THROMBOPHILIA AND ADVERSE PREGNANCY OUTCOME


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INTRODUCTION

THROMBOPHILIAS - DEFINITION

• Disorders of the haemostatic mechanisms which are likely to predispose to thrombosis

1

• The presence of inherited and acquired thrombophilias has been linked to most cases of maternal venous thrombotic events and adverse obstetric outcomes.

2

• Although present in about 15% of white European populations, these disorders are responsible for more than half of all maternal thromboembolic events and have been linked to a five-fold increased risk of stillbirth, IUGR, abruption and severe preeclampsia.
INTRODUCTION

THROMBOPHILIAS

Studies suggests that all patients with a history of prior venous thrombotic events and those with adverse pregnancy events such as fetal loss, abruptions, severe intra-uterine growth restriction and early onset severe preeclampsia, should be evaluated for thrombophilias.

Screening tests for inherited and acquired thrombophilias
### INTRODUCTION

#### RISK OF THROMBOSIS

<table>
<thead>
<tr>
<th>HIGH RISK</th>
<th>MEDIUM RISK</th>
<th>LOW RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiphospholipid Syndrome</td>
<td>• Protein C deficiency</td>
<td>• Heterozygosity for FV Leiden mutation</td>
</tr>
<tr>
<td>• Antithrombin deficiency</td>
<td>• Protein S deficiency</td>
<td>• Heterozygosity for PT G20210A mutation</td>
</tr>
<tr>
<td></td>
<td>• Homozygosity for FV Leiden mutation</td>
<td></td>
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<tr>
<td></td>
<td>• Homozygosity for PT G20210A mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Combined heterozygosity (FV de Leiden and PT 20210A)</td>
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</table>

FV Leiden: factor V Leiden; PT G20210A: prothrombin G20210A
There is a consensus on the diagnosis and treatment of antiphospholipid syndrome in pregnancy. However, detection and management of inherited thrombophilias remains controversial.
INTRODUCTION

INHERITED THROMBOPHILIAS

- Association between early pregnancy loss and inherited thrombophilias
- Occurrence of activated protein C (APC) resistance in the absence of FV Leiden
- Link between hyperhomocysteinemia and recurrent miscarriage
- Detection of methylenetetrahydrofolate reductase (MTHFR) mutation
- Tests for mutation in the plasminogen activator inhibitor (PAI-1) gene
- Screening for inherited dysfibrinogenaemia
OBJECTIVE

- To describe the population with criteria for thrombophilias screening
- To identify the abnormal results
- To evaluate choice of prophylaxis and pregnancy outcome
MATERIAL AND METHODS

• We reviewed the charts of 46 women studied for thrombophilias between June 2004 and September 2006

• Our institution:
  - a maternity, with around 3 500 deliveries per year
  - without other medical specialities, as in a central hospital

• 40 cases: screening during preconception
  6 cases: screening during pregnancy

• Ages between 20 and 45 years old
• Median = 30
INCLUSION CRITERIA FOR TROMBOPHILIAS SCREENING

OBSTETRIC CRITERIA

- Second and third trimester unexplicated fetal loss
- Abruption
- Severe intrauterine growth restriction (IUGR)
- Severe Preeclampsia
- Recurrent miscarriage
INCLUSION CRITERIA FOR TROMBOPHILIAS SCREENING

NON-OBSTETRIC CRITERIA

- Previous personal thromboembolic disease
- Personal history of stroke
- First-degree history of thromboembolic disease / thrombophilia
- False positive VDRL
## LABORATORY TESTS FOR TROMBOPHILIAS SCREENING

**Acquired Trombophilias**
- Lupus anticoagulants
- Anticardiolipin antibodies
- β2-glycoprotein antibodies
- Anti-nuclear antibodies

**Inherited Trombophilias**
- Activated protein C resistance (APCR)
- Protein S
- Protein C
- Antithrombin III (AT III)
- Homocysteinemia
- Factor VIII
- Genetic tests:
  - Factor V Leiden mutation
  - Prothrombin gene mutation (PT G20210A)
RESULTS

OTHERS RISK FACTORS FOR THROMBOTIC EVENTS

4 women ≥40 years

- Age >40: 42 (91.3%)
- Age <40: 4 (8.7%)

5 women ≥4G

- >4G: 41 (89.1%)
- <4G: 5 (10.9%)

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Fraga Marantes S, Sampaio MM, Silva S, Lima ML, Cunha AC
RESULTS

INCLUSION CRITERIA FOR SCREENING

The majority with obstetric criteria (84.8%)

n=46

4 (8.7%)

3 (6.5%)

39 (84.8%)

Obst criteria  Non-obst criteria  Both
RESULTS

INCLUSION CRITERIA FOR SCREENING

Recurrent miscarriage was the most frequent criteria, in more than half of the patients

- FL: fetal loss
- RM: recurrent miscarriage
- PE: preeclampsia
- IUGR: intrauterine growth restriction

n= 43
### RESULTS

<table>
<thead>
<tr>
<th>Other factor</th>
<th>Criteria for screening</th>
<th>anticard antib.</th>
<th>Lupus anticoag.</th>
<th>ANA’s</th>
<th>ATIII def.</th>
<th>APCR</th>
<th>FV leiden</th>
<th>PT G20210A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Multiparity</td>
<td>RM + Non-obstet.</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>(none)</td>
<td>RM + FL</td>
<td>+</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(none)</td>
<td>RM + FL + Non-obstet.</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(none)</td>
<td>RM</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(none)</td>
<td>RM</td>
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<td>+</td>
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<tr>
<td>6</td>
<td>Age&gt; 40</td>
<td>RM</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>Heterozy</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Multiparity</td>
<td>RM + FL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Homozy</td>
</tr>
</tbody>
</table>

- 7 cases with positive screening tests (15.2%): 3 cases of AFS (6.5%)
  - 4 cases of inherited thrombophilia (8.7%)
- All cases had history of adverse pregnancy outcome, including recurrent miscarriage.
<table>
<thead>
<tr>
<th>Criteria for screening</th>
<th>Thrombophilia</th>
<th>Thromboprophylaxis</th>
<th>Pregnancy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RM + Non-obst</td>
<td>AFS</td>
<td>LMWH: prophylatic dose (40mg/day) Aspirin 100mg/day</td>
<td>Delivery at 38 weeks; No adverse outcome in pregnancy; Healthy neonate</td>
</tr>
<tr>
<td>2 RM + FL</td>
<td>AFS</td>
<td>LMWH: therapeutic dosage 120 mg/day Aspirin 100mg/day</td>
<td>Pregnancy ongoing</td>
</tr>
<tr>
<td>3 RM+PE + Non-obst</td>
<td>AFS</td>
<td>LMWH: therapeutic dosage (120 mg/day) Aspirin 100mg/day</td>
<td>MISCARRIAGE</td>
</tr>
<tr>
<td>4 RM</td>
<td>APCR</td>
<td>LMWH: prophylatic dose (40mg/day)</td>
<td>Delivery at 40 weeks; No adverse outcome in pregnancy; Healthy neonate</td>
</tr>
<tr>
<td>5 RM</td>
<td>AT III deficiency</td>
<td>LMWH: therapeutic dosage (120 mg/day)</td>
<td>Delivery at 37 weeks; No adverse outcome in pregnancy; Healthy neonate</td>
</tr>
<tr>
<td>6 RM</td>
<td>APCR + Heterozygosity for FV</td>
<td>LMWH: prophylatic dose (40mg/day)</td>
<td>Delivery at 40 weeks; No adverse outcome in pregnancy; Healthy neonate</td>
</tr>
<tr>
<td>7 RM + FL</td>
<td>Homozygosity for PT G20210A</td>
<td>None</td>
<td>No attempt for pregnancy</td>
</tr>
</tbody>
</table>

LMWH: low molecular weight heparin; in our institution: enoxaparin
COMMENTS

• Limitations:  - a reduced number of cases included in the study
  - early stage of thrombophilia screening

• The most frequent adverse outcome in women with thrombophilia was recurrent miscarriage

• Thrombophilia was present in about 15% of the women - in agreement with the percentage described in literature

• Inherited thrombophilia was significantly present.

• LMWH was well tolerated and with good results in reducing adverse obstetrical outcomes in most woman with thrombophilia (including the inherited)
The need of confirming:
- Prot S deficiency after delivery and breastfeeding
- APS 12 weeks after the first test

Laboratory investigations should only be applied when clinically justified

It is important to consider the clinical history ahead of laboratory test results
REFERENCES