Consensus conference

THROMBOPHILIA AND PREGNANCY
PREVENTING MATERNAL AND PLACENTAL THROMBOSIS

14 March 2003 - Institut Pasteur – Paris, France

GUIDELINES (SHORT VERSION)
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NOTE

This conference was organised and conducted in accordance with the method recommended by the French National Agency for Accreditation and Evaluation in Health (ANAES). The conclusions and recommendations contained in this document were drawn up by an independent conference jury. ANAES is not responsible for their content.

The pharmaceutical industry did not participate in this consensus conference.
QUESTIONS DISCUSSED

1 – What are the risk factors for maternal venous thromboembolism?

2 - What are the risk factors for placental vascular disease?

3 - Which further investigations should be performed, and for which patients?

4 - What treatments are available? Which patients should be treated, and what form should that treatment take? What information should patients be given?

A grade A guideline is based on scientific evidence established by trials of a high level of evidence. A grade B guideline is based on presumption of a scientific foundation derived from studies of an intermediate level of evidence. A grade C guideline is based on studies of a low level of evidence. If the grade of evidence is not specified, the guidelines are based on a consensus expressed by the jury.
INTRODUCTION - DEFINITION OF THROMBOPHILIA

- In order to distinguish between the very different concepts of risk factor and disease, the jury proposed the following clinical and biological definition of thrombophilia.

A diagnosis of thrombophilia is made in the following situations:

1. **confirmed personal history AND/OR a family history of venous thromboembolism (VTE), characterised by recurrent thrombosis; or onset of thrombosis before the age of 45; or an unusual location (i.e. other than the lower limbs);**

2. **evidence of at least one clearly defined genetic risk factor (currently, deficiency of antithrombin (AT), protein C (PC) or protein S (PS), factor V Leiden, factor II 20210A).**

Over the next few years, further genetic factors may be added to those cited above, when it has been shown that they are directly and independently responsible for thrombosis.

Thrombophilia may be combined with acquired risk factors for deep vein thrombosis (DVT). A diagnosis of thrombophilia does not dispense with the need to look for acquired risk factors for VTE.

- It has been shown that there is a link between certain hereditary biological risk factors VTE and placental vascular disease (PVD). Nevertheless, the jury felt that at present these data are inadequate and too varied to be referred to as exclusively obstetric thrombophilia (i.e. in the absence of venous thrombosis), although this hypothesis may be proved in the future.

- **Acquired VTE.** Patients presenting recurrent VTE combined only with acquired biological risk factors and with no family history are defined as having acquired VTE.

- **Idiopathic familial VTE.** Patients presenting recurrent VTE with no identified genetic risk factors, but with a documented family history of DVT, will be defined as having idiopathic familial VTE.

**QUESTION 1**

*What are the risk factors for maternal venous thromboembolism?*

VTE is rare in pregnant women, occurring in approximately 1 in 1 000 pregnancies. However, pregnancy is a risk factor for VTE, which is approximately 5 times more common in pregnant women than in the general population. It causes between 5 and 10 deaths a year in France, a third of which are avoidable. VTE is attributed to both mechanical factors (compression of veins by a pregnant uterus) and biological factors (which in particular explain the occurrence of phlebitis and pulmonary embolism during the first trimester). It may occur at any time during pregnancy and the postpartum, with a higher risk during the first few days after labour.

In addition to these factors, which apply to all pregnancies, there are a number of additional risk factors derived from history-taking, clinical examination and laboratory tests.
• **Risk factors established from the history:**
  - confirmed personal history of VTE or pulmonary embolism, especially significant if the event occurred at a young age, with no trigger factors, or has recurred;
  - confirmed family history of similar events.

• **Risk factors established from the clinical examination:**
  - age > 35 years;
  - obesity with body mass index (BMI) > 30 or weight > 80 kg;
  - hypertension;
  - varices;
  - underlying thrombogenic disease (nephrotic syndrome, chronic inflammatory bowel disease, infection, etc.);
  - multiparity;
  - prolonged bed rest;
  - pre-eclampsia (PE);
  - caesarean section, especially as an emergency.

• **Risk factors established from biochemistry values:**
  - inherited:
    - antithrombin deficiency,
    - protein C deficiency,
    - protein S deficiency,
    - factor V Leiden,
    - 20210A allele of the prothrombin gene;
  - acquired:
    - antiphospholipid antibody syndrome (APLS),
    - hyperhomocysteinaemia.

As most studies of risk factors have involved univariate analyses, the possible relationships between the different factors and the specific weight of each have only very rarely been analysed. This makes it difficult to define different risk levels for VTE in pregnant women. However, a classification of level of risk for pregnancy-associated VTE would help to optimise medical care, and so, with these reservations, the following classification has been proposed (*Table 1*).

**QUESTION 2**

*What are the risk factors for placental vascular disease?*

1. DEFINITION AND EPIDEMIOLOGY OF PLACENTAL VASCULAR DISEASE (PVD)

PVD is a term used to cover certain obstetric disorders related to abnormal vascularization of the placenta, causing placental ischaemia: **PE, eclampsia, retroplacental haematoma (RPH), a high proportion of fetal deaths in utero (FDIU) and intrauterine growth retardation (IGR).** Careful aetiological investigation is needed to establish that the IGR or FDIU is probably vascular, by eliminating other non-vascular causes.
Prevalence of these disorders is approximately 3% for PE, 5 per 10 000 for eclampsia, 5-15‰ for RPH, 3-10% for IGR and 5‰-3% for FDIU, depending on the specific definitions used.

Table 1. Risk categories for maternal VTE

<table>
<thead>
<tr>
<th>Major risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who have received anticoagulant therapy before pregnancy for an episode of VTE related to thrombophilia</td>
<td>History of VTE, without trigger factors, with or without biological risk factors</td>
</tr>
<tr>
<td>Symptomatic AT deficiency*</td>
<td>The following asymptomatic biological risk factors screened for in relation to familial VTE:</td>
</tr>
<tr>
<td>APLS (clinical signs and laboratory markers)</td>
<td>- heterozygote status for PC or PS deficiency</td>
</tr>
<tr>
<td></td>
<td>- homozygote status for factor V Leiden</td>
</tr>
<tr>
<td></td>
<td>- homozygote status for 20210A allele of the factor II gene</td>
</tr>
<tr>
<td></td>
<td>- combination of disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of VTE, with trigger factors and no biological risk factors</td>
<td>Age &lt; 35 years</td>
</tr>
<tr>
<td>The following asymptomatic biological risk factors screened for in relation to familial VTE:</td>
<td>No other concomitant risk factors</td>
</tr>
<tr>
<td>- heterozygote status for factor V Leiden</td>
<td></td>
</tr>
<tr>
<td>- heterozygote status for 20210A allele of the factor II gene</td>
<td></td>
</tr>
<tr>
<td>Risk factors established from clinical examination:</td>
<td></td>
</tr>
<tr>
<td>- Caesarean section (especially as an emergency)</td>
<td></td>
</tr>
<tr>
<td>- age &gt; 35 years</td>
<td></td>
</tr>
<tr>
<td>- 1 or more clinical factors predisposing to VTE: obesity (BMI &gt; 30 or weight &gt; 80 kg), varices, hypertension</td>
<td></td>
</tr>
<tr>
<td>- 1 or more obstetric factors predisposing to VTE: multiparity &gt; 4, pre-eclampsia, prolonged bed rest, etc.)</td>
<td></td>
</tr>
<tr>
<td>- underlying thrombogenic disease (nephrotic syndrome, chronic inflammatory bowel disease, infection, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

* for asymptomatic forms, major or high risk should be assessed on a case-by-case basis, attaching particular importance to family history of the disease.

VTE: venous thromboembolism; APLS: antiphospholipid antibody syndrome

2. DEFINITION OF GROUPS AT RISK FOR PVD

- Patients at high risk of PVD
  - related to clinical history:
    - chronic hypertension: increases risk of PE (x 3 – 5), FDIU and IGR,
    - complicated renal disease (grade A) or kidney transplant,
    - complicated diabetes (risk of PE x 5),
    - active systemic lupus or with antiphospholipids (aPL) or involving the kidneys,
    - APLS (increased risk of serious PVD),
    - active systemic disease with renal or other internal organ involvement,
    - essential thrombocythaemia;
  - related to obstetric status:
    - personal history of severe PE (risk of PE x10–15, risk of RPH x 10), eclampsia, FDIU, RPH (risk of RPH x 4 – 5) or severe hypotrophy,
    - clear abnormalities on Doppler ultrasound of the uterine arteries at 24 weeks. Doppler ultrasound should be performed in a high risk population (i.e. in patients with a history
of PVD or another risk factor for PVD) in which it is discriminatory, but not in the general population;

- related to biochemistry values:
  - significant and persistent aPL levels (IgG anticardiolipin (aCL-IgG)), with circulating lupus-like anticoagulant (LA): increase in fetal losses after 12 weeks (approximately a third of cases) and risk of IGR, PE and FDIU,
  - thrombophilia with factor V Leiden or FII 20210A in the homozygote state, or combined abnormalities or AT deficiency: increase in fetal losses after 28 weeks (x 3 - 4).

- Patients with a moderate risk of PVD

- related to clinical history:
  - age < 20 and > 40 years: risk of PE x 2-3,
  - obesity (BMI > 30): risk of PE x 2,
  - family history of PE (risk up to x 5),
  - moderate elevation of risk (x 1.5) in West Indians of African descent,
  - cocaine: increased risk of RPH (grade C),
  - heavy smoking: increased risk of RPH (x 2), IGR and perinatal mortality; decreased PE (x 0.5),
  - lupus and other systemic disease in remission,
  - controlled diabetes;

- related to obstetric status:
  - primiparity: risk of PE approximately x 5,
  - pregnancy with new partner,
  - uterine hypoplasia and uterine malformation, particularly DES syndrome (exposure to diethylstilboestrol),
  - pregnancy achieved after medically assisted conception,
  - multiple pregnancies: twin pregnancy increases risk of PE (x 3), RPH (x 7) and of IGR (x 2),
  - gestational diabetes: risk of PE x 3,
  - hCG > 2 multiples of mean (MoM) during the second trimester (screening test for chromosome disorders);

- related to biological factors:
  - factor V Leiden or FII 20210A in the heterozygote state, or isolated deficiency of PC or PS,
  - hyperhomocysteinaemia.

QUESTION 3

Which further investigations should be performed, and for which patients?

1. WHICH LABORATORY TESTS ARE CURRENTLY AVAILABLE?

The tests currently available are listed in Tables 2 and 3. Samples should ideally be taken at the laboratory itself, or sent within an hour. If not tested immediately, citrated plasma should be centrifuged and then frozen. Normal values should be supplied by the laboratory. Any abnormal results should be verified by a second test performed 1 month later.
According to French regulations, when genetic tests are ordered, the patient must be given full information about them and must give their written consent. The prescribing doctor, the only person to whom the laboratory results are to be sent, should personally give the results to the patient during a consultation. If anything abnormal is revealed, a specialist consultation may be proposed, to assess the benefit in investigating the family. In the case of thrombophilia, a report should be given to the patient with advice for prevention.

### Table 2. Biological risk factors for thrombophilia

<table>
<thead>
<tr>
<th>Assay method</th>
<th>Interference</th>
<th>Precautions</th>
<th>Specific benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antithrombin (AT)</strong></td>
<td>• Heparin cofactor activity (chromogenic method)</td>
<td>• Test without heparin if deficiency</td>
<td>• Determination of activity detects all deficiencies</td>
</tr>
<tr>
<td></td>
<td>• Antigen if activity reduced (ELISA)</td>
<td></td>
<td>• Determination of antigen deficiency differentiates between quantitative and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>qualitative deficiency</td>
</tr>
<tr>
<td><strong>Protein C (PC)</strong></td>
<td>• Activity (chromogenic method more reliable than</td>
<td>• Prothrombin time normal</td>
<td>• Determination of activity detects most deficiencies</td>
</tr>
<tr>
<td></td>
<td>chromometric)</td>
<td>• Stop VKA for 2 weeks</td>
<td>• Determination of antigen deficiency differentiates between quantitative and</td>
</tr>
<tr>
<td></td>
<td>• Antigen if activity reduced (ELISA)</td>
<td></td>
<td>qualitative deficiency</td>
</tr>
<tr>
<td><strong>Protein S (PS)</strong></td>
<td>Free antigen (ELISA) alone or with activity</td>
<td>• Prothrombin time normal</td>
<td>• Diagnosis of inherited deficiency sometimes difficult (benefit of investigating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stop VKA for 2 weeks</td>
<td>family)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stop COC for 1 month or replace with</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>progestagen alone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Test 2 months after labour</td>
<td></td>
</tr>
<tr>
<td><strong>Factor V Leiden (FV Leiden)</strong></td>
<td>• APCR by chronometric assay</td>
<td>• Acquired APCR if pregnancy, COC or lupus anticoagulant</td>
<td>• Determine homozygote or heterozygote status</td>
</tr>
<tr>
<td></td>
<td>• Molecular biology (factor V Leiden)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>20210A allele of the prothrombin gene (F II 20210A)</strong></td>
<td>• Molecular biology</td>
<td>• If APCR, genetic testing compulsory</td>
<td>• Determine homozygote or heterozygote status</td>
</tr>
</tbody>
</table>

DIC = Disseminated intravascular coagulation; COC = combined oral contraceptive; APCR = activated protein C resistance; VKA: vitamin K antagonists.
Table 3. Biological risk factors for venous thromboembolism

<table>
<thead>
<tr>
<th>Biological risk factors</th>
<th>Assay method</th>
<th>Interference</th>
<th>Precautions</th>
<th>Specific benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine</td>
<td>• High performance liquid chromatography</td>
<td>• Many reasons for elevation (impaired renal function, vitamin deficiency, etc.)</td>
<td>• To test for hyperhomocysteinaemia &gt; 18 µmol/L (N: 6–15 µmol/L)</td>
<td></td>
</tr>
<tr>
<td>677T allele of methylenetetrahydrofolate reductase (MTHFR ) gene</td>
<td>• Molecular biology</td>
<td>• Test if hyperhomocysteinaemia</td>
<td>• Determine homozygote or heterozygote status</td>
<td></td>
</tr>
<tr>
<td>CBC platelets</td>
<td></td>
<td></td>
<td>• Test for thrombocythaemia</td>
<td>Reference before treatment with UHF or LMWH</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
<td></td>
<td>• Eliminate vitamin K deficiency</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, thrombin time</td>
<td></td>
<td></td>
<td>• Detect dysfibrino-genaemia</td>
<td></td>
</tr>
<tr>
<td>APTT and test for circulating LA</td>
<td></td>
<td></td>
<td>• Suspect CAC if APTT prolonged</td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibodies (aCL)</td>
<td>• β2GP1-dependent ELISA method</td>
<td>• Further test compulsory if result positive after 6 weeks</td>
<td>• Essential for diagnosis of APLS</td>
<td></td>
</tr>
<tr>
<td>Anti-β2GP1 antibody (Aβ2GP1)</td>
<td>• ELISA</td>
<td></td>
<td>Diagnosis of APLS</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipids (aPL)</td>
<td>• ELISA</td>
<td></td>
<td>Not routine</td>
<td></td>
</tr>
<tr>
<td>Antiprothrombin and anti-annexin V antibodies</td>
<td>• For research purposes</td>
<td></td>
<td>Not routine</td>
<td></td>
</tr>
</tbody>
</table>

APLS: antiphospholipid syndrome; APTT: Activated partial thromboplastin time; CAC: circulating anticoagulant; LA: lupus anticoagulant; LMWH: low molecular weight heparin; UHF: unfractionated heparin.

2. WHICH TESTS SHOULD BE ORDERED? FOR WHICH PATIENTS?

Biological risk factors for VTE or PVD should not be tested for routinely in pregnant women. Testing is only justified if there is a confirmed personal or family history (first-degree relative) of VTE (DVT including ovarian veins and upper vena cava, recurrent superficial vein thrombosis, pulmonary embolism) or a personal history of severe PVD for which no other cause has been found, and with the proviso that the results of these tests are likely to impact on treatment.

In the event of known familial PS deficiency, a direct relative who is pregnant should be automatically regarded as a carrier of the disorder until after labour, when a test may be performed.

A summary of the tests to be ordered in different clinical situations is given in Table 4.
Table 4. Further investigations to be ordered depending on clinical situation

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>First choice tests</th>
<th>Second choice tests</th>
<th>Tests not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy with active thrombosis or personal history of VTE</td>
<td>• CBC, platelets, PT, APTT, AT, PC, FV Leiden, FII 20210A, aCL</td>
<td>• If APTT prolonged: test for CAC, If APTT normal: test for CAC using sensitive method, Anti-β2GP1 if aCL or LA</td>
<td>• PS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Homocysteinaemia</td>
</tr>
<tr>
<td>Pregnant woman with family history of VTE in context of APLS</td>
<td>• aCL, LA</td>
<td>• If aCL negative: anti-β2GP1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant woman with family history of VTE with cause not diagnosed</td>
<td>• AT, PC, APCR or FV Leiden, FII 20210A</td>
<td></td>
<td>• PS</td>
</tr>
<tr>
<td>Pregnant woman with family history of VTE and known hereditary disorder</td>
<td>• AT, PC, APCR or FV Leiden, FII 20210A</td>
<td></td>
<td>• PS</td>
</tr>
<tr>
<td>Pregnant woman with history of:</td>
<td>• AT, PC, APCR or FV Leiden, FII 20210A</td>
<td></td>
<td>• PS</td>
</tr>
<tr>
<td>• 1 or more fetal losses after 12 weeks</td>
<td>• AT, PC, APCR or FV Leiden, FII 20210A</td>
<td></td>
<td>• PS</td>
</tr>
<tr>
<td>• 1 or more births before 34 weeks and PE</td>
<td>• AT, PC, APCR or FV Leiden, FII 20210A</td>
<td></td>
<td>• PS</td>
</tr>
<tr>
<td>• severe PVD or multiple events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant woman with history of PE or IGR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman who is not pregnant with at least 3 spontaneous abortions before 10 weeks</td>
<td>• aCL, APTT and test for CAC, CBC, Homocysteinaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant woman with current severe PVD</td>
<td>• Test for APLS, AT, CAC negative: anti-β2GP1, If hyperhomocysteinaemia: MTHFR 677T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If aCL and CAC negative: anti-β2GP1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If hyperhomo-cysteinaemia: MTHFR 677T</td>
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</tbody>
</table>

QUESTION 4

What forms of treatment are available? Which patients should be treated, and what form should that treatment take? What information should patients be given?

1. DRUGS AVAILABLE

The drugs that can be used to treat or prevent VTE during pregnancy or the postpartum are unfractionated heparin (UFH) given intravenously (IV) or subcutaneously (SC), low-molecular-weight-heparin (LMWH) given SC, heparinoids and vitamin K antagonists (VKA). The advantages of LMWH is that it is easier to use than UFH, requires less monitoring of laboratory values, and has fewer side effects.

Use of VKA is limited to thrombosis prophylaxis in pregnant patients with mechanical heart valves.

There is no indication for aspirin in VTE (grade A). It may be used if there is a history of PVD (grade B), particularly to prevent the onset of PE and IGR, although it has no marketing authorisation in these indications. It must be given at a very early stage. It is not curative.

Risk of harmful effects of treatment in the fetus and newborn

- UFH does not cross the placenta and does not cause fetal or neonatal haemorrhage. It does not pass into the breast milk and is not a contraindication to breastfeeding.
- At present, two forms of LMWH – enoxaparin and dalteparin – may be used in France during the 2nd and 3rd trimesters of pregnancy. LMWH is not recommended during the 1st trimester of pregnancy as the safety data currently available on its use during this period are not considered to be adequate. LMWH is permitted during lactation.
- VKA cross the placenta, are teratogenic and cause bleeding in the fetus. The use of VKA is formally proscribed between 6 and 12 weeks of pregnancy. Cerebral disorders have been reported at any stage of pregnancy. VKA are not recommended at the end of pregnancy because of the time required for their action to be reversed, and because of their anticoagulant action in the fetus and newborn (risk of post-traumatic intracranial bleeding). In France, VKA have no marketing authorisation for use during lactation.
- For aspirin, the risk of teratogenicity generally appears to be low. However, there have been suggestions that it increases (x 2) the risk of gastroschisis. No maternal or fetal complications have been reported after low doses given for several months.

Risks of harmful effects of treatment in the mother

- **Bleeding:**
  - the estimated prevalence of UFH-related bleeding in the general population is 2%. It has been suggested that the action of UFH is prolonged (> 24 hours) during pregnancy, so UFH should be stopped 24 hours before a scheduled labour;
  - no major bleeding has been reported under LMWH during pregnancy;
- no maternal complications of bleeding have been reported in women treated with aspirin.

- **Heparin-induced thrombocytopenia (HIT):**
  - HIT is often complicated by aggravation of pre-existing VTE or by new venous or arterial thromboses. HIT should be suspected when the platelet count falls by at least 50% compared with the value before treatment with UFH or LMWH. In this event, tests for heparin-dependent antibodies should always be performed. Suspected HIT is an emergency which requires a specialist opinion:
  - in pregnant women who develop HIT, only danaparoid sodium can be used to prevent the risk of major thrombosis inherent to HIT, as it does not cross the placenta. LMWH should not be used when HIT is caused by UFH.

- **Osteoporosis:**
  - onset of osteoporosis which may cause fractures, particularly vertebral fractures, has been reported during prolonged use of UFH during pregnancy. The action persists after the drug has been discontinued;
  - the osteoporosis-inducing action of LMWH is markedly lower in the general population. It does not occur consistently and when it does, it is reversible.

2. WHICH PATIENTS SHOULD BE TREATED?

2.1. Prevention and treatment of maternal VTE

- **Prevention:** All women at major, high or moderate risk should wear an elastic support (grade B) throughout pregnancy and the postpartum. Patients should be advised to give up smoking, and appropriate support should be given.

- **If venous thromboembolism occurs during pregnancy:** Anticoagulant therapy with curative doses of UFH or LMWH should be started at the time of diagnosis (grade A), and continued with VKA for at least 3 months after labour.

- **In other situations:** Recommended treatment strategies vary according to assessed risk level for VTE; they are given in *Table 5*.

**Table 5.** Treatment according to risk of maternal VTE

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Moderate risk</th>
<th>High risk</th>
<th>Major risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No routine anticoagulant therapy during pregnancy or the postpartum</td>
<td>1. No routine anticoagulant therapy during pregnancy 2. Preventive therapy with high dose LMWH (enoxaparin 4 000 IU/day or dalteparin 5 000 IU/day) for 6–8 weeks during the postpartum. The adminstration period may be shorter when the risk is lower (age &gt; 35 yrs or Caesarian section with no other risk factors)</td>
<td>1. Preventive therapy with high dose LMWH during 3rd trimester (e.g. enoxaparin 4 000 IU/day), extended for 6–8 weeks during the postpartum 2. May be started earlier if there are additional risk factors, or 4–6 weeks before the time of previous DVT or pulmonary embolism</td>
<td>Curative therapy with UFH during 1st trimester, then LMWH during 2nd and 3rd trimesters. VKA for a minimum of 3 months during the postpartum</td>
</tr>
</tbody>
</table>
2.2. Placental vascular disease

- Preventive therapy with low dose aspirin (100–160 mg a day) should be given between the 12th and 35th week of pregnancy to patients with a history of PVD (PE, RPH, FDIU or IGR when the origin has been shown to be PVD).
- LMWH therapy may be combined with aspirin therapy if the PVD is associated with a risk of VTE (depending on level of risk established earlier).
- A combination of aspirin and LMWH prescribed from the start of pregnancy has been shown to be effective (grade B) in preventing repeated early fetal losses associated with aPL.
- Current data do not support a recommendation of preventive therapy for PVD in a patient with minor biological risk factors for thrombophilia and no history of PVD.
- In other situations (minor biological risk factors for thrombophilia combined with a history of PVD or isolated major biological factors), recommendations cannot be made as there is currently an inadequate level of evidence in the literature that treatment (aspirin +/- LMWH) is effective.

3. TREATMENT STRATEGIES

3.1. Curative therapy for maternal VTE: doses and monitoring

- A curative dose of LMWH (enoxaparin or dalteparin with an initial dose of 100 units anti-Xa/kg/12 h) maintaining blood heparin anti-Xa concentration at between 0.5 and 1 U/ml offers the best benefit/risk ratio (grade B). It should be continued until the end of pregnancy.
- During the first trimester of pregnancy, use of a UFH calcium given SC or a UFH sodium given IV complies with the current marketing authorisation.
- In the event of pulmonary embolism, a UFH given IV is indicated, later replaced by a UFH calcium given SC, to give an APTT within the therapeutic range (2–3 times the control depending on the sensitivity of the reagent used, to be determined by the laboratory). In addition, treatment should be adjusted regularly during the course of the pregnancy by determining blood heparin by measuring anti-Xa levels, which should be between 0.3 and 0.7 U/ml.
- A platelet count should be performed twice a week for the first three weeks of treatment, then once a week up to the end of treatment.
- UFH or LMWH therapy should be discontinued 24 hours before scheduled labour. If there is a very high risk of VTE (DVT or pulmonary embolism within previous 4 weeks), LMWH may be replaced by UFH, or UFH already prescribed may be continued up to 4–6 hours before labour.
- When spontaneous labour occurs in patients being treated with UFH, elimination of the UFH after withdrawal should be verified by determining APTT. If it has not been eliminated, UFH can be neutralised with protamine sulphate. In the case of curative LMWH therapy, if the patient is assumed to be or is still within the therapeutic range, epidural analgesia is contraindicated, and all methods for preventing bleeding should be used. In such a situation it is imperative that treatment be resumed, and this should be done 12 hours after delivery.
3.2. Preventive treatment for maternal VTE: doses and monitoring

- As preventive therapy, a fixed dose of UFH (5 000 IU SC every 12 hours) should be given twice a day, without monitoring of blood heparin, or at a dose adjusted to blood heparin level with anti-Xa activity of between 0.1 and 0.2 U/ml. Platelet count should be monitored in the same way as for curative therapy.
- During preventive therapy with LMWH (enoxaparin 4 000 IU anti-Xa/24 h or dalteparin 5 000 IU anti-Xa/24 h, given as single injections), blood heparin measurement by anti-Xa activity is only recommended in the case of overweight patients, renal impairment or bleeding. Platelet count should be monitored twice a week for the 1st month of treatment, then once a week until the end of treatment.
- Treatment should be discontinued 12 hours before the start of labour.

3.3. Preventive aspirin therapy for PVD: doses and monitoring

- Effective doses of aspirin for PVD prevention are in the range 100–160 mg/day.
- Prescribing aspirin as preventive therapy in a patient with a history of PVD does not exclude concomitant prescription of LMWH in the event of acquired or familial VTE, using the regimens given above.
- There are no laboratory tests predicting treatment efficacy or assessing risk of bleeding.
- Treatment should be discontinued at 35 weeks of pregnancy.

4. WHAT INFORMATION SHOULD PATIENTS BE GIVEN?

The jury confined itself to specifying information that must be included in information leaflets to support information given orally. Information leaflets should be produced by the professional societies concerned with management of these diseases.

4.1. VTE

The patient should be given information about:
- the seriousness of the disease and the risk of pulmonary embolism, or even death;
- the risk that DVT may develop into venous insufficiency and cause related skin damage.

4.2. PVD

The patient should be given information about:
- the anticipated benefits of aspirin therapy and any LMWH therapy, and practical advice on how these drugs should be used;
- the persistence of risk of recurrence of PVD in spite of preventive therapy, even though a recurrence is often less serious and/or occurs later than previous incidents.

4.3. Treatment and workup

The patient should be given information about:
- the nature of any treatment needed, and of any side effects for the mother and fetus;
- any tests recommended, including laboratory tests, and their results.

Under current French legislation, when the workup includes genetic testing, the person ordering the tests must obtain the patient’s written consent.
The full French text of these guidelines is available on written request to:
Agence Nationale d’Accréditation et d’Évaluation en Santé
Service communication
2 avenue du Stade de France – 93218 Saint-Denis La Plaine Cedex
or it is available on the ANAES website: www.anaes.fr under “Publications”