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Long-term outcome after pregnancy-related venous thrombosis

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ABSTRACT

There is limited knowledge of the long-term outcomes after pregnancy-related venous thrombosis (VT). Cohort studies monitoring long-term complications have never been conducted in this population, and the present evidence is based on data from a few observational studies. The risk of post-thrombotic syndrome (PTS) as a long-term complication after deep vein thrombosis (DVT) in pregnancy is considerable. It is most pronounced in women with a proximal DVT occurring postpartum. Quality of life (QOL) is reduced, but limited to women who develop PTS. Mortality is higher than in the general population during the first year after acute thrombosis, but not thereafter, and the long-term risk of cancer does not seem to be increased. The long-term risk of recurrent VT, subsequent arterial thrombosis, or chronic thromboembolic pulmonary hypertension is unknown and more research is highly warranted.

Long-term outcomes of venous thrombosis outside pregnancy

The knowledge of long-term complications after pregnancy-related venous thrombosis (VT) is limited. Outside pregnancy approximately 50% of patients with a proximal deep vein thrombosis (DVT) in a lower limb develop post-thrombotic syndrome (PTS) [1,2]. PTS is a chronic and burdensome complication that comprises various degrees of pain, swelling, skin changes, varicose veins and sometimes overt ulcers in the leg previously affected by a DVT. Symptoms aggravate when the patient is standing or walking and improve when the leg is elevated [1,2]. PTS is associated with considerable costs for the society [3]. After pulmonary embolism (PE) 0.5–4% suffer chronic thromboembolic pulmonary hypertension (CTEPH) [4]. Patients with PTS and CTEPH report reduced quality of life (QOL) [5]. Even patients with PE in the absence of CTEPH experience reduced QOL [6,7]. Klok et al. recently suggested that some patients may develop a post-PE syndrome many years after an acute PE even in the absence of CTEPH, but this syndrome is not well characterized [8].

Patients with VT outside pregnancy are also at risk of recurrent VT. The risk peeks during the first months after discontinuation of anticoagulation and remains increased for many years. The cumulative recurrence rate may be as high as 30–40% over 10 years after VT. Patients with a transient risk factor for VT, such as surgery, trauma or use of a plaster-cast have a lower risk of recurrence (absolute risk of recurrence during the first five years 30–150 per 1000), while male gender seems to double the risk [9–13]. Patients with unprovoked VT are at higher risk for recurrent VT (absolute risk 300 per 1000), and these patients have a two to three fold increased risk of subsequent arterial thrombosis [13,14], show increased mortality [15,16], and have a two to three fold increased risk of developing subsequent cancer compared to patients without VT, particularly the first year after VT [17].

Risk of recurrent thrombosis

We are not aware of studies that have assessed the long-term risk of recurrent VT after pregnancy-related VT. Also the risk of subsequent arterial thrombosis is not known. In women with a previous VT (pregnancy-related or not) the recurrence rate is increased during a subsequent pregnancy unless prophylaxis is used [18]. Women with a history of VT associated with use of combined oral contraceptives or postmenopausal hormonal replacement therapy seem to have a lower risk for recurrence than women with unprovoked VT, but not as low as for provoked VT [19]. Hence it is likely that the recurrence rate after pregnancy-related VT is lower than after unprovoked VT and higher than VT provoked by surgery.

Brill-Edwards and co-workers investigated the safety of withholding heparin during pregnancy in 125 women with a single previous VT. Prophylaxis was given 4–6 weeks postpartum. Of these women 31 had their first VT in relation to a previous pregnancy and one of these experienced a recurrent VT two days postpartum. Twenty women used oral contraceptives at the time of their first VT and one had a recurrent VT in the last trimester. The two women with recurrent VT were both heterozygous for the F5 rs6025 (factor V Leiden) polymorphism. The authors concluded that women with a

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previous VT with a temporary risk factor, such as pregnancy, should not be given antepartum prophylaxis, unless they carry a thrombophilia, e.g., factor V Leiden. This study has several limitations including few women in each subgroup, inclusion late in pregnancy (15 ± 6 weeks), and exclusion of women screened for thrombophilia prior to inclusion [20]. The recent 2012 ACCP guidelines suggest antepartum and 6 weeks postpartum prophylaxis with low molecular weight heparin to women with a single unprovoked episode of VT or a previous pregnancy- or estrogen-related VT regardless of thrombophilia [21]. However, a recent study by Roeters van Lennep and co-workers suggested that a low-dose of LMWH (nadroparin 2850 IU once daily or equivalent dose of another LMWH) may not be sufficiently effective to prevent recurrent VT in women with a high risk of VT during pregnancy or postpartum [22]. A randomized controlled trial comparing two doses of LMWH in this population is ongoing (ClinicalTrials.gov number NCT01828697).

Risk of post-thrombotic syndrome (PTS)

The prevalence of PTS after pregnancy-related VT has not been evaluated in prospective studies. In the Norwegian Venous thrombosis In Pregnancy (VIP) study, 313 women with pregnancy-related VT during 1990–2003 and 353 controls were identified and met to participate in the study in 2006. Thirty-nine patients and four controls were excluded because of VT outside the lower limbs/lungs or missing data. Two-hundred-and-four of the included patients suffered DVT in the lower limb and 70 had pulmonary embolism (PE). The control group comprised 349 women naive for VT at the time of the index pregnancy. Forty-two percent of 204 women were diagnosed with PTS 3–16 years after an objectively verified pregnancy-related DVT and 7% had severe PTS. Proximal post-partum DVT was the most important predictor for PTS in this study and higher age and smoking were also independently associated with PTS [23]. Even patients with pregnancy-associated PE without documented concomitant DVT had significantly higher Villalta scores as compared with the controls (Table 1). These patients were not routinely tested for DVT if they did not have symptoms, and asymptomatic DVT in a lower limb in these patients is a plausible explanation for their higher Villalta scores.

Four smaller Swedish studies have also assessed chronic leg complaints after pregnancy-related DVT. These studies found that 16–35% of the women clinically had deep vein insufficiency or symptoms from the affected leg many years after the event [24–27]. Many definitions of PTS have been used, which probably explain the conflicting prevalences reported across the different studies. Recently, the Villalta score (Table 2) was recommended by the International Society on Thrombosis and Haemostasis (ISTH) for diagnosing and grading of PTS [28]. The above mentioned studies have not applied the Villalta score [24–27], but in the VIP-study a self-reported version of this score was used [16]. There is, however, growing awareness that the Villalta score may have limited sensitivity for PTS, is unspecific, and does also detect leg complaints caused by other diseases than DVT. This lack of sensitivity and specificity of the Villalta score implies uncertainness of existing knowledge of PTS.

Table 2
The Villalta score.

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

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 $\geq$5 points corresponds to any grade of PTS, 5–14 points to mild/moderate PTS, and $\geq$15 points or the presence of a venous ulcer to severe PTS. A score $<$5 indicates no PTS. Adapted from Villalta et al. [35].

Risk of chronic thromboembolic pulmonary hypertension

No studies have assessed the risk of developing CTEPH after pregnancy-related PE.

Osteoporosis after anticoagulation in pregnancy

Most reports on osteoporosis are based on older studies and treatment with unfractionated heparin, which found that approximately 3% developed osteoporosis during heparin therapy [29]. During the last one to two decades low molecular weight heparins have almost completely replaced use of unfractionated heparin for prophylaxis and treatment of VT in pregnancy, and the risk of osteoporosis and osteoporotic fractures during such therapy is very low. One large retrospective study on tinzaparin reported only 0.2% of the women developing osteoporosis that might be related to treatment with low molecular weight heparin, but all these women also had other contributing risk factors, such as treatment with corticosteroids, low body weight, pre-existing osteoporosis, and smoking [30]. Other studies report no osteoporosis or osteopenia [31]. Whether osteoporosis in pregnancy is caused by low molecular weight heparin alone or occurs in women with additional risk factors for osteoporosis remain to be identified.

Quality of life after pregnancy-related venous thrombosis

In the VIP-study women with PTS had a significantly lower disease-specific QOL 3–16 years after the event compared to controls as assessed by the VEINES-QOL/Sym questionnaire (mean VEINES-QOL scores 36.5 versus 52.3, lower scores meaning poorer QOL). The cases without PTS had mean scores comparable with controls (52.8) [23]. The VEINES-QOL/Sym questionnaire is the most frequently used disease-specific QOL questionnaire for patients with previous DVT [32]. The reduction in QOL remained at the same level when adjusting for possible confounders [23]. When we included the patients with PE and DVT outside the lower limbs (311 women in total), the long-term generic QOL and the subjective well-being three to 16 years after a pregnancy-related VT assessed by the Ferrans and Powers QOL Index (QLI) and the General Health Questionnaire (GHQ-20) were not different from a reference population. However, the cases reported pain outside the

Table 1
Villalta scores of the VIP study population [23].

Group	*N*	Villalta score	Villalta score $\geq$5		Villalta score $\geq$15	
		mean (SD)	*n*	% (95% CI)	*n*	% (95% CI)
Deep vein thrombosis	204	5.1 (5.8)	85	42 (35–49)	14	7 (3–11)
Pulmonary embolism	70	3.2 (4.7)	17	24 (14–34)	3	4 (0–9)
Controls	349	1.6 (2.7)	34	10 (7–13)	3	1 (0–2)

SD, standard deviation; CI, confidence interval.
The Villalta score after deep vein thrombosis is the score of the affected limb, and after pulmonary embolism the score of the lower limb with the higher score.