

# Risk and management of congenital thrombophilia in transgender individuals on hormone therapy



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## BACKGROUND

Gender-affirming hormone therapy (GAHT), particularly estrogen-based regimens, is associated with an increased risk of venous thromboembolic events (VTE), which may be exacerbated in individuals with hereditary thrombophilia. On the other hand, testosterone therapy has been associated with secondary erythrocytosis, but does not show an increase thromboembolic risk. Despite this risk, the prevalence and clinical implications of hereditary thrombophilia in transgender individuals remain underexplored.

## AIM

This study investigates the prevalence of hereditary thrombophilia in a cohort of TGD individuals undergoing GAHT. By characterizing the distribution of thrombophilic conditions in this population, we aim to provide insights into the intersection of gender-affirming care and thrombotic risk management.

## MATERIALS AND METHODS

This study is part of the HYPERGENDER study: a longitudinal study designed to evaluate the haematological effects of GAHT in TGD individuals. Participants were assessed at baseline and after 3, 6, 12 and 24 months of GAHT.

We screened 114 transgender individuals (54 AMAB, 60 AFAB) at the University Hospital of Padua (Italy) for hereditary thrombophilia, including factor V Leiden (FVL), prothrombin G20210A (PT20210A), antithrombin (AT), protein C (PC), and protein S (PS) deficiencies, as well as antiphospholipid antibodies.

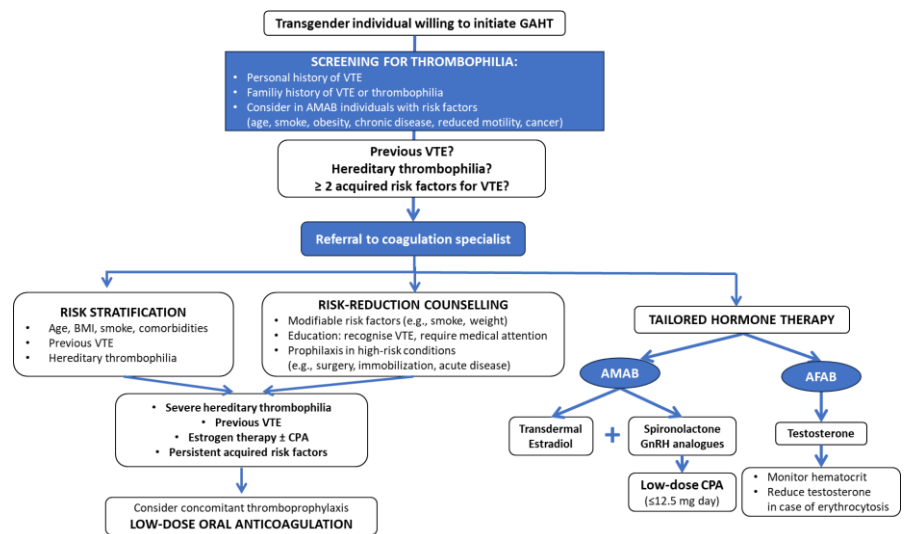
## RESULTS

Hereditary thrombophilia was identified in 9.6% of participants, including two cases of severe thrombophilia. No participants tested positive for antiphospholipid antibodies. Individuals with thrombophilia had a higher prevalence of personal and family history of VTE. Three thrombotic events were recorded prior to GAHT: one transgender woman (heterozygous FVL) with unprovoked lower limb VTE, one transgender man (PC deficiency) with neonatal cerebral ischemia, and one transgender man (heterozygous FVL) with subclavian VTE during chemotherapy. **Figure 1** explains how we managed TVE risk in the our population.

Sex assigned at birth (age)	Thrombophilia type	BMI (Kg/m <sup>2</sup> )	Smoke	VTE family history	Previous VTE	Anticoagulant therapy	GAHT regimen	Follow-up (months)
AFAB (22 years)	het FVL	21.0	no	no	no	-	T gel 69 mg/day	18
AFAB (26 years)	PC deficiency	36.9	yes	no	yes	-	T gel 46 mg/day	6
AFAB (23 years)	het FVL	21.0	no	no	yes	Rivaroxaban 10 mg/day	TU 1000 mg every 12 weeks	24
AFAB (25 years) <sup>§</sup>	het FVL	27.0	no	yes	no	-	TU 1000 mg every 12 weeks	24
AFAB (30 years)	het FVL	17.0	no	yes	no	-	T gel 23 mg/day	27
AMAB (39 years)	hom G20210A	24.5	no	no	no	-	E2 patch 50 mcg day + spironolactone 50 mg/day	3
AMAB (49 years)	het G20210A	22.1	no	no	no	-	E2 gel 1.5 mg/day + CPA 12.5 mg/day	12*
AMAB (20 years)	het FVL	29.7	no	no	no	-	E2 gel 2 mg/day + CPA 25 mg/3 day per week	12*
AMAB (18 years)	het G20210A	20.9	yes	yes	no	-	E2 spray 6.12 mg day + spironolactone 50 mg day	12
AMAB (26 years)	het G20210A	26.5	no	yes	no	-	E2V pills 4 mg + CPA 12.5 mg day	15**
AMAB (31 years)	het FVL	30.4	yes	no	yes	Rivaroxaban 20 mg/day	E2 spray 6.12 mg/day + CPA 25 mg/3 days per week	38

T: testosterone; TU: testosterone undecanoate; E2: estradiol; E2V: estradiol valerate; CPA: cyproterone acetate; GAHT: gender-affirming hormone therapy; FVL: Factor V Leiden; G20210A: prothrombin mutation G20210A; het: heterozygous; hom: homozygous. <sup>§</sup>Spironolactone was not tolerated or not effective. <sup>\*\*</sup>Self-administered GAHT. \*The patient developed mild erythrocytosis.

**Table 1.** Clinical characteristic of transgender individuals with congenital thrombophilia.



**Figure 1.** Management of thromboembolic risk in transgender individuals undergoing gender-affirming hormone therapy.

## CONCLUSIONS

A multidisciplinary approach involving coagulation specialists and endocrinologists was implemented to optimize risk reduction strategies, including tailored GAHT regimens and anticoagulation when necessary. No VTE occurred during a 15-month follow up. These findings highlight the importance of thrombophilia screening to enable individualized care and enhance the safety of GAHT protocols.



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