

Guidelines for Thrombophilia Testing

Maidstone and Tunbridge Wells NHS Trust

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1. Introduction

Heritable thrombophilia describes an inherited tendency for venous thromboembolism (VTE). Testing for heritable thrombophilia does not typically predict recurrence in unselected patients. In a large cohort study, testing for inherited thrombophilia did not reduce VTE recurrence. Moreover, in affected asymptomatic relatives followed prospectively, there is a low risk of VTE.

Thrombophilia testing is expensive and time-consuming. Indiscriminate testing can result in uncertainty about the practicalities of dealing with positive results. Positive results may cause unjustified concern to an individual and their families whereas a negative result may provide false reassurance. It is important, therefore, that screening is targeted appropriately and only performed when the results will have a direct impact on clinical management

2. Aims of guideline

To provide pragmatic recommendations to clinicians in relation to testing for thrombophilia in the clinical management of

- a. VTE
- b. Thromboprophylaxis in pregnancy
- c. Oestrogen therapy
- d. Pregnancy morbidity

3. Policy

Thrombophilia testing will only be carried out on patients who fulfill the criteria outlined below in section 6. A copy of these guidelines will be kept on the Kinesis system. All requests from primary care should be discussed via the Kinesis system or by speaking to the Haematology Lead for Thrombosis (Dr Clare Wykes at MTW). Requests from within MTW NHS Trust should be discussed with the Haematology Lead for Thrombosis (Dr Clare Wykes). Clear indications (see section 6 below) must be supplied on the requesting form. Any samples from patients not fulfilling these criteria will not be sent for testing. Wherever possible, the Haematology Laboratory staff will try to contact the requesting clinician before discarding the sample. Difficult cases can be referred to Dr Clare Wykes' clinic.

4. What is included in the Thrombophilia screen?

Heritable thrombophilias tested for at MTW are:

- Antithrombin
- Protein C

- Protein S
- APCR (screening test for Factor V Leiden)
- Prothrombin (PT) gene mutation

The only acquired thrombophilia tested at MTW is Antiphospholipid Syndrome (APLS) in which two separate investigations are used:

- DRVVT (to detect the lupus anticoagulant)
- Anticardiolipin antibodies

Investigations for other acquired pro-thrombotic conditions such as myeloproliferative neoplasms (MPNs) and paroxysmal nocturnal haemoglobinuria (PNH) should be discussed with a Consultant Haematologist at MTW NHS Trust.

5. Who should have Thrombophilia testing?

5.1. Venous thromboembolism

- Patients in whom a decision has been made to remain on long-term anticoagulation (including but not exclusively: recurrent VTE, unprovoked proximal DVT or PE): *Testing for thrombophilia is **not** indicated as results will not affect management*
- Unprovoked proximal DVT or PE with decision to stop anticoagulation: *DRVVT, anticardiolipin antibodies. Consider full thrombophilia screen if there is a history of VTE in first-degree relative.*
- Women of childbearing age with minor, non-oestrogen provoking factor if undecided regarding future antenatal thromboprophylaxis: *Full thrombophilia screen.*

5.2. For Decisions regarding Thromboprophylaxis in Pregnancy

- Women should be assessed for risk of pregnancy-associated VTE primarily in relation to clinical risk factors (RCOG green top guidelines).
- Women with previous VTE due to major provoking factor not related to pregnancy or use of oestrogens would not usually qualify for thromboprophylaxis. *Thrombophilia testing not indicated*
- Women with previous unprovoked VTE or pregnancy or combined oestrogen contraception (COC)-related VTE will qualify for thromboprophylaxis on clinical risk alone. *Testing for heritable thrombophilia is not indicated*
- Women with previous non-oestrogen related VTE due to a minor provoking factor e.g. long-distance travel. *Full thrombophilia screen.* The presence of a high-risk thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, homozygosity for factor V Leiden and homozygosity for prothrombin 20120A mutation) will influence the decision to institute ante partum thromboprophylaxis.
- Asymptomatic women without clinical risks sufficient to warrant thromboprophylaxis but with a family history of VTE in a first degree relative (**thrombophilic status unknown**), if the VTE was unprovoked, provoked by a minor risk factor, related to pregnancy or combined oral contraceptive. The presence of a high-risk thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, homozygosity for factor V Leiden and homozygosity for prothrombin 20120A mutation) will influence the use of ante partum thromboprophylaxis: *Full thrombophilia screen.*

- Asymptomatic women without clinical risks sufficient to warrant thromboprophylaxis but with a family history of VTE in first degree relative (**with known thrombophilia**) if the VTE was unprovoked, provoked by a minor risk factor, related to pregnancy or combined oral contraceptive. *Test only for known defect* and consider thromboprophylaxis in conjunction with clinical risk factors.

5.3. For decisions regarding prevention of VTE in patients considering oestrogen preparations

Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended.

- If there is a history of VTE in a first-degree relative that is unprovoked, provoked by a minor risk factor, related to pregnancy or combined oral contraceptive (regardless of known heritable thrombophilia status) alternative contraception, such as progesterone-only preparations or transdermal hormone replacement therapy (HRT) should be suggested.

5.4. Pregnancy Morbidity

In women with one or more of the following

- One or more morphologically normal fetal deaths after 12 weeks of gestation
- Three or more unexplained consecutive miscarriages before 12 weeks of gestation
- One or more pre-term births before 34th week due to severe pre-eclampsia, eclampsia or placental insufficiency

testing for APLS (DRVVT, anticardiolipin antibodies on two separate occasions at least 6 weeks apart) is warranted.

Decisions to test for inherited thrombophilias should be made after discussion with Consultant Obstetrician, Consultant Haematologist and patient. Until recently the evidence that the use of low molecular weight heparin (LMWH) in women with heritable thrombophilias reduces pregnancy morbidity has been weak. A recent randomized study (Rodger, 2014) suggests that giving LMWH to women with thrombophilia does not reduce pregnancy morbidity.

5.5. Other Indications for Thrombophilia Testing

a. Arterial thrombosis

Consider testing for APLS if patient under 60 years. These should be discussed with Consultant Haematologist.

b. Unusual sites: e.g. abdominal, central nervous system.

These should be discussed with Consultant Haematologist (Dr Clare Wykes at MTW).

c. Patients developing warfarin skin necrosis

These patients should be discussed with Consultant Haematologist. *Protein C and protein S testing is indicated.*

6. Timing of tests

At least 4 weeks after stopping warfarin

At least 24 hours after stopping rivaroxaban/apixiban

At least 8 weeks after most recent miscarriage/birth where relevant

7. Samples required

Full thrombophilia screen

- 4 x citrate (light blue top, filled to correct level)
- 1 x clotted (red top)

Antiphospholipid syndrome

- 2 x citrate (light blue top, filled to correct level)
- 1 x clotted (red top)

Known defects

- Antithrombin: 1 x citrate (light blue top, filled to correct level)
- Protein C: 1 x citrate (light blue top, filled to correct level)
- Protein S: 1 x citrate (light blue top, filled to correct level)
- Factor V Leiden or PT gene mutation: 1 x EDTA (purple top)

Ideally samples should be taken in hospital phlebotomy department. If this is not practical samples must reach laboratory within four hours.

8. References

Baglin, T. et al. (2010). Clinical guidelines for testing for heritable thrombophilia, *British Journal of Haematology*, 149: 209-220

Royal College of Obstetricians and Gynaecologists Green-top Guidelines 37a, April 2015

NICE Guidelines [CG144] June 2012

Rodger, M. et al. (2014). Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial, 384: 1673 – 1683.