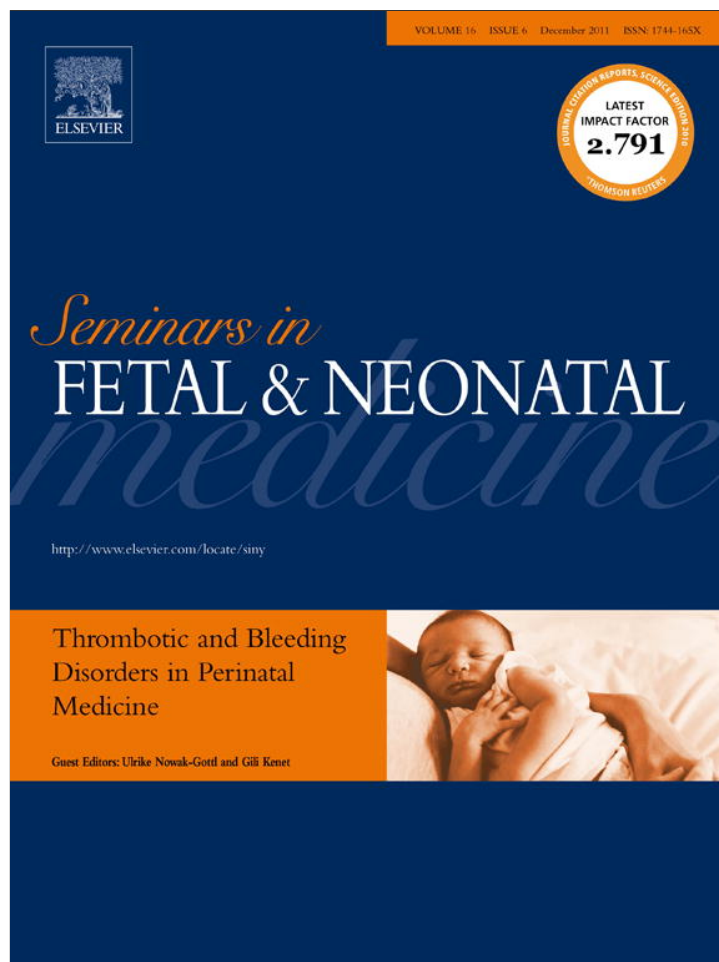


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## Thrombophilia testing in neonates and infants with thrombosis

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## S U M M A R Y

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In neonates and infants with idiopathic venous thrombosis (VTE) and in pediatric populations in which thromboses were associated with medical diseases, inherited thrombophilia (IT) have been described as risk factors. Follow-up data for VTE recurrence in neonates suggest a recurrence rate between 3% in provoked and 21% in idiopathic VTE. Apart from underlying medical conditions, recently reported systematic reviews on pediatric VTE have shown significant associations between factor V G1691A, factor II G20210A, and deficiencies of protein C, protein S and antithrombin, even more pronounced when combined IT were involved. Independent from the age at first VTE onset, the pooled odds ratios (OR: single IT) for VTE ranged from 2.4 for the factor II G20210A mutation to 9.4 in neonates and infants with antithrombin deficiency. The pooled OR for persistent antiphospholipid antibodies/lupus anticoagulants was 4.9 for pediatric patients with venous VTE. The factor II G20210A mutation (OR: 2.1), and deficiencies of protein C (OR: 2.4), S (OR: 3.1) and antithrombin (OR: 3.0) also played a significant role at recurrence. Based on these data, screening and treatment algorithms must be discussed.

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## 1. Introduction

Venous thromboembolism (VTE) in neonates and infants is a rare disease which is increasingly diagnosed, usually as a secondary complication of primary underlying diseases such as sepsis, cancer, congenital heart disease, elevated endogenous testosterone or after therapeutic interventions such as central venous lines (Table 1).<sup>1–13</sup> Pediatric VTE is a severe disease for which long term outcomes include lack of thrombus resolution in 50% of cases and the development of post-thrombotic syndrome in more than one-third of patients.<sup>8–11</sup> Within the entire childhood population, neonates are at the greatest risk for VTE,<sup>1,2,6,14</sup> with a second peak in incidence during puberty and adolescence. The annual incidence of venous events in the first year of life was estimated to be 5.1/per 100,000 live births in Caucasian children and 24 per 10,000 admissions of neonates to neonatal intensive care units.<sup>1,6,12–14</sup>

As in adults in children with idiopathic VTE and in pediatric populations in which thromboses were associated with underlying

diseases, lupus anticoagulants, deficiencies of antithrombin, protein C or protein S, the mutations of coagulation factor V (G1691A) and of factor II (G20210A) have been described as an additional risk factors.<sup>15–58</sup> Follow-up data for VTE recurrence in children are available from few reports and suggest a recurrence rate of ~3% in neonates and 21% in children with idiopathic VTE.<sup>7,9,12,13,38,48,49,51,54,56</sup>

## 1.1. Thrombotic locations in neonates and infants

In neonates and infants the most commonly reported VTEs diagnosed with suitable imaging methods<sup>59</sup> are renal vein thrombosis (Figure 1),<sup>1,6,42,49,51</sup> vena caval occlusion, and thromboembolic stroke (Figure 1), mainly of venous origin.<sup>6,13,14</sup> In addition, central-line-associated VTEs have been reported.<sup>2–4,13,14</sup> Further locations of childhood thromboembolism are cerebral venous thrombosis,<sup>39,41,43,45,47,56,57</sup> and portal or mesenteric vein thrombosis.<sup>27,46</sup> Purpura fulminans, a life-threatening event characterized histologically by microvascular thromboses in the dermis followed by perivascular hemorrhage, has been reported in neonates with congenital absence of protein C or protein S, or the presence of homozygous or heterozygous factor V G1691A mutation.

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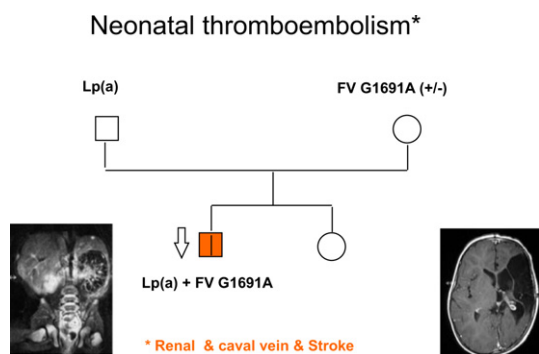
**Table 1**  
Examples for acquired risk factors associated with pediatric thromboembolism.

Perinatal diseases	Birth asphyxia Respiratory distress syndrome Infants of diabetic mothers Neonatal infections Necrotizing enterocolitis Dehydration Congenital nephrotic syndrome Polycythemia
Medical interventions	Central lines (arterial or venous) Surgery Immobilization Plaster casts Extracorporeal membrane oxygenation
Acute diseases	Trauma Sepsis Dehydration Acute rheumatic diseases Neprotic syndrome Acute lymphoblastic leukemia
Chronic diseases	Malignancies Renal diseases Cardiac malformations Chronic rheumatic diseases Metabolic diseases
Drugs	<i>E. coli</i> asparaginase Prednisone Coagulation factor concentrates Heparins Antifibrinolytic agents

1.2. Role of inherited thrombophilias [IT] in pediatric VTE

The distribution of IT varies in different countries with respect to the population background and the number of patient/controls investigated.

In recently published systematic reviews and meta-analyses, including observational studies in pediatric patients with deep venous VTE and cerebrovascular occlusion (cerebral venous thrombosis and stroke), >70% of patients had at least one clinical risk factor, independent from the age of first VTE onset.<sup>60–62</sup> The pooled odds ratios (OR) showed statistically significant associations between factor V G1691A; factor II G20210A; deficiencies of protein C, protein S, or antithrombin; elevated lipoprotein (a); combined IT (pedigree: Figure 1) and the presence of lupus anticoagulants/antiphospholipid antibodies and VTE onset (Table 2).<sup>62,63</sup> For second VTE events, statistically significant associations with recurrence were found for protein S or antithrombin deficiency, the factor II variant and combined IT.<sup>50</sup> In addition, the pooled OR for persistent antiphospholipid antibodies/lupus anticoagulants was



**Fig. 1.** Pedigree and thromboembolic manifestation in a male neonate (grey square) with combined thrombophilic traits [elevated lipoprotein (a): Lp(a) and factor V G1691A:FV]; renal vein thrombosis as origin for thromboembolic stroke (age of onset and three months).

**Table 2**  
Pooled odds ratios (95% confidence intervals) for genetic traits and persistent antiphospholipid antibodies associated with a first VTE onset in children and in pediatric patients with recurrent VTE<sup>60,62</sup>.

Inherited thrombophilia	First VTE onset fixed-effects model	Recurrent VTE fixed-effects model
Protein C deficiency	7.7 (4.4–13.4)	2.4 (1.2–4.4)
Protein S deficiency	5.8 (3.0–11.0)	3.1 (1.5–6.5)
Antithrombin deficiency	9.4 (3.3–26.7)	3.0 (1.4–6.3)
Factor V G1691A	3.6 (3.8–4.8)	1.4 (0.4–1.2)
Factor II G20210A	2.6 (1.6–4.4)	2.1 (1.01–3.5)
Lipoprotein (a)	4.5 (3.3–6.2)	0.8 (0.5–1.4)
LA/aPL	4.9 (2.2–10.9)	Not available
≥2 inherited traits	9.5 (4.9–18.4)	4.5 (4.5–6.9)

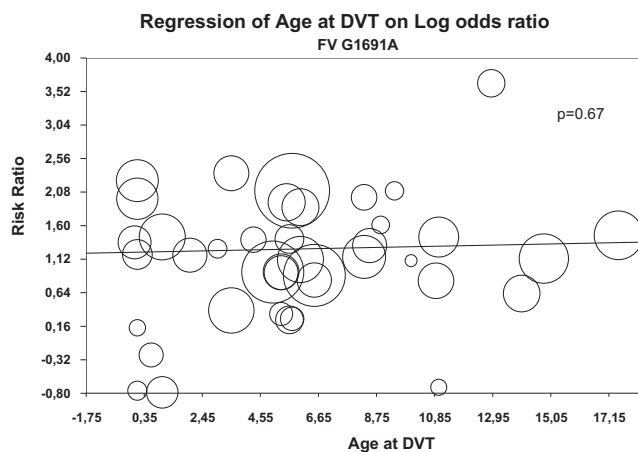
VTE, venous thromboembolism; LA/aPL, lupus anticoagulants/antiphospholipid antibodies.

6.6 for children with cerebrovascular occlusion and 4.9 for pediatric cases with venous VTE.<sup>61,62</sup> The factor II G20210A mutation, protein C, protein S and antithrombin deficiency also played a significant role in recurrent VTE. In all three pediatric meta-analyses, age at first thromboembolic onset (Figure 2), publication year or study country did not play a significant role on the OR obtained, thus data are valid for the entire pediatric population aged neonate to 18 years.

1.3. Inherited thrombophilia screening in neonates and children

Follow-up data for VTE recurrence in children are available from few reports, suggesting a recurrence rate between 3% in neonates and 21% in children with idiopathic VTE.<sup>7,9,12,13,38,48,49,51,54,56,64,65</sup> However, in the pediatric age group, it remains a controversial issue as to whether patients with thrombosis or offspring from thrombosis-prone families benefit from screening for IT.<sup>64,66–74</sup>

Based on the data obtained from the recent meta-analyses and systematic reviews, at least the symptomatic propositus should be screened in a specialized coagulation unit for prothrombotic defects,<sup>60–63</sup> such as antithrombin, protein C or protein S deficiency. Furthermore, since the rate of combined IT associated with a first symptomatic onset is not negligible in the pediatric population, non-major risk factors such as the factor V G1691A mutation or the prothrombin G20210A variant should be included in a screening program. Since a second VTE after a first episode of spontaneous VTE, i.e. thrombosis in the absence of further secondary causes, has indicated a subgroup of pediatric patients suffering from combined prothrombotic risk factors to be at high



**Fig. 2.** Influence of factor V G1691A on age at first thromboembolic onset (regression analysis: data set from Young et al.<sup>60</sup>). DVT, deep vein thrombosis.

risk of recurrent thrombosis,<sup>38</sup> the latter approach to search for multiple risk factors is stressed.

Based on the fact that an effective primary prophylactic anticoagulant therapy is available in risk situations, IT screening programs must be individually discussed in selected non-symptomatic siblings and further first degree family members in high risk families such as antithrombin, protein C or protein S deficiency carriers, or in cases in which combined IT are identified.

#### 1.4. Treatment modalities

As in adults it is still a matter of debate whether long term continuation of anticoagulant treatment should be considered after a first VTE in carriers of a thrombophilic trait.<sup>75</sup> In neonates and infants with a first VTE, randomized therapeutic trials are lacking and treatment guidelines are mainly adapted from adults,<sup>76–78</sup> but more than in adults, the prolonged use of anticoagulant treatment in a physically active age group must be weighed against the risk of bleeding.

## 2. Conclusions

Apart from risk stratification in neonates and infants with VTE based on clinically acquired circumstances along with acquired and genetic thrombophilic risk factors, future evidence-based prospective anticoagulant/antithrombotic treatment trials including newly available anticoagulants are mandatory to effectively prevent thrombosis-related long term complications in children, such as the post-thrombotic syndrome.<sup>79</sup>

#### Practice points

- Thrombotic locations in neonates and infants include unusual and multiple sites.
- Presence of thrombophilic risk factors are not age dependent.
- Screening is recommended on the individual population-based background.

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