLOGY AND RISK FACTORS OF VENOUS THROMBOSIS

VT is a multifactorial disorder that arises as a result of genetic and environmental factors that interact. In the Norwegian HUNT 2 study, that included residents of the Nord-Trøndelag county aged 20 years and older, a triggering factor could not be identified in about 50% of the cases (commonly called idiopathic VT). Active cancer and recent surgery were the most important triggering factors for VT in this study, together with immobilization, trauma, pregnancy, puerperium, and the use of combined oral contraceptives (COCs).[3] These findings were in general in line with results from other studies.[6–8] Patients often have more than one triggering factor for VT.[7,9] The incidence of VT in Western countries is approximately 1 per 1000 individuals per year and increases with age.[3,10,11] VT occurs as often in men as in women, but women are overrepresented among patients younger than 45 years.[1,3,10] This is probably due to the risk associated with pregnancy and the use of COCs containing estrogen, both well known risk factors for VT among fertile women. COCs increase the risk of VT about 2-6 fold compared to non-users.[12–14] The natural history of untreated symptomatic VT is not well-known, but the randomized trial by Barritt and Jordan in 1960 showed that approximately 50% of the patients with PE who did not receive anticoagulation therapy had recurrence and half of these were fatal.[15]

1.2. TREATMENT OF VENOUS THROMBOSIS

Unfractionated heparin was first introduced as treatment for VT in 1938, becoming standard therapy along with the use of oral vitamin K antagonists (VKA) during the 1960s.[16] All anticoagulants can potentially cause severe bleedings (see section "1.5.3.3. Bleeding"). Unfractionated heparin must been given parenterally. Both unfractionated heparin and VKA require regular laboratory monitoring of the anticoagulant effect. VKAs have numerous of food and drug interactions and a narrow range for safety and effectiveness. Studies on low molecular weight heparin (LMWH) were conducted from the early 1980s[17] and LMWH was introduced in Norway in the late 1980s. As LMWH can be given as body weight adjusted fixed doses without any need for monitoring, treatment of VT can be given outside hospital.[16] Recently, oral direct inhibitors of either thrombin or factor Xa have been developed. These new oral anticoagulants (NOAC) can be given in fixed doses independent of body weight and essentially without need for monitoring.[18] After proximal DVT elastic compression stockings (ECS) may reduce the incidence of the frequently occurring chronic complication post-thrombotic syndrome (PTS).[19] Recently catheter-directed thrombolytic therapy (CDT) for proximal DVT was reported to reduce the frequency of PTS.[20]

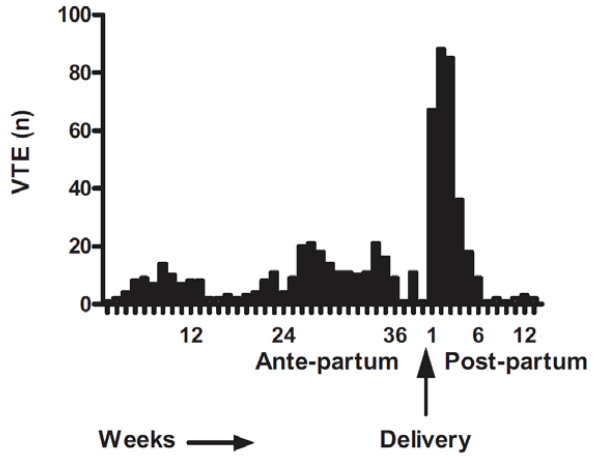
According to the current American College of Chest Physician's (ACCP) guidelines (9th edition 2012), an acute DVT or PE should be treated initially with subcutaneous LMWH for minimum five days in combination with oral VKA. LMWH can be discontinued when the international normalized ratio (INR) has been in the therapeutic range (2.0-3.0) for at least 24 hours. Minimum duration of anticoagulation is three months. Therapy can be extended if the risk of recurrence is high (see section "1.5.3.2. Recurrent venous thrombosis"), but bleeding risk and preference of the patient should be taken into account. The rationale for treatment of VT is prevention of thrombus extension and embolization. Daily use of ECS on the affected limb is recommended for two years after a proximal DVT.[21]

1.3. PREGNANCY-RELATED VENOUS THROMBOSIS

In countries with good perinatal care VT occurs in approximately 1 woman per 1000 pregnancies.[22–25] The risk of VT seems to be about equally distributed between the antenatal and postnatal period and is increased in all three trimesters.[23,25–27] The risk of

postnatal VT is very high during the first weeks after delivery and then rapidly declines (Fig.1).

Fig.1 Numbers of VT per week during and early after pregnancy



From Jacobsen et al.[25] (with permission)

DVT in lower limbs is the dominant presentation of VT during pregnancy, but the relative frequency of PE increases after delivery.[25,28] During pregnancy, 80-90% of the DVTs affect the left lower limb.[29,30] This might be explained by compression of the left common iliac vein by the growing uterus at the point where it is crossed by the right common iliac artery. Moreover, DVTs occurring during pregnancy predominantly affect the ileofemoral veins rather than the calf- and popliteal veins.[25,26,30] Pregnancy induces major changes in the hemostatic system in a pro-thrombotic direction, an adaption that is likely to have developed to provide efficient hemostasis and to protect the pregnant woman from serious bleeding during delivery. Pregnancy may be considered a hypercoagulable state because of the increased levels of clotting factors (such as factors II, VII, VIII, IX, and XI) and reduction of natural anticoagulants (protein S).[31,32] After delivery coagulation rapidly normalizes during the first postnatal weeks.[33] In addition, pregnancy induces venous stasis that predisposes to VT; compression from the enlarged uterus reduces venous blood flow from the lower limbs and hormonal changes induce venous dilatation.[34,35] Endothelial damage in the pelvic blood vessels may occur during vaginal delivery or Cesarean section and may contribute to the increased postnatal risk of VT.[36] Table 1 summarizes clinical risk factors that may predispose to VT in pregnancy.[23,26,37,38]

Table 1 Risk factors for pregnancy-related VT (modified from [25,39])

Risk factor	Adjusted odds ratio* (95% CI)
Antenatal VT	
Assisted reproductive technology	4.3 (2.0-9.4)
Spontaneous twins	2.6 (1.1-6.2)
Weight gain <7.0 kg	1.7 (1.1-2.6)
Pre-pregnancy BMI ≥25 kg/m^2 – no immobilization	1.8 (1.3-2.4)
Pre-pregnancy BMI <25 kg/m^2 – combined with strict immobilization**	7.7 (3.2-19.0)
Pre-pregnancy BMI ≥25 kg/m^2 – combined with strict immobilization**	62.3 (11.5-337)
Smoking (10-30 cigarettes/day prior to or during pregnancy)	2.1 (1.3-3.4)
Postnatal VT	
Non-emergency Cesarean section	1.3 (0.7-1.2)
Emergency Cesarean section	2.7 (1.8-4.1)
Vaginal delivery complicated with postnatal infection***	20.2 (6.4-63.5)
Cesarean section complicated with postnatal infection***	6.2 (2.4-16.2)
Pre-pregnancy BMI <25 kg/m^2 – no immobilization	2.4 (1.7-3.3)
Pre-pregnancy BMI <25 kg/m^2 – combined with strict immobilization**	10.8 (4.0-28.8)
Pre-pregnancy BMI ≥25 kg/m^2 – combined with strict immobilization**	40.1 (8.0-28.8)
Postpartum haemorrhage ≥1000 mL – no surgery£	4.1 (2.3-7.3)
Postpartum haemorrhage ≥1000 mL – surgery£	12.0 (3.9-36.9)
Intrauterine foetal growth restriction	3.8 (1.4-10.2)
Preeclampsia	3.1 (1.8-5.3)
Smoking (10-30 cigarettes/day prior to or during pregnancy)	3.4 (2.0-5.5)

*Adjusted for age, parity, smoking, weight gain, preeclampsia, foetal growth restriction, gestational diabetes, premature rupture of membranes, body mass index (BMI), immobilization, multiple pregnancy, method of conception, mode of delivery, postnatal infection, bleeding and surgery; **immobilization = strict bed-rest ≥1 week antenatal; ***postnatal infection = clinical symptoms/signs + fever + elevated WBC; £surgery = curettage, evacuation of haematoma, or re-operation after Cesarean. Adapted from Jacobsen et al. (with permission)[40]

1.4. TREATMENT OF PREGNANCY-RELATED VENOUS THROMBOSIS

According to the ACCP-guidelines, LMWH is recommended for the prevention and treatment of VT in pregnant women because LMWH does not pass the placenta and is safe for the fetus. In opposite, VKAs cross the placenta and have the potential to cause fetal bleeding and teratogenicity.[41] The use of VKA or LMWH in postnatal women who are breastfeeding is safe.[42] For women with acute VT during pregnancy, the minimum recommended duration of anticoagulant therapy is three months and should be continued for at least 6 weeks after delivery.[43] Randomized controlled trials are mainly lacking as background for recommendations of treatment and prophylaxis for pregnancy-related VT. Guidelines are to a large extent based upon results from observational studies, indirect evidence from other populations and expert opinions. There is an urgent need for randomized controlled trials in different pregnancy-related settings to give better advices to these women.

1.5. LONG-TERM COMPLICATIONS AFTER VENOUS THROMBOSIS

1.5.1. POST-THROMBOTIC SYNDROME

The post-thrombotic syndrome (PTS) is a common chronic complication after DVT in the lower limbs. PTS is a clinical condition that comprises various degrees of pain, swelling, skin changes, varicose veins and sometimes overt ulcers in the limb previously affected by a DVT. PTS is associated with reduced QOL[44] and considerable costs for the society.[45] Any degree of PTS occurs in 20-50% of patients after a DVT, whereas severe PTS occurs in 5-10%.[46,47] Symptoms are aggravated when the patient is standing or walking and improves when the limb is elevated. The clinical picture of PTS is non-specific and patients without a history of DVT in the actual limb can experience similar complaints after other diseases or trauma affecting the lower limbs. However, such chronic symptoms and signs in a patient with a previous objectively confirmed lower limb DVT are most likely due to PTS. Not to be forgotten, these patients are also at increased risk for recurrent DVT, and this must be ruled out if the symptoms and signs are acute and do not improve after rest.[48] Regarding PTS following a pregnancy-related DVT, see section "1.5.1.7. Post-thrombotic syndrome after pregnancy-related DVT."

1.5.1.1. HISTORY OF POST-THROMBOTIC SYNDROME

The American surgeon John Homans was probably the first to describe what was previously known as the postphlebitic syndrome in 1917; "symptoms of swelling, ulceration, and pain which followed extensive thrombosis in the deep veins of the lower limbs".[49] In contrast to the extensive documentation from clinical studies on local extension of DVT, embolization, and recurrent VT during the first months after an acute episode, the frequent long-term complication PTS has over the years received little attention from researchers, and among the numerous large trials that have evaluated the efficacy of various antithrombotic treatments for DVT, none have evaluated PTS as a pre-specified or primary endpoint. This might be explained by the lack of a commonly accepted definition of PTS and that studies of PTS require longer follow-up.

1.5.1.2. PATOPHYSIOLOGY OF POST-THROMBOTIC SYNDROME

The patophysiologic mechanisms leading to PTS is not completely understood. It is suggested that persistent obstruction to blood flow caused by residual thrombosis and the development of venous valve incompetence due to activation of inflammation or scarring associated with the acute and resolving thrombus lead to ambulatory venous hypertension. Persistent venous hypertension may result in pain, swelling, hyperpigmentation and venous ulcers, i.e., the symptoms and signs of PTS.[48] Nevertheless, patients with persistent vein abnormalities do not necessarily develop PTS and vein abnormalities and venous dysfunction is not always detected in a patient with PTS.[50–52]

1.5.1.3. DIAGNOSIS OF POST-THROMBOTIC SYNDROME

There is so far no single objective test to diagnose the presence of PTS, and it is usually diagnosed on the basis of typical symptoms and signs in a limb previously affected by DVT.[53] Many different definitions have been used, and to a great extent this is likely to explain the differences in reported prevalence across studies. The Villalta score, the CEAP (clinical, etiologic, anatomic, pathophysiologic) classification, and the Ginsberg measure have all been used to diagnose PTS as summarized in Table 2. In 2005, Kolbach et al compared different classifications of PTS. The Villalta score, the CEAP-classification, the Ginsberg measure, and 3 other scoring systems were compared among 124 patients with objectively confirmed DVT 3-9 years earlier. The presence of any PTS in DVT limbs varied from 30% to 66% between the different scoring systems and the

ability to discriminate between DVT and controls limbs differed substantially.[54] The Ginsberg measure and the Villalta scale were also compared by Kahn et al; one year after an objectively diagnosed DVT, 37% of the patients had PTS according to the Villalta scale, but only 8.1% according to the Ginsberg measurement, and poor agreement was found between the two scores.[55] The symptoms and signs for PTS may resemble those for acute and sub-acute DVT, and there is no consensus for the optimal time to diagnose PTS. In some studies the prevalence of PTS increased gradually from the first months to several years after the diagnosis of DVT,[19,20,56] but in other studies the prevalence did not increase after the first 4-6 months.[46,51,57] In a randomized controlled trial from our research group on the efficacy and safety of additional CDT in patients with high femoral and/or iliac vein DVT (the CaVenT study), the prevalence of PTS assessed by Villalta score after 24 months was 56% in the patients who had received conventional anticoagulant treatment compared to 41% in those getting additional CDT. In this study, no differences in PTS could be detected between the two groups after 6 months (32% versus 30%, P=0.77).[20] In recent studies PTS has often been assessed only once from 4 months to 2 years after an acute DVT in a lower limb.[20,58,59]

1.5.1.3.1. THE VILLALTA SCORE

In 2008, the Control of Anticoagulation Subcommittee of International Society on Thrombosis and Haemostasis (ISTH) recommended use of the Villalta score (Table 3) to standardize the diagnosis and grading of PTS in clinical studies.[53] This is hopefully a step towards improved reporting in studies on DVT outcomes. According to this score the patient grades the presence and severity of 5 symptoms (0-3 points) and the physician/nurse grades 6 clinical signs after examination of the lower limb (0-3 points). The presence of a venous ulcer automatically grades PTS to the severe category. The Villalta score has now been widely used by various groups in clinical studies.[19,20,46,60–62]

Arguments for using the Villalta score as the standard measure of PTS in clinical studies were that both subjective symptoms and physical signs of PTS are included and rated, the measurement has been shown to be valid, responsive to clinical change, and acceptable for users, it can be reproduced between different raters, and the score can be used to sub-classify PTS; PTS/no PTS, no/mild/moderate/severe PTS, or as a continuous outcome.[53]

Table 2 Diagnostic instruments for post-thrombotic syndrome

PTS instrument	Criteria	Made for PTS	Rates PTS
Villalta 1994[63]	5 symptoms 6 clinical signs (see Table 3)	Yes	Yes
CEAP 1995[64,65]	7 clinical classes according to clinical signs (0-6)* Each clinical class subclassified according to Etiology (congenital, primary, secondary) Anatomy (superficial, deep, perforator veins) Pathophysiology (reflux, obstruction, both)	No#	No
Ginsberg[66,67] **2000&2001**	Pain and swelling (made worse by standing/walking and relieved by rest/elevation of the leg) of ≥ 1 month duration and ≥ 6 months after DVT and Valvular incompetence (pletysmography/Doppler) Global rating questionnaire – assess changes over time	Yes	No

C0: No visible or palpable signs of venous disease; C1: Telangiectasies or reticular veins;
C2: Varicose veins; distinguished from reticular veins by a diameter of 3mm or more; C3:Edema;
C4: Changes in skin and subcutaneous tissue secondary to chronic venous disease
(C4a: Pigmentation or eczema or C4b: Lipodermatosclerosis or atrophie blanche);
C5: Healed venous ulcer; C6:Active venous ulcer;
* Many studies have utilized only the clinical part of the CEAP classification[68,69]
# tool for categorization of the whole spectrum of chronic venous diseases including complication after DVT (PTS).

Table 3 The Villalta score

Symptoms	Clinical signs
Pain	Pretibial oedema
Cramps	Skin induration
	Hyper-pigmentation
Heaviness	Redness
Paresthesia	Venous ectasia
	Pain on calf compression
Itching	

All symptoms and signs are scored from zero (absent) to three (severe) and summarized to produce a total score ranging from zero to 33. A total score of ≥5 points corresponds to any grade of PTS, 5-14 points to mild/moderate PTS, and ≥15 points or the presence of a venous ulcer to severe PTS. A score <5 indicates no PTS. Adapted from Villalta S et al.[63]

1.5.1.4. PREDICTORS FOR POST-THROMBOTIC SYNDROME

Defining the risk factors for PTS is an area of ongoing research. Several factors have consistently been shown to be associated with PTS in clinical studies, while others results are conflicting or remain to be confirmed (Table 4).

Table 4 Predictors for PTS

Established predictors	• Recurrent ipsilateral DVT[46,56,61,70] • Iliofemoral DVT[46,47,71,72] • Obesity[46,47,61,73]
Possible predictors	• Poor quality of oral anticoagulation with VKA (INR <2.0 the more than 50% of the time) the first months after DVT[61,74] • Inflammatory- and coagulation markers (interleukin-6, intercellular adhesion molecule-1, CRP, D-dimer)[58,69,70,75,76] • Persistent symptoms one month after DVT[46] • Age and sex (conflicting results)[46,47,51,71] • Residual obstruction and/or valvular reflux (conflicting results)[50–52,72] • Level of exercise after VT[77,78]

1.5.1.5. HOW TO PREVENT POST-THROMBOTIC SYNDROME

As PTS is a complication of DVT in a lower limb, the best way to reduce its frequency is to prevent DVT. It is well known that there is room for improvement in adherence to current guidelines regarding primary prophylaxis for hospitalized patients at risk for VT.[21,79,80] Unfortunately, about 50% of all VTs are unprovoked, i.e., no triggering factor can be identified, and hence they are not easily avoided. As a recurrent ipsilateral DVT is associated with PTS, it is likely that better secondary prophylaxis to reduce recurrence also will reduce the frequency of PTS, but prolonging treatment with VKA from six weeks to six months did not reduce prevalence of PTS the next 10 years in a randomized Swedish study.[81]

Two randomized controlled trials have shown that use of elastic compression stockings (ECS) reduces the risk of PTS by approximately 50% after a proximal DVT.[19,82] In both trials, knee-high ECS class II with compression at ankle level of 30-40 mmHg was worn daily for two years. These studies were not blinded and did not include placebo stockings. A third study reported no difference in frequency of PTS between patients that used ECS 20-30 mmHg and those using placebo stockings, but in this study the use of ECS was started not earlier than one year after proximal DVT.[67] One recent study found that below-knee ECS is as efficient as thigh-length ECS, and that thigh-length ECS is less well tolerated.[83] The Canadian SOX-trial, a multicenter, randomized, double-blind trial that compares two years wear of knee-length ECS against placebo stockings, have included 803 patients, but the final results are still pending. Primary outcome is prevalence of PTS after two years.[58]

Early removal of the thrombus is hypothesized to prevent valvular damage and thus prevent development to venous incompetence and PTS in patients with iliofemoral DVT. In the CaVenT study (see section "1.5.1.3 Diagnosis of PTS"), 209 patients were randomly assigned to conventional treatment with LMWH and VKA alone or conventional therapy with additional CDT with alteplase.[20] After two years of follow-up, 56% of the patients in the control group compared to 41% of patients allocated additional CDT presented with PTS (P=0.047). The difference in PTS corresponded to an absolute risk reduction of 15%, but CDT gave also a small additional risk of bleeding compared to the control group. Although additional studies regarding the role of CDT for the prevention of PTS are needed and currently ongoing,[84] CDT should be considered in patients with a high proximal DVT and low risk of bleeding.[20]

There is weak evidence suggesting that treatment with LMWH instead of VKA the first months after the acute VT can reduce the frequency of PTS, but studies with longer follow-up and validated assessment of PTS are needed for confirmation.[85] Poor quality of VKA treatment the first months after an acute DVT seems to be associated with PTS.[61,74] As NOAC have been shown to be at least as effective as VKA in preventing recurrence of VT,[86,87] NOAC or LMWH may improve quality of anticoagulation and hence perhaps reduce frequency of PTS.[88,89]

1.5.1.6. TREATMENT OF POST-THROMBOTIC SYNDROME

Currently, there is no identified curative treatment for PTS. ECSs are often recommended for symptom relief, but its benefit is not documented.[67] In patients with severe PTS with complaints not relieved by ECS an intermittent compression device can be tried, but neither this is well documented.[62] Venoactive medications (e.g. rutosides, defibrotide, and hidrosmin) are not recommended according to the current ACCP guidelines; the evidence for these compounds being limited and of low quality.[21,90] Surgery is sometimes chosen as a therapeutic approach in moderate and severe PTS when symptoms are not relieved by ECS, but randomized controlled trials are lacking and evidence of success of surgery is scarce.[91]

1.5.1.7. PTS AFTER PREGNANCY-RELATED DVT

We are not aware of more than four studies that have assessed the risk of PTS or persistent symptoms of the lower limb after a pregnancy-related DVT. These studies have included a limited number of patients and have employed different diagnostic tools for the diagnosis of PTS.[92–95] These studies are all from Sweden and are summarized in Table 5. Two additional studies have evaluated PTS in young women, but in these studies very few of the participants had DVT related to pregnancy.[96,97]

1.5.2. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a long-term complication that may develop after acute PE and is caused by incomplete resolution of the PE. CTEPH is defined by a mean pulmonary artery pressure ≥25 mmHg at rest and a left ventricular end-diastolic pressure <15 mmHg, both measured invasively while undergoing right heart catheterization. In addition multiple chronic occlusive thrombi/emboli that persist in the elastic pulmonary arteries after at least three months on effective anticoagulation have to be present to distinguish CTEPH from other forms of pulmonary hypertension.[98,99] More recent studies suggest that the prevalence of CTEPH is up to 4-5% in survivors of a first episode of acute PE and that this complication occurs within the first one or two years after the event.[100,101]

Table 5 Studies addressing lower limb complaints and PTS after pregnancy-related DVT

Year, first author	Population	Methods	Results
A.Lindhagen, 1986[92]	23/31 objectively diagnosed DVT during pregnancy/first week after delivery. Mean follow-up 7 years.	Clinical deep venous insufficiency: venous leg ulcer after DVT and/or at least 2 symptoms or signs of venous insufficiency (swelling, discoloration, crural eczema, nightly cramps, or need for constant compression therapy).	• 35% had clinical deep venous insufficiency in a post-DVT limbs versus 0% in non-DVT limb • 2 DVT-limbs had a venous ulcer
A.Bergqvist, 1990[93]	104 DVT from previous Swedish studies, 62/69 antenatal and 33/35 postnatal. 6% had previous VT. Median 11 years follow-up.	Questionnaire sent by post. No PTS scoring system was used.	• 21% with antenatal and 30% of postnatal DVT had no complaints from affected lower limb. • No significant differences in symptoms • Leg ulceration in 4% of total, all antenatal.
S.Törngren, 1996[94]	30/37 pregnancy-related iliofemoral DVT treated with thrombectomy and 25/37 comparable controls. Mean follow-up 9 years. Not a RCT.	Clinical examination for leg symptoms and signs. No PTS scoring system was used.	• No symptoms in 53% (surgery) versus 44% (no surgery). • Relatively mild symptoms in both groups • Surgical thrombectomy not beneficial.

S.Rosfors, 2001[95]	25/37 conservatively treated DVT (part of the 9 year follow-up in the study above). 18 antenatal/7 postnatal. Mean follow-up 16 years.	CEAP-classification (0-6).	• 52% CEAP 0 (no signs of venous disease) • Relatively mild symptoms • 16% were symptomatic, but undertaking full daily activity with stockings. • No progression of venous symptoms from 9 to 16 years of follow-up.

1.5.3. OTHER LONG-TERM CONSEQUENCES AFTER VENOUS THROMBOSIS

1.5.3.1. MORTALITY

Data on mortality after VT are in general limited and estimates vary considerably. This can be explained by different populations in the studies, including selected age groups and various comorbidity; in particular cancer and cardiovascular diseases. Most studies do not include cases of VT diagnosed post mortem, but if VT diagnosed by autopsy was included, the mortality rates would be influenced by the various autopsy rates in different countries. All these factors make it difficult to compare mortality between studies. In the Norwegian HUNT 2 study, the overall 30-days and one year case-fatality rate (the number of deaths from any cause after the event/the number of first VT events) after a first objectively verified VT in the total population in this area was 6.4% and 21.6%, respectively. The risk of dying was highest during the first months, after which it gradually approached the mortality in the general population.[3] Cancer was the most frequent cause of death in this study, and that is in line with other studies.[7,102] The mortality also seems to be increased in populations without cancer.[3,103] Other data on 30-days and one year case fatality rates vary from 10-30% [7,104] and 20-40%,[103–105] respectively. In a study of young Austrian women VT did not reduce long-term survival after the initial phase.[106] It is currently not known whether the increased mortality after VT is limited to the first months after VT,[3] or persists for extended periods.[103,104] Pregnancy-related VT accounts for about 0.5-1.2 deaths per 100000 deliveries and the majority of these deaths are caused by PE and occur postpartum.[25,26,107] We are not aware of studies reporting on the 30-days case-fatality rate and long-term mortality after pregnancy-related VT.

1.5.3.2. RECURRENT VENOUS THROMBOSIS

10-30% of patients with first-time VT develop a recurrent episode within the first 5 years after discontinuing oral anticoagulation.[108–110] The recurrence rate may be as high as 40% after 10 years.[81] Patients with idiopathic VT or cancer related VT are at increased risk.[102,108,109] Patients with VT precipitated by surgery have a low risk for recurrence, thrombophilia do not seem to predict recurrence, while male gender seems to increase the recurrence risk.[102,108,109,111–113] The risk of recurrence after an episode of pregnancy-related VT is not known. In women with a previous VT the risk of a pregnancy-related recurrence is substantial during the whole pregnancy unless prophylaxis is used.[114]

1.5.3.3. BLEEDING

Bleeding is an inherent complication associated with any anticoagulant treatment, especially at the start of treatment.[115] After the first three to six months of treatment, long-term anticoagulation with VKA targeted to INR 2.0-3.0 is associated with major bleedings of approximately 2% per year in patients with previous VT. About 10% of these major bleedings are fatal. Age >75 years, concomitant antiplatelet therapy, and previous bleeding are among the risk factors for bleeding on anticoagulation therapy.[116–118] The duration of anticoagulation treatment after VT should be a balance of the risk of recurrent VT with and without treatment, and the risk of treatment induced bleeding.[116]

1.5.3.4. CANCER

Patients with an episode of acute VT have a two to three times increased risk to develop cancer, particularly during the first year after the VT. The increased risk is similar for cases with DVT and PE. The association between VT and cancer is particularly strong for primary cancers of the pancreas, ovaries and liver, in patients less than 60 years of age and those having recurrent VT.[119–122] It is not known if the increased risk for cancer the first year after VT also applies to women who have experienced pregnancy-related VT.

1.5.3.5. CARDIOVASCULAR DISEASE

Patients with unprovoked VT are at higher risk for subsequent arterial cardiovascular disorders as compared to those with provoked VT and controls.[123] The risk is highest the first year after the VT, but seems to persist for many years.[124] The association between venous and arterial diseases could be explained by common risk factors, but results are diverging.[125,126]

1.6. QUALITY OF LIFE

In 1948 the World Health Organization (WHO) defined health to include physical, emotional, and social well-being in addition to absence of disease.[127] Over the past decades the patient's point of view has been recognized as increasingly important in clinical studies in addition to clinical and laboratory indicators of illness, especially in patients with cancer and chronic disorders.[128,129]

A major problem in quality of life (QOL) research is the lack of a commonly accepted definition of QOL. WHO has not changed their definition of health since 1948. Many other definitions of health and QOL have been proposed, emphasizing components as happiness and satisfaction with life. Obviously, QOL means different things for different people. In health research we are often not interested in QOL in the broad sense, but only those aspects relevant for disease and treatment. To distinguish this from QOL in general, many investigators use the term health-related quality of life (HRQOL). Others prefer to use the term patient-reported outcomes (PROs).[130,131] A PRO is any report coming directly from patients, without interpretation by physicians or relatives.[132] It is generally accepted that QOL should be self-reported, multidimensional, and include at least three domains; physical, physiological, and social functioning. An overall question regarding general health or QOL should also be included.[133] Non-patient based assessments, e.g., by proxy or health care personnel, are documented to be poor estimates of individual patients' QOL.[134,135] In the absence of any formal definition of QOL, all investigators should describe what they mean by QOL. Some questionnaires focus more on physical symptoms, and others more on the impact of the symptoms on psychological aspects or satisfaction with life. To be clinically useful, all QOL questionnaires should satisfy the basic psychometric properties validity, reliability, sensitivity, and responsiveness. These properties are defined in Table 6. Most QOL questionnaires used in Norway are translated from English, and translations should adhere to suggested guidelines.[131]

Table 6 Definitions of psychometric properties of QOL questionnaires[131]

• **Validity**	The QOL questionnaire measures what it is intended to measure and that it is useful for its intended purpose - Internal: the results are correct for the particular group of people being studied - External: generalizability
• **Reliability**	The ability to yield the same score each time a measure is administered
• **Sensitivity**	The ability to detect differences between patients or groups of patients
• **Responsiveness**	The ability of a measure to reflect underlying change when a patient improves or deteriorates

1.6.1. QUALITY OF LIFE AFTER VENOUS THROMBOSIS

Generic QOL questionnaires can be used across diseases and treatment groups and also among healthy individuals, and they enable comparison between different patient groups and the general population. The Short Form (SF)-36 is the most commonly used generic QOL questionnaire and normative data from the general population in many countries are available.[136,137] Generic QOL questionnaires may not detect clinically important problems in a specific population with a chronic disease, e.g. chronic venous disease after DVT in a lower limb. Different disease-specific QOL questionnaires, which focus on a particular condition or disease, have been developed to capture aspects closely related to the disease of interest. Disease specific questionnaires are regarded as more sensitive than generic questionnaires to detect clinical relevant outcomes in the patient population of interest.[138] Several disease specific instruments have been developed and validated for the use in DVT patients.[44,68,139–148] One disease specific questionnaire has been developed for the assessment of QOL after PE.[149]

Long-term QOL after DVT and PE have been shown to be reduced compared to population norms when using SF-36 as a generic QOL questionnaire.[143,150] Beyth et al. found that symptoms in the affected leg six to eight years after the acute DVT compared to no symptoms was associated with worse QOL when using 19 items from SF-36.[139] PTS is an important predictor for reduced QOL and patients with severe PTS seems to have worse QOL than those with mild to moderate PTS.[44,142,147] One study found that PTS had a negative impact on QOL when assessed by the disease specific questionnaire VEINES-QOL/Sym, but not by SF-36.[142] In another study QOL was found to be poorer among patients with prior VT compared to patients having other forms of chronic venous disease.[145]

2. AIMS

Long-term outcomes after pregnancy-related VT are not known. The aims of the current thesis were:

- To assess the prevalence of PTS 3-16 years after a first-time pregnancy-related DVT of the lower limb and to identify possible predictors for PTS in this population.

- To evaluate long-term disease specific QOL after pregnancy-related DVT and to identify socioeconomic factors or comorbidity as predictors of reduced QOL.

- To assess short- and long-term mortality and incidence of cancer after pregnancy-related DVT.

3. MATERIALS AND METHODS

This thesis is a sub-study of the Venous thromboembolism In Pregnancy (VIP) study, which is a large epidemiological study on clinical, biochemical, and genetic risk factors of pregnancy-related VT.[25] The VIP study started in 2004 and one thesis on clinical and epidemiological risk factors and one on intrauterine fetal death have been completed.[151,152] In addition to the present project two more PhD projects are ongoing focusing on biological risk markers of VT and on QOL after intrauterine fetal death. Data from questionnaires completed in 2006 by a selection of cases and controls participating in the original VIP study was used in papers I and II. The original study population (both cases and controls) from the VIP study was linked to the Norwegian Cause of Death Registry and the Cancer Registry of Norway in paper III. I became involved in the project from September 2009, and hence was not involved in the design of the study or in the collection of the main data, but was responsible for linking the registries in 2012.

3.1. STUDY POPULATION

3.1.1. IDENTIFICATION OF CASES

For the VIP study the Norwegian Patient Register retrospectively identified women with a first-time VT (i.e. DVT, PE, or DVT in other veins) during pregnancy or within the first 12 weeks postpartum in 11 out of 19 counties (18 hospitals) in Norway during 1990 through 2003 using selected ICD 8, ICD 9 or ICD 10 codes. The ICD codes used for the identification of cases is presented in Table 7.[25] Additionally, women aged 16-50 years with a VT diagnosis in the registry without simultaneously having a registered ICD code corresponding to pregnancy was cross-checked for pregnancy-related discharge codes 9-12 months before and after the VT code. The latter search identified some extra patients because pregnancy-related codes are not always added to the VT code when these women are discharged from hospital.

The source population comprised 377155 women with 613232 pregnancies during the study period. Additional cases were identified at three major Norwegian university hospitals (Ullevål in Oslo, Haukeland in Bergen, and St.Olavs in Trondheim) using the Medical Birth Registry of Norway. These three hospitals counted for 32% of the deliveries in the VIP study. In the Medical Birth Registry only antenatal cases were registered, and 3% of the cases were exclusively identified in this registry. The Medical

Birth Registry was not used to identify additional cases outside the three mentioned hospitals. One physician reviewed all medical records at the treating institutions and validated each case as a pregnancy-related first-time VT. Cases with questionable findings were reviewed by an experienced hematologist. DVT was diagnosed according to standard local operating procedures using compression or color Doppler ultrasonography or venography, whereas PE was diagnosed using high probability perfusion lung scanning, spiral computed tomography, magnetic resonance imaging, or pulmonary angiography.[25,39] Cases with VT associated with miscarriage, induced abortion, or ectopic pregnancy terminated before gestational week 23 were excluded from the study. Clinical diagnoses with no confirmatory test or with undetermined results were not included. More than 50% of cases with VT indentified through the two registries could not be included in the study because of invalid diagnosis of VT (Figure 2). The reasons for an invalid VT diagnosis were mainly a previous diagnosis of VT (not an acute event in the actual pregnancy) or referral to hospital with a suspected VT which was not confirmed.

3.1.2. IDENTIFICATION OF CONTROLS

As possible controls the Norwegian Medical Birth Registry was used to select four women who gave birth at one hospital (Oslo University Hospital, Ullevål) at the same time as one case. We utilized the two first listed women as controls. If their medical records were not retrievable, we included the third or fourth selection. In total 1230 controls were identified. According to the medical records, one woman from the control group had been treated for VT before the index pregnancy and was excluded. The pregnancy leading to labor at the same time as for a case was defined as the index pregnancy for each control. The final control population comprised 1229 women naïve for VT at the time of their index pregnancy.[25,39]

3.1.3. STUDY POPULATION FOR PAPERS I AND II

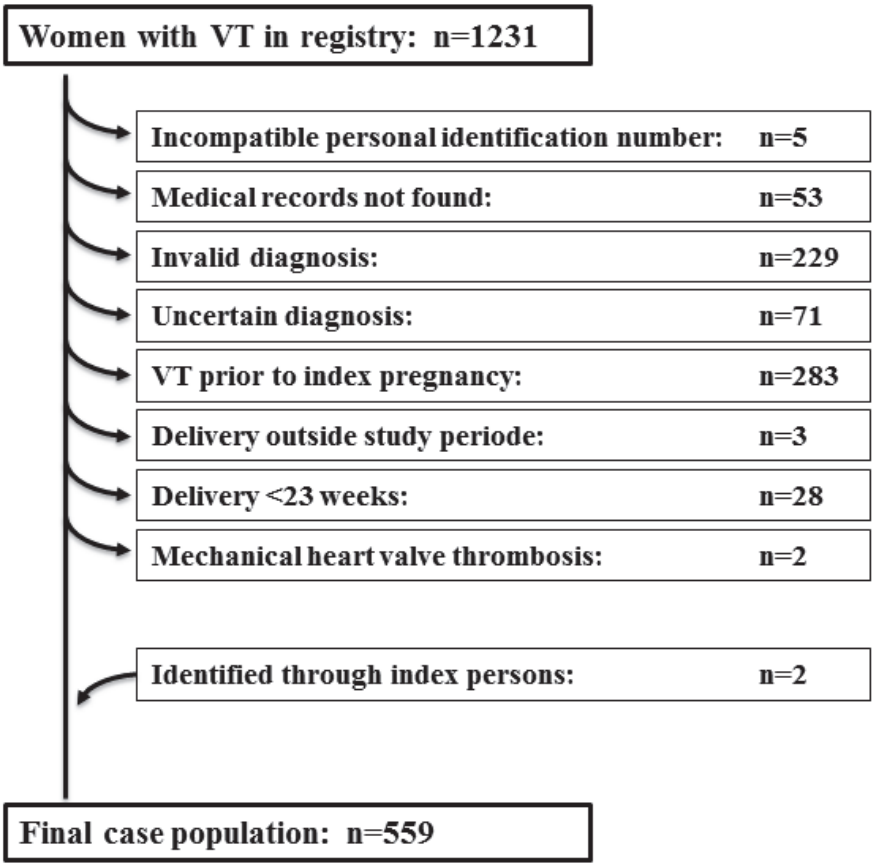
The 559 cases and 1229 controls who could be reached were invited to the study and asked to answer a comprehensive questionnaire and to deliver a single blood sample in 2006. Total 313 patients and 353 controls met to participate in the study in 2006 and all of them signed informed consent (Figure 3). These 666 women constituted the study population for papers I and II in the present thesis.

Table 7 International classification of diseases codes related to pregnancy

ICD 8	Cerebral vein thrombosis
	450 Pulmonary embolism
	Portal vein thrombosis
	Venous thrombosis
	Venous thrombosis in puerperium
	673 Pulmonary embolism during pregnancy and puerperium
ICD 9	325 Phlebitis and thrombophlebitis of intracranial venous sinuses
	415.1 Pulmonary embolism
	451 Venous thromboembolism
	452 Portal vein thrombosis
	453 Other vein thrombosis
	671.3, 4, 5, 9 Deep phlebothrombosis, antepartum, postpartum and other thrombosis during pregnancy
	673.2, 3 Obstetric blood clot embolism, puerperal pulmonary
ICD 10	G08 Phlebitis and thrombophlebitis of intracranial venous sinouses
	I26 Pulmonary embolism
	I80 Venous thromboembolism
	I 82 Other venous thrombosis
	O 22.3, 5, 8, 9 Venous complications in pregnancy
	O 87.1, 3, 9 Venous thromboembolism in puerperium
	O 88.2 Pulmonary embolism in puerperium

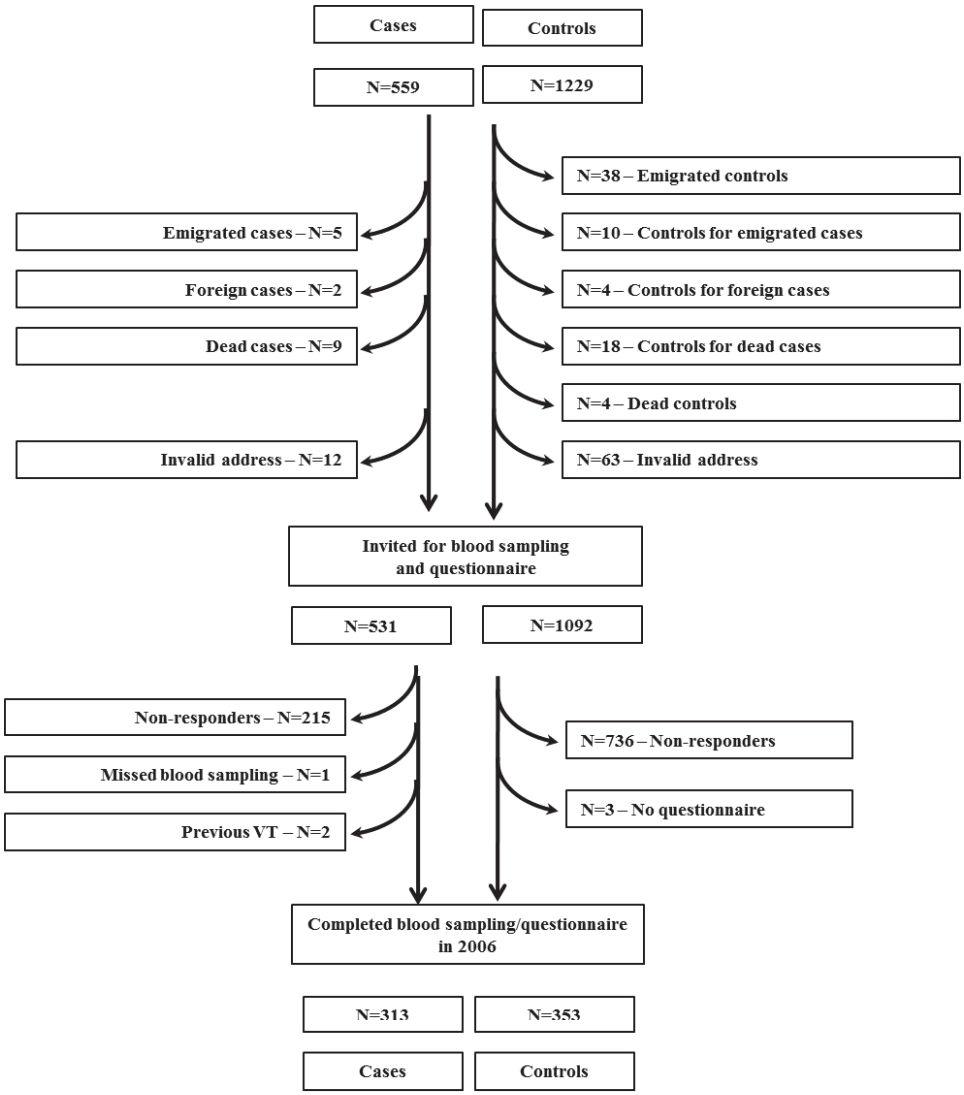
From Jacobsen et al.[25] (with permission)

Fig.2 Selection of cases from the Patient Register and the Medical Birth Registry



Adapted from Jacobsen et al.[25,39] (with permission)

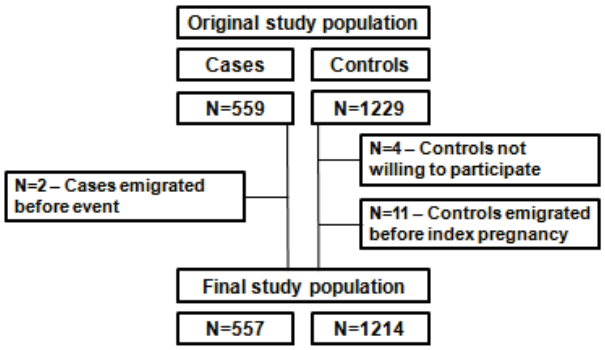
Fig.3 Study population for papers I and II (the sub-study in 2006)



3.1.4. STUDY POPULATION FOR PAPER III

In paper III the study population consisted of the whole original VIP population of 559 cases and 1229 controls. Only four controls declined to consent to the linking to the Norwegian Cause of Death Registry and the Cancer Registry of Norway. Linking these 1784 women with the Norwegian National Population Register in June 2012 identified two cases and eleven controls who had emigrated from Norway before the index pregnancy even though they gave birth in a Norwegian hospital; these were excluded from the study (Fig 4).

Figure 4 Study population for paper III



3.2. COLLECTION OF DATA

3.2.1. DATA FROM THE PARTICIPANTS' MEDICAL RECORDS

Cases and controls were identified at each of the 18 participating hospitals. A specific case report form was developed for the study. The medical records were retrieved and predefined information for cases and controls was collected and registered in the case report forms. The index pregnancy for cases was defined as the pregnancy in which the first lifetime VT occurred, and for controls, it was the pregnancy leading to labor at the

same time as matching cases. Date of inclusion in the study was date of delivery in the index pregnancy. Demographic information and detailed information regarding the index pregnancy was collected, as well as parity, previous and present health/comorbidity, weight, height, and smoking habits at the beginning of the index pregnancy. Body mass index (BMI) was calculated from weight and height, and overweight was classified according to the World Health Organization definition (BMI $\geq$25.0 kg/m^2). For cases, detailed information regarding the actual VT, including the type of diagnostic verification, type of VT (i.e. DVT, PE, DVT+PE, DVT in other locations), extension of the thrombus, and lateralization was recorded. A proximal DVT in a lower limb was defined as a DVT at or above popliteal vein, possibly extending up to the iliac vein. A distal DVT included only the calf veins, i.e., below the popliteal vein. All cases of combined symptomatic DVT in a lower limb and PE were categorized in the analyses as DVT. These data from the case report forms are the basis for the predictor analyses in paper I and are used for description of the population in papers I and III.

3.2.2. QUESTIONNAIRE DATA FROM 2006

In 2006 the 666 participants of the VIP sub-study met to answer a comprehensive questionnaire at their local hospitals after giving informed consent. The whole questionnaire was self-completed, but health personnel were present to answer any question if necessary. The questions concerned socio-demographic factors, obstetrical history, history on VT, general health, use of medication and contact with health personnel the last 12 months, self-reported Villalta score to assess PTS, one disease specific QOL questionnaire (the VEINES-QOL/Sym), and two different generic QOL questionnaires (Ferrans and Powers QOL Index and the General Health Questionnaire 20). The questionnaire data were used to assess PTS and QOL in papers I and II and were also the basis for the predictor analyses for QOL in paper II. Questionnaire data were not used in paper III.

3.2.2.1. ASSESSMENT OF POST-THROMBOTIC SYNDROME

In paper I we utilized a self-reported Villalta score, modified from the original Villalta score (Table 3), to diagnose and grade PTS. The self-reported Villalta score included the same 11 items as in the original, but all were completed by the patient herself. No health personnel were involved in the scoring, but a nurse was present when completing the questionnaire to answer questions if necessary. Each item in the self-reported Villalta

score was scored from zero (no complaints) to three (severe complaints) as in the original Villalta score and we defined any PTS as self-reported Villalta score ≥5 and severe PTS as a score ≥15 in a lower limb with a previous DVT. A question regarding the presence of a venous ulcer was not included. The self-reported Villalta score in Norwegian is included in the appendix of this thesis, and the version translated to English is available online as a supplemental file for paper I.

3.2.2.2. ASSESSMENT OF DISEASE SPECIFIC QUALITY OF LIFE

The Venous Insufficiency Epidemiologic and Economic Study (VEINES) – quality of life (QOL) and symptoms (Sym) questionnaire was used to assess disease specific QOL in papers I and II. The VEINES-QOL/Sym questionnaire is the most frequently used disease-specific QOL questionnaire for DVT in the lower limbs. It was modeled after SF-36 and comprises 26 items regarding leg problems. Items regarding symptoms, limitations in daily activity and psychological impact during the previous 4 weeks are included. Two summary scores are computed. The VEINES-QOL summary score assesses QOL, and the VEINES-Sym score measures symptom severity; higher scores represent better QOL and/or fewer symptoms. One item concerns the time of day of greatest symptom intensity and one covers change over the past year. These two items are not included in the summary scores.[153] The VEINES-QOL/Sym questionnaire is validated in Norwegian and have been used in two Norwegian studies in addition to the VIP study (the QOL results from the CaVenT study are not published yet).[148,154,155] The Norwegian version of the VEINES-QOL/Sym questionnaire is included in the appendix of this thesis. The English version is included in the paper "Evaluation of outcomes in chronic venous disorders of the leg: Development of a scientifically rigorous, patient-reported measure of symptoms and quality of life" by Lamping et al.[153]

3.2.3. BLOOD SAMPLING AND ANALYSIS

At the same time as completing the questionnaires and signing informed consent in 2006, all 666 study participants also donated a single blood sample. The handling of the blood samples is described in a previous publication.[156] In paper I, we investigated on the role of factor V Leiden (F5 rs6025) and the prothrombin gene G20210A (F2 rs1799963) polymorphisms, and plasma D-dimer level (assayed using Asserachrom D-Dimer kit from Stago, Asnière, France) as possible predictors for PTS. The cut-off level for D-dimer was 0.4 μg/L.

3.3. STATISTICS

All statistical analyses were performed using the Statistical Package for Social Science version 18.0 (SPSS Inc, Chicago, IL, USA) or Stata 12 (StataCorp LP, College Station, TX, USA). Findings with P-values below 0.05 were considered statistically significant.

Descriptive statistics were used to present the characteristics of the study population in all three papers, presented as frequencies, n (%), medians and means together with standard deviation (SD) or 95% confidence interval (CI). A two-sample *t*-test was used to compare two continuous variables if their distribution was close to normal; otherwise, a non-parametric test (Mann-Whitney) was used. A two-sided chi-square test was used to compare dichotomous variables, but a Fisher's exact test was used in situations where the expected counts of events or nonevents were less than five. When adjusting for possible confounders, linear or logistic regression was used depending of a continuous or a dichotomous variable of interest (dependent variable). When the dependent variable was continuous, but deviated extensively from the normal distribution, a logarithmic transformation of the variable was used in the regression analysis.

Papers I and II: In both papers the variable of interest was dichotomized, i.e., PTS versus no PTS in paper I and VEINES score $<25^{th}$ percentile versus scores $\geq 50^{th}$ percentile in paper II. We performed bivariate and multivariate logistic regression analyses to identify possible predictors for PTS and for reduced disease specific QOL. Backward variable selection was used to make the final model of predictors and the results were presented as odds ratios (OR) and adjusted OR with 95% CI. Possible interactions were checked. In papers I and II we computed the scores for the VEINES-QOL and VEINES-Sym using standard scoring algorithms obtained from Donna Lamping, London, United Kingdom.[153] For computing the self-reported Villalta score for each patient with previous pregnancy-related DVT in a lower limb, the points (0-3) for each of the 11 questions were just added. For the eight cases with no information on which limb was affected, we used the highest score of the two limbs and we did the same for cases with PE. We used the mean score for both legs when assessing self-reported Villalta scores among controls.

Paper III: The frequency of comorbidity before index pregnancy was very low for both cases and controls, and when the expected counts of different diseases were less than five, we performed a Fisher mid-p test instead of the Fisher's exact test when comparing

comorbidity between the two groups.[157] Cox regression was used to calculate crude hazard ratios (HR) for mortality and cancer, with 95% CI, for cases compared with controls and to identify possible confounders for the association between VT and death or cancer. The observed mortality and incidence of cancer in our cohort was compared to the expected total mortality and incidence of cancer in the general Norwegian female population adjusted for age to obtain standardized mortality ratio (SMR) and standardized incidence ratio (SIR) for cancer. The statistics Norway[158] and the Cancer Registry of Norway[159] provided tables on the mortality and incidence of cancer in different age groups stratified for sex per 100000 inhabitants per year. A SMR/SIR above 1.0 means that the cohort has a higher mortality or incidence of cancer than observed in the sex- and age- matched Norwegian population, less than 1.0 means lower incidence than expected.

3.4. POWER ANALYSIS

The VIP study was originally designed to identify clinical risk factors and possible biomarkers for pregnancy-related VT and power-analysis was performed to estimate the sample size needed for the VIP study. Power-analysis was not done for PTS/QOL until writing papers I and II.

In paper III, we intended to identify mortality and incidence of cancer after pregnancy-related VT. The complete study population of 559 cases and 1229 controls was planned linked to the Norwegian Cause of Death Registry and the Cancer Registry of Norway. Using data from Statistics Norway we expected that 1.3% of the controls would have died from the time of the index pregnancy until linking. We assumed it was realistic that 3.5% of the cases had died in the same period and this would give a statistical power of 80%. We also assumed that the incidence of cancer among the controls during the follow-up period was approximately 1.4% (personal communication, senior researcher Steinar Tretli, the Cancer Registry of Norway). Using a two-sided chi-square test and a significance level of 5%, we were able to show that a cancer incidence of 4.0% among cases during follow-up, which we considered to be a realistic estimate, would make the power of this part of the study to be 90%. This power analysis was included when we applied the Southeastern Regional Committee for Research Ethics for permission to conduct the sub-study.

3.5. RECOMMENDATIONS AND PERMISSIONS

The project was approved by the Southeastern Regional Committee for Research Ethics (REK), the Norwegian Data Inspectorate, and the Norwegian Ministry of Health and Social Affairs. The study is registered at ClinicalTrials.gov with the unique identifier NCT 00856076. The project was in line with commonly accepted ethical principles. Informed consent was obtained from the 313 cases and 353 controls before they answered the comprehensive questionnaire. Letters of information were sent to a all the 1788 women in 2011 and the linking with the Cancer Registry of Norway and the Norwegian Cause of Death Registry was done after passive informed consent as approved by REK, and only four women actively declined to be included in the linkage studies. The studies were only descriptive and did not include randomization or treatment. The implementation of the project was not likely to cause any harm because the project was only descriptive.

4. SUMMARY OF RESULTS

4.1. PAPER I

Prevalence and predictors for post-thrombotic syndrome three to 16 years after pregnancy-related venous thrombosis: a population-based, cross-sectional, case-control study. Wik HS, Jacobsen AF, Sandvik L, Sandset PM. Journal of Thrombosis and Haemostasis 2012 May; **10**:840-7.

In this paper we assessed the prevalence of PTS using self-reported Villalta score after a first-ever DVT during pregnancy or the first 12 weeks after delivery. Mean follow-up was 9.1 years. 204 women with a previous DVT, 70 with PE only, and 349 controls completed the self-reported Villalta score. Forty-two % had PTS after DVT, and 24% of those with PE and 10% of controls also had a self-reported Villalta score of five or more. The total scores after DVT and PE were significantly higher than for controls, also when adjusted for possible confounders (P< 0.001 and P=0.025, respectively). A proximal DVT occurring after delivery was the strongest predictor for PTS, but also smoking and higher age were independently associated with PTS.

4.2. PAPER II

Long-term quality of life after pregnancy-related deep vein thrombosis and the influence of socioeconomic factors and comorbidity. Wik HS, Enden TR, Jacobsen AF, Sandset PM. Journal of Thrombosis and Haemostasis 2011; **9**: 1931–6.

In this paper we assessed disease specific QOL and symptom severity in 208 patients with previous first-ever pregnancy-related DVT in a lower limb after a mean follow-up of 9.5 years compared with 347 controls consisting of women naïve for VT at the time of index pregnancy. The VEINES-QOL/Sym questionnaire was used to assess QOL and symptoms. Mean scores for VEINES-QOL were 45.6 (SD 12.4) for cases and 52.8 (SD 7.0) for controls, and mean VEINES-Sym scores were 45.4 (SD 12.0) and 52.7 (SD 7.4). Both scores differed statistically significant between cases and controls (P<0.001). We

defined a score <25th percentile as a clinically relevant reduced outcome compared to a score ≥50th percentile. Cases had poorer outcomes regarding both QOL and symptoms compared to controls, also when adjusted for possible confounders. Adjusted OR for reduced QOL and more symptoms among cases compared with controls were 5.0 (95% CI 2.8-9.1, P<0.001) and 5.9 (95% CI 3.2-10.8, P<0.001), respectively. Low education was the only socioeconomic parameter to independently predict both reduced QOL and increased symptom scores among cases.

4.3. PAPER III

Long-term mortality and incidence of cancer after pregnancy-related venous thrombosis: results of a population-based cohort study. Wik HS, Jacobsen AF, Fagerland MW, Sandvik L, Sandset PM. Submitted.

In this paper we assessed mortality and incidence of cancer after VT in 557 women with pregnancy-related VT during 1990-2003 (cases) and 1214 controls without VT at the time of index pregnancy during a mean follow-up of 13.0 years. The Norwegian Cause of Death Registry and the Cancer Registry of Norway provided data on deaths and diagnoses of cancer. Ten cases (1.8%) and 7 controls (0.6%) died from any cause during follow-up. Mortality was 3.0 times higher among cases compared with controls (HR 3.0, 95% CI 1.1-7.9, P=0.024). Mortality among cases was also significantly higher than among the sex- and age- adjusted Norwegian population the first year after VT (SMR 18.8, 95% CI 7.8-45.3), but thereafter the mortality was comparable (SMR 0.9, 95% CI 0.4-2.0). Fifteen cases (2.7%) and 13 controls (0.4%) were diagnosed with cancer after index pregnancy. The incidence of cancer was 2.5 higher among cases compared with controls (HR 2.5, 95% CI 1.2-5.2, P=0.017). Cases had similar incidence of cancer after VT as the sex-and age- adjusted Norwegian population (SIR 1.0, 95% CI 0.6-1.7).

5. DISCUSSION

5.1. METHODOLOGICAL CONSIDERATIONS

5.1.1. STUDY POPULATION

5.1.1.1. SELECTION OF CASES FOR THE VIP STUDY

Due to the strict validation criteria used it is likely that all identified cases actually had a pregnancy-related VT. Almost 50% of the patients that were identified in the registries proved not to have VT and were thus not included in the study, revealing the weakness of research based on hospital discharge codes only without validation. On the other hand, we cannot exclude that there may have been underreporting of cases. The Medical Birth Registry was only used to identify cases at the three large hospitals. Cases with inaccurate ICD coding at discharge from hospital, with missing medical records (n=53, Fig.2), or women who died from a pregnancy-related VT outside hospital were not included. The latter cases, if any, were probably not registered in the patient registry even if the VT diagnosis was identified by autopsy. These limitations make it likely that there is a small underestimation of cases in the original VIP study.

5.1.1.2. SELECTION OF CONTROLS FOR THE VIP STUDY

The controls were selected from Ullevål hospital in Oslo only while the cases were recruited from a broader Norwegian population of young women. Women who gave birth at Ullevål hospital differed slightly from the case population; they were slightly older (mean 30.7 versus 29.6 years at the time of index pregnancy), of lower parity order, conceived more often after assisted reproductive technique, had more operative deliveries, and had more pregnancy complications in the index pregnancy. Ideally the controls should have been selected from the same hospitals as the cases, but this was not feasible because of practical and economic reasons. We cannot rule out that this selection of controls from one hospital has introduced a selection bias.

We do not know if our findings only apply to long-term outcomes after pregnancy-related VT or if they can be generalized to a broader young female VT population. Therefore, another control group consisting of young women with VT not related to pregnancy could have provided additional valuable information. The resources in this study did not allow us to include another control population.

5.1.1.3. SELECTION OF CASES AND CONTROLS FOR PAPER I AND II

As in most studies based on questionnaires,[160] the drop-out rate from the VIP study was significant, when the participants were invited to meet for a visit to donate a blood sample and to answer a questionnaire in 2006. Of the original study population that comprised 559 cases and 1229 controls, 531 (94%) of cases and 1092 (89%) of controls were invited to participate; some were not invited due to reasons given in Figure 3, however, only 313 (56%) of cases and 353 (29%) of controls agreed to participate. Hence, we cannot be certain whether the cases and controls are representative for the entire population. One of the reasons for the large drop-out was probably the inconvenience of having to present at the hospital for participation. We had access to the medical records for those participating and those who did not, thus to some extent we do know how they differed with regards to clinical variables (see Table 8). Participating cases and controls were slightly older, of lower parity, fewer were smokers, and they had slightly lower BMI compared to those not participating, but the differences were not considered substantial. Moreover, we cannot exclude that those who responded did so because they were symptomatic, creating a possibility of overestimating PTS.

5.1.2. DATA SOURCES

5.1.2.1. DATA FROM MEDICAL RECORDS

All data regarding VT were obtained from the medical records of the participants at the hospital where the event took place. As described earlier, these data were validated and had thus good quality. An advantage of using medical records as a source of information is that a large number of different variables can be collected. We used some of these variables for the predictor analyses in paper I. However, the quality of these variables may differ since they were collected retrospectively. It is not known whether the information regarding weight and height are self-reported or actually measured, and in particular self-reported weight can be systematically underestimated.[161] Other have reported that self-reported weight and height can be relatively accurate.[162] However, missing values may be high in special weight groups, e.g. obese.[162] Smoking at the beginning of the index pregnancy may also be underestimated.[163] Data regarding delivery mode, parity, age, and multiple pregnancies are probably more accurate.

Table 8 Distribution of demographic and clinical variables among cases and controls who did not or did participate in the questionnaire and blood sample sub-study of the VIP study

Risk factors	Cases not participating (n=218)	Cases participating (n= 313)	Controls participating (n=353)	Controls not participating (n= 739)
	%	%	%	%
Age (years)				
17-24	24.3	15.7	4.8	16.6
25-29	34.4	30.4	26.1	31.7
30-34	23.9	34.2	37.7	29.6
35-54	17.4	19.8	31.4	22.1
Parity				
0	52.3	55.9	49.9	49.5
1	26.6	28.8	39.7	29.1
2	12.4	12.5	8.2	14.7
≥3	8.7	2.9	2.3	6.6
Assisted reproduction therapy				
Yes	2.8	5.8	2.3	1.5
No	97.2	94.2	97.7	98.5
Cigarettes/day				
0	71.1	80.2	90.1	85.0
1-4	3.7	4.5	2.0	4.7
5-9	8.3	6.4	4.5	4.6
10-30	17.0	8.9	3.4	5.7
Immobilization*				
Yes	5.0	7.7	0.8	1.1
No	95.0	92.3	99.2	98.9
Body mass index (kg/m^2)				
missing data	21.6	17.9	7.6	9.2
<25	48.2	55.0	74.5	68.2
25-30	18.3	18.5	11.6	16.0
≥30	11.9	8.6	6.2	6.6
Weight gain (kg)				
<7.0 (<10 percentile)	14.2	11.8	8.2	8.4
7-21 (10-90 percentile)	38.1	43.5	38.0	41.0
>21.0 (≥90 percentile)	47.7	44.7	53.8	50.6
Cesarian section				
Yes	32.6	31.0	21.0	19.4
No	67.4	69.0	79.0	80.6
Bleeding >1000 mL				
Yes	13.3	13.4	2.0	4.2
No	86.7	86.6	98.0	95.8

From Bergrem et al.[164] (with permission)

5.1.2.2. QUESTIONNAIRE DATA

The whole questionnaire was self-reported, and data were not ascertained by actual measures (e.g., weight and height) or by comparison with medical records or registries (e.g., parity, income, education, comorbidity, a.o.), and this can lead to inaccuracy and measurement bias. For paper II we used questionnaire data only for both the main outcome, i.e., the VEINES-QOL/Sym scores, and the different exposure variables. However, the main exposure variable VT was captured from the medical records and thus considered accurate.

The information regarding socioeconomic variables was collected only once and 3-16 years after the index pregnancy. It could have been valuable to have this information also from the time of index pregnancy to see if some of the variables had changed over time or if the differences detected between cases and controls already existed at the time of index pregnancy. Cases and controls differed significantly in 2006 regarding education, income, and employment. This can be explained by selection bias as controls were not selected from the exact same population as cases or the drop-out rate, but may also represent real differences between the two groups as low socioeconomic status has been shown to be associated with VT.[165]

5.1.3. ASSESSMENT OF PTS

There is currently no gold standard for diagnosing PTS. According to the current recommendations from ISTH, the Villalta score should be used as the standard diagnostic scoring system for PTS in clinical studies.[53] When planning the VIP study in 2003-4 there was no consensus on how to diagnose PTS, and there were limited number of publications that had reported use of the Villalta score. For operational reasons, the use of a self-reported version of the Villalta score was chosen.

5.1.3.1. VILLALTA SCORE

The original Villalta score is not specific for PTS, and symptoms and signs from other diseases or previous trauma affecting the lower limbs may also contribute to high scores. We are not aware of studies that have applied Villalta score to people without PTS to estimate such “back-ground noise”. Hence, PTS frequency according to Villalta score may be too high in most studies due to registration of symptoms and signs not related to

PTS. Some studies have assessed PTS in the contralateral limb in DVT patients finding a Villalta score ≥5 in as many as 14-21%.[54,59]

The chosen cut-off of ≥5 points on the Villalta score to diagnose PTS is also debatable and may seem arbitrarily; does a patient with 5 points differ significantly from one with 4 points? Because there is no gold standard for the diagnosis of PTS, the cut-off value of ≥5 points was chosen using overall interference of venous symptoms and signs with the patient's daily life as well as QOL as surrogate endpoints.[63,166] An association between Villalta scores and disease specific QOL has also been used for validation,[166] but this is even more challenging to interpret because the VEINES-QOL/Sym items to a great extent overlap with the symptoms and signs that constitute the Villalta score; six of the 11 items of the Villalta score are included in VEINES-QOL/Sym.

5.1.3.2. ASSESSMENT OF PTS IN PAPER I

In paper I we used a self-reported version of the Villalta score for the assessment of PTS. The 5 symptom items were scored as in the original score. The 6 clinical signs were self-assessed instead of by a nurse or physician. Some of the clinical signs may have been difficult to understand by the participants, like indurated skin that was explained as thickened and hardened skin. We only asked for varicose veins, not for venous ectasia, and we asked for pain when using compression stockings, not for pain during calf compression. This may have caused the self-reported Vilalta score to diverge from the original score, but to which extent or direction is unknown. Ideally the self-reported Villalta score should have been validated in a pilot study before used in a large scale study.

Our questionnaire left out the question about venous ulcer. A venous ulcer automatically categorizes the PTS as severe independent of the total Villalta score,[63] thus we may have underestimated the frequency of severe PTS in paper I. The probability of having a venous ulcer with a Villalta score of 5-15 is, however, very low, as Kahn et al only found 2 of 147 patients with Villalta scores of 5-15 having a venous ulcer.[60]

Another limitation of our PTS assessment is that we lack information regarding the use of ECS which may reduce the frequency of PTS after a proximal DVT with 50%.[19] Unfortunately, we do not have validated information on recurrent VT either. In the questionnaire, 10% of cases with DVT stated that they had experienced more than one

event, but we have no information whether these were PEs, or contra- or ipsilateral DVTs, and they are not validated. Only ipsilateral DVT has been shown to predict PTS.[70]

5.1.4. ASSESSMENT OF QUALITY OF LIFE

5.1.4.1. GENERIC QOL

The patient's experience and opinion are unarguable of great value, but the interpretation of patient reported outcomes is difficult. It is recommended to use both a generic and disease specific questionnaire in clinical studies reporting on QOL, and inclusion of frequently used instruments like SF-36 or EQ-5D may have provided valuable additional information to the results in paper II.[142,167] Additionally, a generic questionnaire is generally accepted for use in healthy controls in contrast to VEINES-QOL/Sym, which has not been developed for this purpose, nor for patients with a PE or DVT in other locations. The SF-36 or EQ-5D are the most commonly used generic questionnaires, and results are therefore more easily communicated and can also be compared to population norms.

The two generic QOL measurements used in the VIP study were the Ferrans and Powers QOL Index and the General health questionnaire 20. These instruments are not widely accepted and population norms do not exist. Finally, these scores did not differ between cases and controls in our population; and these results were recently accepted for publication.[168]

5.1.4.2. DISEASE SPECIFIC QUALITY OF LIFE

In paper II the disease specific QOL was assessed by using the VEINES-QOL/Sym questionnaire. This is the disease specific QOL measure most frequently utilized in this population and it has been found to be reliable and valid.[147] It is also validated in Norwegian.[148] As for the Villalta score, a gold standard does not exist for disease specific QOL after DVT which makes validation difficult. The VEINES-QOL/Sym questionnaire was modeled after the SF-36.[153] SF-36 and the Villalta scores one and four months after the acute DVT were used for the validation of VEINES-QOL/Sym, and this may rather reflect QOL related to a sub-acute phase and not long-term QOL after suffering a DVT.[147]

As for several studies,[44,145,169,170] we found that the two sub-scores QOL and Sym yielded very similar values, and it can be argued that the use of two scores is redundant. I also

suspect that the symptoms have a large impact on both the total scores, but that is difficult to interpret due to the rather complex calculation of the scores including transformations to *z*- and T-scores.

Reporting results from one or two items from the questionnaire in addition to the total scores could have provided additional information on the impact of the leg problems on daily life. One example of such an item is: "Does your leg problem now limit you in these daily activities (at work, at home, social or leisure activities when standing for long periods, social or leisure activities when sitting for long periods)?" The three possible answers are "Yes – limited a lot", "yes limited a little" and "no, not limited at all."[153]

5.1.4.3. CLINICALLY RELEVANT DIFFERENCES IN VEINES-QOL/SYM SCORES

The developers of the VEINES-QOL/Sym questionnaire have proposed that a difference of 3-4 points on either of the two scores can be considered to be of clinical significance to the patients.[44] This was inferred from the SF-36 questionnaire[171] and has not been confirmed e.g. by asking the patients if their QOL/ or symptoms were very good, good, poor, bad, or very bad and comparing these answers to their actual scores. Hence, it may be argued that the clinically relevant differences in VEINES-QOL/Sym scores remain unknown. In addition QOL scores often deviate from the normal distribution making it difficult to analyze them as continuous measures by using the *t*-test and linear regression.[131] Hence for the analyses in paper II we assumed and defined a clinically relevant difference of VEINES-QOL/Sym scores based on the observed percentiles with scores $<25^{th}$ percentile representing a reduced outcome and scores $\geq 50^{th}$ percentile representing the preferred outcome. This definition was predefined and not an approach to find statistically significant results.

Using the VEINES-QOL/Sym scores as a continuous measure may have made the results easier to communicate, as this is the approach used by other authors. The scores in our study deviated substantially from the normal distribution and therefore linear regression could not be applied. Transforming the scores to a more normally distributed scale would have been another approach. This would not have solved the problem with defining the minimal important difference between scores, but for many QOL scores it has been shown that approximately 0.5 x the SD corresponds well with a clinically important difference.[172,173] This is called a distribution-based method and is based on statistical

characteristic of the QOL scores in the actual population.[174] Applying this definition to our results in paper II, the difference in disease specific QOL and symptoms between cases and controls can be considered to represent clinical important differences; the differences in mean values were 7.2 and 7.3 and 0.5 x SD among controls were 3.5 and 3.7, respectively. Whether this approach is valid for the VEINES-QOL/Sym questionnaire remains unknown and was not investigated in this thesis. Another way of defining the minimal important difference would have been to ask the patients (or some of them) if they considered their QOL to be very good, good, bad, or very bad and compare these answers to their obtained scores. This is called an anchor-based method.[175]

5.1.5. MISSING DATA

Missing values in self-reported Villalta and VEINES scores were replaced the same way as generally accepted for SF-36. This method is called the half-item rule and missing values are replaced with mean of answered values if more than half of the items in the questionnaire are correctly completed.[176] Different ways of handling the missing values in the self-reported Villalta score such as leaving out all scores that were not complete, did not change the PTS results, indicating that the obtained scores were robust. We have not replaced missing values of demographic variables, but the extent of missing values for the different variables are presented in tables of all our reports. Due to missing values the number of women taken into the multivariate analysis was reduced and may have introduced bias in analysis when adjusting for possible confounders and identifying possible predictors.[160]

5.1.6. LINKING TO THE REGISTRIES

The attrition from the original VIP study population when linking to the registries was low, but as discussed previously, there was a possible selection bias due to selection of controls from a slightly different population than cases (from one hospital only). We consider the introduction of another control group in paper III by using general population data of age-matched Norwegian females, in addition to the original controls from the VIP study, as an advantage to overcome these potential problems. The Norwegian Cause of Death Registry covers all persons registered as inhabitants in Norway at time of death and the Cancer Registry of Norway is regarded as high quality.[177] Reporting to these registries is mandatory in Norway. However, causes of

death are less accurate,[178] and was not the focus of paper III. The main problem in paper III may have been some cases who died shortly after a VT outside hospital as these may have not been included in the VIP population, leading to an underestimation of the short-term mortality. Because only five cases died during the first year of follow-up, this bias may have had a large impact on the estimates. These missing cases, if any, may have died from cancer, leading to underreporting of cancer diagnoses as well. Confounders that were not identified could explain the differences in mortality and incidence of cancer between cases and controls, but due to the relatively young population and very low frequency of comorbidity at the time of VT, such confounders are not easily identified. The number of deaths and cases diagnosed with cancer were low, and did not allow us to identify any predictors for these outcomes.

5.2. DISCUSSION OF MAIN FINDINGS

5.2.1. PAPER I

5.2.1.1. PTS AFTER PREGNANCY-RELATED DVT

We found a prevalence of PTS of 42% 3-16 years after pregnancy-related DVT in lower limbs. This corresponds well to the small study of Lindhagen et al. from 1986 with a mean follow-up of 7 years where 35% of 23 women had clinical deep venous insufficiency after DVT during pregnancy or the first week after delivery.[92] Clinical deep venous insufficiency as defined in Table 5 was a different definition than we used for PTS, and the data are therefore not directly comparable. The few other studies on long-term symptoms and signs in this type of population are also difficult to compare with due to their methods of PTS assessment and small samples.[93–95]

Our result also corresponds well with the PTS prevalence of 56% in the conventional treatment arm of the CaVenT study.[20] The DVTs in the CaVenT study were all high proximal, similar to the majority of DVTs (83%) in paper I. The participants in the CaVenT study were older and had more comorbidity, and only a few had pregnancy-related DVT.

5.2.1.2. SELF-REPORTED VILLALTA SCORE AMONG WOMEN WITH NO PREVIOUSLY KNOWN DVT

Twenty four % of PE cases with no symptoms of DVT at the time of diagnosis and 10% of controls had a self-reported Villlalta score of ≥5. Also PE cases had significantly higher scores than controls (P=0.017). Only one study have assessed Villalta scores after PE identifying 20% with a score ≥5 (compared to 34.2% after symptomatic DVT in the same study).[179] These findings are very similar to ours. Most PE patients have concomitant DVT in a lower limb, even if they are not symptomatic.[180] Whether asymptomatic DVT also leads to PTS remains unknown; only two studies in highly selected populations of small sample-sizes have been published.[181,182] However, this could be a reasonable explanation of our findings. It is not likely that 10% of the controls had DVT after index pregnancy as explanation of the ≥5 scores in this group; this rather corresponds to the fact that self-reported Villalta score and other PTS measurements are not necessarily thrombosis specific. As far as we know Villalta scores have not been previously reported in healthy controls.

5.2.1.3. PREDICTORS FOR PTS

We found that a proximal DVT occurring after delivery was the most important predictor for PTS. A proximal DVT is a well established risk factor for PTS, identified in a number of studies using different diagnostic methods for PTS. Hence our result corresponds well with previous findings.[46,47,71,72]

Our finding of a postnatal DVT as an independent predictor for PTS compared to an antenatal DVT was more surprising. A previous smaller study did not find this association, but this may be due to low power since only 95 women were included.[93] In paper I we have speculated of several possible mechanisms for this association, including longer duration of LMWH among those having antenatal thrombosis, different pathophysiological mechanisms for the development of DVT in the two groups, and a delayed diagnosis of DVT after delivery as the focus is shifted towards the newborn baby and not the mother anymore. In addition, damage of the vascular endothelium during delivery may also contribute to the higher frequency of PTS after postnatal DVT, but there is little evidence for any of these explanations in the literature.

We found a significant interaction between proximal and postnatal DVT as predictors for PTS; a proximal DVT occurring antenatally was not associated with PTS. This interaction was not pre-specified and was not expected. Only 17% (35 women) had a distal DVT,

and the statistical power to detect a difference between ante- and postnatal DVT in this group was probably too small.

Smoking and age were also identified as predictors for PTS. Age has been associated with PTS in other studies, but the mean age in these studies were higher than in our study and the results from different studies are conflicting.[46,47,51] Smoking has, as far as we know, never been evaluated as a predictor for PTS. Possible speculative mechanisms for this association, such as increased inflammation among smokers, which might increase the risk for PTS, are discussed in paper I.

A recurrent ipsilateral DVT has been associated with the development of PTS in many studies,[46,56,70] but could not be evaluated in the present study because the lack of information on recurrence. Recurrences may have contributed to the relatively high prevalence of PTS in paper I.

We did not find an association between high BMI and PTS even if obesity has been identified by others as a predictor for PTS.[46,47,73] One third of the women in our study without missing values for BMI (65/190) were registered in the medical hospital records with a BMI >25 kg/m^2 corresponding to overweight, and this is about the same frequency of overweight found in a large Danish cohort of pre-pregnant women.[183] In studies identifying overweight as a predictor for PTS, about 60-70% of included patients have been overweight, and the association with PTS was with BMI >25 kg/m^2.[46,47,73] The present study was not powered to identify an association between obesity, defined as BMI >30 kg/m^2, and PTS.

Our findings of a proximal postnatal DVT, higher age, and smoking as predictors for PTS after pregnancy-related DVT have to be confirmed in other studies, because of methodological limitations and the fact that paper I is the first to report on predictors for PTS in this population.

5.2.2. PAPER II

5.2.2.1. DISEASE SPECIFIC QOL AFTER PREGNANCY-RELATED DVT

QOL has previously not been evaluated after pregnancy-related VT; nor has VEINES-QOL/Sym scores been reported for use in healthy controls. Hence our findings cannot be compared to other studies. However, the association between previous VT and reduced

disease specific and/or generic QOL has been identified by others in general VT populations.[143,145,150]

5.2.2.2. PREDICTORS FOR REDUCED VEINES-QOL/SYM SCORES

No education beyond high school was identified as a predictor for both reduced disease specific QOL and increased symptom burden in paper II. This association has not previously been described for VEINES-QOL/Sym scores. Low education has been found to be associated with poor generic and disease specific QOL in a broad range of populations.[184–186] Hence, this finding was not unexpected. The reported comorbidity among the young female population was low and this can to some extent explain why comorbidity was not associated with reduced QOL. Chronic diseases are known to affect QOL, but it is not obvious that disease specific QOL should be affected if the comorbidity did not involve the lower limbs. The association between high symptom burden from lower limbs as assessed by the VEINES-Sym score and marriage/cohabitation is difficult to explain, and may represent an incidental finding.

The presence of PTS has been shown to be an important predictor of reduced QOL in several studies.[44,142] Both the QOL and the symptom scores of the VEINES-QOL/Sym questionnaire include symptoms and signs likely to be present in patients with PTS. As PTS was found in almost half of the cases, it was not surprising that the VEINES scores among cases were lower than for controls. From this follows that PTS could have been included in the predictor analyses for reduced QOL in paper II. In paper I (published after paper II), we identified that women with a self-reported Villalta score ≥5 after DVT in lower limbs had a significantly lower mean VEINES-QOL score compared to women with Villalta scores <5 (see Table 9). These women also had reduced generic QOL compared to controls as assessed by the Ferrans and Powers QOL Index indicating that both these instruments were sensitive to the presence of PTS.[168]

Table 9 Mean VEINES-QOL scores

Group	N	VEINES-QOL scores, mean (95% CI)
Controls	347	52.8 (52.0-53.5)
DVT, no PTS	119	52.6 (51.7-53.5)
DVT, PTS	85	36.2 (33.4-38.9)
DVT, severe PTS	14	23.7 (15.6-31.8)

No PTS: self-reported Villalta score <5; PTS: self-reported Villalta score ≥5; severe PTS: self-reported Villalta score ≥15.

5.2.3. PAPER III

5.2.3.1. MORTALITY AFTER PREGNANCY-RELATED VT

We found that the long-term mortality after a pregnancy-related VT was increased compared to the control group. When comparing to an age-matched Norwegian female population we also found an increased mortality the first year after the event, but not the years thereafter. We are not aware of other studies assessing short-and long-term mortality in this population; but some studies have reported on deaths per delivery.[25,26,107] Hence, our findings cannot easily being compared to other studies.

The case-fatality rates in other VT populations have been reported to be 10-30% after 30 days and 20-40% after one year.[7,104,105] This is much higher than in our population where the corresponding case-fatality rates were 0.36% and 0.9%, even when we included deaths of all causes and not only VT related deaths. Obviously, one of the explanations for this discrepancy is that our population consisted of young, healthy women very different from more general or unselected VT populations. Nonetheless, there is probably an underreporting of cases dying shortly after a VT, as women with a VT diagnosis established after an autopsy is likely to not have been included (see section "5.1.1.1. Selection of cases for the VIP study"). Several studies have reported increased mortality after VT in more general populations.[3,81,103,104]

5.2.3.2. CANCER AFTER PREGNANCY-RELATED VT

It is generally accepted that the risk of cancer is increased after suffering a VT, especially the first years.[119–122] In paper III we found that cases with a pregnancy-related VT had a

higher incidence of cancer after the index pregnancy compared to our control group. This difference was not confirmed when comparing the cases with the age-matched Norwegian female population during the study years. Due to very few cancer diagnoses, the diverging results from these two control groups may be due to lack of statistical power. Also, all controls had at least one pregnancy compared with the general Norwegian female population where about 12% were childless, hence, the control group may represent healthier women who to some extent are protected from cancer as discussed in paper III. Another possible explanation is that the controls in the VIP population are not representative for the case population due to the fact that they are identified from a slightly different population from one hospital only. From this follows that cancer diagnosed after a pregnancy-related VT is very rare and screening for cancer in this group is probably not justified.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

The present studies indicate that pregnancy-related, first-time VT has important long-term complications in terms of high prevalence of PTS, reduced QOL, increased mortality, and possibly increased risk of subsequent cancer. As far as we know long-term outcomes in this population have not previously been studied. Despite the methodological concerns extensively discussed in this thesis, our work contributes to the scarce knowledge in this field. These women, who represent a young and in other ways a healthy population, need information and counseling about risk, prevention and treatment of PTS, in addition to close follow-up from the health care system including VT treatment in accordance with guidelines. When involving a proximal DVT, ECS should be worn daily for at least two years, and if no risk of bleeding, additional CDT should be considered after delivery.

There is a need for validation of the self-reported Villalta score and we are currently performing such a study. Long-term frequency of recurrent VT has not been assessed after pregnancy-related VT and can possibly be done in our VIP study population. Ideally a prospective cohort study should be conducted to assess the prevalence of PTS after pregnancy-related DVT and identify predictors/biomarkers of importance, but this would require a multinational study over many years. To confirm the mortality and incidence of cancer in this population and to identify predictors for death an even larger study must be conducted. A disease specific questionnaire for assessing QOL after PE has been developed and the validation of the Norwegian version is ongoing. This questionnaire could be used in the women with PE in the VIP study. I plan and hope to contribute to a number of these research questions.

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A) SELF-REPORTED VILLALTA SCORE (NORWEGIAN VERSION)

28 Beinplager

Har du i dag plager i beina (fra hoften til tærne).
Sett ett kryss for hver linje!

28a Høyre ben	Ingen	Lett	Moderat	Uttalte
1. Smerter	☐	☐	☐	☐
2. Kramper	☐	☐	☐	☐
3. Tyngdefornemmelse	☐	☐	☐	☐
4. Kløe	☐	☐	☐	☐
5. Parestesier (stikninger, ubehag)	☐	☐	☐	☐
6. Hevelse	☐	☐	☐	☐
7. Hyperpigmentering (misfarging av huden)	☐	☐	☐	☐
8. Åreknuter	☐	☐	☐	☐
9. Rødlig misfarging av hud	☐	☐	☐	☐
10. Fortykket, herdet hud	☐	☐	☐	☐
11 Smerter ved bruk av kompresjonsstrømper	☐	☐	☐	☐

28b Venstre ben	Ingen	Lett	Moderat	Uttalte
1. Smerter	☐	☐	☐	☐
2. Kramper	☐	☐	☐	☐
3. Tyngdefornemmelse	☐	☐	☐	☐
4. Kløe	☐	☐	☐	☐
5. Parestesier (stikninger, ubehag)	☐	☐	☐	☐
6. Hevelse	☐	☐	☐	☐
7. Hyperpigmentering (misfarging av huden)	☐	☐	☐	☐
8. Åreknuter	☐	☐	☐	☐
9. Rødlig misfarging av hud	☐	☐	☐	☐
10. Fortykket, herdet hud	☐	☐	☐	☐
11 Smerter ved bruk av kompresjonsstrømper	☐	☐	☐	☐

B) VEINES-QOL/SYM QUESTIONNAIRE (NORWEGIAN VERSION)

Besvar hvert spørsmål nedenfor ved å krysse av svaret som angitt. Hvis du er usikker på hva du skal svare, vennligst svar etter beste evne.

Disse spørsmålene er om din oppfatning av beina dine.

1. I løpet av de 4 siste ukene, hvor ofte har du hatt noen av disse plagene i beina?

(Sett ett kryss på hver linje)	**Daglig**	**Flere ganger i uka**	**Omtrent én gang i uka**	**Sjeldnere enn én gang i uka**	**Aldri**
1. Tunge bein	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Vondt i beina	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Hevelse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Kramper om natta	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Varme eller brennende følelse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Urolige bein	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Banking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Kløe	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. Prikking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Når på dagen er **plagene i beina** mest uttalte? *(Sett ett kryss)*

- ☐ 1 Når jeg våkner
- ☐ 2 Midt på dagen
- ☐ 3 På slutten av dagen
- ☐ 4 Om natta
- ☐ 5 Når som helst i løpet av dagen
- ☐ 6 Aldri

3. Sammenlignet med for ett år siden, hvordan vil du vurdere dine **plager i beina** nå? *(Sett ett kryss)*

- ☐ 1 Mye bedre nå enn for ett år siden
- ☐ 2 Noe bedre nå enn for ett år siden
- ☐ 3 Omtrent det samme nå som for ett år siden
- ☐ 4 Noe verre nå enn for ett år siden
- ☐ 5 Mye verre nå enn for ett år siden
- ☐ 6 Jeg hadde ingen plager i beina i fjor

4. Følgende spørsmål gjelder daglige aktiviteter. Setter **plagene i beina** begrensninger for dine daglige aktiviteter? Hvis « ja », i hvilken grad?

(Sett ett kryss på hver linje)	Jeg jobber ikke	JA, begrenser meg mye	JA, begrenser meg litt	NEI, begrenser meg ikke
a. Daglige aktiviteter på jobb.	☐ 0	☐ 1	☐ 2	☐ 3
b. Daglige aktiviteter hjemme (husarbeid, småjobber, hagearbeid, o.l.)		☐ 1	☐ 2	☐ 3
c. Fritidsaktiviteter hvor du må stå lenge (selskap, ta buss, handle o.l.)		☐ 1	☐ 2	☐ 3
d. Fritidsaktiviteter hvor du må sitte lenge (kino, teater, på reise o.l.)		☐ 1	☐ 2	☐ 3

5. 3. I løpet av de 4 siste ukene, har du hatt noen av disse problemene i jobb eller i daglige aktiviteter på grunn av **plagene i beina**?

(Sett ett kryss på hver linje)	**JA**	**NEI**
a. Redusert arbeids**tid** eller **tid** til andre aktiviteter	☐ 1	☐ 2
b. **Gjennomført mindre** enn du skulle ønsket	☐ 1	☐ 2
c. Blitt begrenset i **type** jobb eller aktiviteter	☐ 1	☐ 2
d. Hatt **vanskeligheter** med å utføre jobben eller andre aktiviteter (f eks det krevde større anstrengelse)	☐ 1	☐ 2

6. I løpet av de 4 siste ukene, i hvilken grad har **plagene i beina** kommet i veien for samvær med familie, venner, naboer eller grupper? *(Sett ett kryss)*

☐ 1 Ikke i det hele tatt
☐ 2 Lett
☐ 3 Moderat
☐ 4 Ganske stor
☐ 5 Svær

7. Hvor mye smerter har du hatt i beina i løpet av de 4 siste ukene? *(sett ett kryss)*

☐ 1 Ingen
☐ 2 Svært lite
☐ 3 Lite
☐ 4 Moderat
☐ 5 Mye
☐ 6 Svært mye

8. Disse spørsmålene er om hvordan du føler deg, og om hvordan du har hatt det de siste 4 ukene som følge av **plagene i beina**. For hvert spørsmål, kryss av for det svaret som passer best med hvordan du har følt deg. Hvor mye i løpet av de 4 siste ukene-

	(Sett ett kryss på hver linje)	**Hele tiden**	**Det meste av tiden**	**Ganske ofte**	**Av og til**	**Sjelden**	**Aldri**
a.	har du vært bekymret for hvordan beina dine ser ut?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b.	har du følt deg irritabel	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c.	har du følt at du har vært til byrde for familie eller venner?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d.	har du vært bekymret for å skumpe borti ting?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e.	har dine beins utseende påvirket ditt klesvalg ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

ERRATUM LIST

Paper I:

Page 843 in paper I, first paragraph in the result section: Eight cases with a diagnosis of both PE and DVT in a lower limb should be included in the 204 with DVT in a lower limb. The correct sentence should be: “Eight cases with DVT in the lower limb had a symptomatic and objectively confirmed PE at the time of diagnosis; for the analyses these were included in the 204 cases with DVT in the lower limb”.

Page 844 in paper I, first paragraph: I have written that “10% of controls had a self-reported Villalta score of ≥5 representing some grade of PTS”. We have defined PTS as a score of ≥5 in a limb with previous DVT, and controls have not had DVT (at least not until delivery in the index pregnancy). The correct had been to leave out the part of the sentence that says “representing some grade of PTS”.

Paper II:

Page 1931 in paper II, patients/methods section in the summary: “313 women with pregnancy-related DVT” should be replaced with “313 women with pregnancy-related VT.” 74 of these 313 cases had PE.

I

II

III