Management of anticoagulant therapy in pregnancy

Prof Serigne Abdou BA
Background

• The association heart disease and pregnancy constitutes a high-risk situation of cardiac and obstetric complications.

• The frequency of the association varies between 1.1 to 4.8% in sub-Saharan Africa.
Background

• Burden in our region related to the high prevalence of rheumatic valvular diseases

• Socio-cultural constraints (poverty, taboos, refusal to contraception, desire for pregnancy).
The use of anticoagulants during pregnancy is of critical importance:

- Pregnancy is associated with a **4-fold** risk of venous thrombosis, with the risk increasing **14-fold** during the puerperium.
Background

• These risks increase in the presence of an underlying thrombophilia
Background

• Pulmonary embolism (PE) remains a leading cause of maternal mortality in the West, the risk among pregnant women is 5 times higher than in non-pregnant women of the same age.
Background

- In our region the indications are dominated by peripartum cardiomyopathy (PPCM), prosthetic valves (mitral valvulopathy ++).
• Deep vein thrombosis (DVT), stroke, and myocardial infarction (MI) may also result from pathological thrombosis.
Pregnancy in Africa

- Legitimate aspiration for every woman
- Proudness in African woman
- Competition: multiparity; tachyparity
- Severe cardiac status: advanced valvular lesions; very low EF; atrial fibrillation
- Women don’t ask our advice before being pregnant
Anticoagulants

History of anticoagulants

- Unfractionated heparin: 1950
- LMWH: 1980
- Direct oral anticoagulants: >2008
- VKA: 1960
- Fondaparinux: 2002

Emmanuel HAZARD, Jean-loup HERMIL: Quoi de Neuf en Médecine Générale 2013
Anticoagulants

For now, guidelines on anticoagulation during pregnancy:

NO PLACE FOR DIRECT ORAL ANTICOAGULANT

(No data)
The pregnant woman

Increased bleeding risk / increased thromboembolic risk

Management with anticoagulants more difficult
It's a question of balance

Risk-Benefit balance

Thromboembolic risk

Increased bleeding risk
Anticoagulants

• Unfractionated heparin and LMWH do not pass across the placental barrier

• No teratogenicity
Anticoagulants

- LMWH is preferable to unfractionated heparin for the prevention and treatment of VTE due to its ease of use, greater efficiency and safety profile.
Anticoagulants

- VKA pass across the placental barrier: risk of bleeding and foetal teratogenic risk in 1\textsuperscript{st} trimester (nasal hypoplasia)
- Risk of miscarriage throughout pregnancy?
- Bleeding and fetal death in utero if hypocoagulability in 3\textsuperscript{rd} trimester
The pregnant woman
The pregnant woman

The difficulty depends on the underlying pathology
The pregnant woman

Venous thromboembolic disease
In the presence of DVT

Prefer LMWH and unfractionated heparin to VKAs; no direct anticoagulants
The pregnant woman

Venous thromboembolic disease

In the presence of DVT

Continue treatment for at least 6 weeks postpartum and for a total duration of at least 3 months

Stop heparins 24 hours before labour or caesarean section
The pregnant woman

Venous thromboembolic disease: Heparins

In patients with a history of DVT

Postpartum prophylaxis for 6 weeks

Antepartum prophylaxis?

Moderate or high risk?
(single spontaneous DVT, DVT secondary to pregnancy or oestrogen therapy, multiple spontaneous DVT)

Yes
Antepartum prophylaxis

No
No prophylaxis
The pregnant woman

Mechanical prosthetic valve: 3 schemes

Schema 1: Dose adjusted x 2 LMWH throughout pregnancy

ACCP, 2012
The pregnant woman

Mechanical prosthetic valve: 3 schemes

Schema 2: adjusted dose (aPTT, anti-Xa activity)
subcutaneous UFH throughout pregnancy
The pregnant woman

Mechanical prosthetic valve: 3 schemes

Schema 3: UFH or LMWH until week 13 and then replace with VKA until around labour

ACCP, 2012
The pregnant woman

Mechanical prosthetic valve

What if the thromboembolic risk is very high with some doubt on the efficacy and safety of heparin (old generation prosthesis, mitral position ...)?

VKA throughout pregnancy (teratogenic risk) +/- Aspirin

ACCP, 2012
The pregnant woman

- Warfarin
  - is more effective than UFH for thromboembolic prophylaxis in pregnant women with mechanical valves.
The pregnant woman

- Unfortunately, warfarin in the first trimester of pregnancy is associated with a substantial increase in foetal anomalies,
And anticoagulation with this drug is associated with an increased incidence of fetal resorption (approximately 30%), prematurity (approximately 45%), and low birth weight (about 50%)
Lactation

- Some anticoagulants pass into breast milk
- The following may be prescribed (ACCP 2012):
  - Warfarin, Acenocoumarol
  - Unfractionated heparin
  - But equally: LMWH, Danaparoid, Hirudin
OUR LAST EXPERIENCE

CLINICAL RESEARCH

Pregnancy in women with heart disease in sub-Saharan Africa

La grossesse des femmes atteintes de cardiopathie en Afrique subsaharienne

Maboury Diao*a,*, Adama Kanea,
Mouhamadou Bamba Ndiayea, Alassane Mbayea,
Malick Bodiana, Mouhamadoul Mounirdia,
Moustapha Sarr*a, Abdoul Kanea,
Jean-Jacques Monsuezb, Serigne Abdou Baba

*a Service de cardiologie, CHU Aristide Le Dantec, faculté de médecine de Dakar, BP 6633, Dakar Étoile, Senegal
b Groupe de cardiologie tropicale, société française de cardiologie, service de cardiologie, hôpitaux universitaires Paris Seine Saint-Denis, 93270 Sevran, France
The study was a retrospective of pregnancy outcome in women with heart disease.

All cases were followed during pregnancy, labour and delivery at the University Hospital of Dakar, Senegal, between February 1996 and February 2004.

Exclusion criteria included: therapeutic abortion for non-cardiac reasons; miscarriage (foetal loss before 20 weeks’ gestation); hypertensive heart disease; and peripartum cardiomyopathy.
OUR LAST EXPERIENCE

RESULTS

• Rheumatic heart disease was observed in 46 women, seven of whom had previously been operated on. Among the remaining 39, 32 had mitral stenosis (isolated or associated with other valvular lesions).

• At admission, 36 women presented with pulmonary oedema, two with pulmonary embolism and 18 with arrhythmia. There were 17 maternal deaths (34%).
<table>
<thead>
<tr>
<th>Major Causes of death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>47%</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>17%</td>
</tr>
<tr>
<td>Hemoraghe</td>
<td>17%</td>
</tr>
</tbody>
</table>
There were 30 live births,

- Six foetal deaths and five therapeutic abortions;
- Nine women were lost to follow-up.
- Delivery was vaginal in 19 out of 30 cases and by caesarean section in 11 cases. Median gestational age at delivery was 28 weeks (range, 8—38 weeks). Five births occurred preterm.
- There were four stillbirths (neonatal mortality, 7.6%).
Maternal death was associated with:
mitral stenosis (p=0.03);
severe tricuspid regurgitation (p=0.001);
NYHA functional class III or IV (P=0.001);
symptoms of heart failure (<0.001).

A favourable maternal outcome was associated with:
prior cardiac events (p<0.001);
prior surgical valve replacement (p = 0.03);
cardiac prosthetic valve (p = 0.03).
My patient taking VKA has a high INR
High INR without bleeding

- INR between 4.5 and 10
  - No bleeding
  - Stop VKA, follow-up INR
  - No routine vitamin K administration

- INR > 10
  - No bleeding
  - Stop VKA, follow-up INR
  - Administer VKA orally
My patient has bled or may bleed...

Cases of stroke
Bleeding whilst receiving VKA

- Major bleeding:
  - Give PPSB (Rapid action on anticoagulation)
  - Concomitant administration of 5 to 10 mg IV Vitamin K
Haemorrhagic stroke

If reduced mobility

- UFH or LMWH especially starting between day 2 and day 4
- or pneumatic compression only (in case of persistent bleeding risk)
- Combination of pharmacological prophylaxis with intermittent pneumatic compression: may improve outcome
Ischaemic Stroke

If reduced mobility

If bleeding risk is low (small cerebral infarction, no haemorrhagic signs on imaging) anticoagulation 1-2 weeks after ischemic stroke

Optimal benefit of antithrombotic treatment in patients at low risk of bleeding with a high risk of thromboembolism (mitral valvulopathy, mechanical prosthesis, CHADS score > 4)
My patient had a heparin-induced thrombocytopenia...

Occur mainly between the 5th and 21st day

Peak at 10th day

Early forms (history of HIT), risk of recurrence
Heparin-induced thrombocytopenia

- More frequent with UFH (x 5-10) vs LMWH
- Rarer in medical conditions (0.25% to 1%) than surgical (1% to 3%)
Heparin-induced thrombocytopenia

Prevention

– If there is risk of HIT > 1%

⇒ platelets levels every 2 to 3 days from 4th to 14th day or until heparin treatment is stopped
Heparin-induced thrombocytopenia

HIT complicated or not by thrombosis

- Stop heparin (UFH or LMWH)
- Prescribe Lepirudin, Argatroban or Danaparoid
- In case of renal failure or pregnancy, give Danaparoid
- Do not give VKA
- Platelet transfusion only if bleeding or invasive procedure with high risk of bleeding
Anticoagulants therapy

• Monthly cost of treatment of VKA including INR follow-up:

  – *Coumadine* = 10,068,94 FCFA = 18 USD
  – *Sintrom* = 7,550,7 FCFA = 13 USD
  – *Préviscan* = 8,199,46 FCFA = 14 USD
Conclusion

• Planned pregnancy

• Prevention through the fight against rheumatic diseases endemic in our regions.

• Patient Education / Communication (results, dose adjustment)
Conclusion

• Self management for patient who are capable

• Good knowledge of the thrombotic risk / haemorrhagic risk balance

• Indispensable multidisciplinary collaboration (clinicians, paramedical, laboratory...)

• Family involvement ++
THANK YOU VERY MUCH
Clinical data were recorded at the first prenatal visit including:

- Age;
- Occupational, Educational And Marital Status;
- Gestational Age; Parity Status;
- Cardiac Conditions, Prior Cardiac Events And Therapy;
- NYHA Functional Class;
- Cyanosis;
- Comorbid Conditions; And Anaemia.
OUR LAST EXPERIENCE

METHODES

- Treatment and outcome data were obtained during hospitalization.
- Prepartum, peripartum and postpartum complications were grouped into cardiac, neonatal or obstetric events.
- The mode of delivery and obstetric complications were documented.
- Data were analysed to evaluate maternal and foetal outcomes.

Diao M et al. Archives of Cardiovascular Disease (2011) 104,370—374
Heparin-induced thrombocytopenia

- In case of HIT only re-start VKA if the platelet count $>150\ 000/\text{mm}^3$, starting with low doses

- If patient is already receiving VKA at the time of occurrence of HIT; give vitamin K

- Patient with a history of HIT with thrombosis (not related to heparin) $\Rightarrow$ start with Fondaparinux and continue with VKA
## RESULTS

**Table 1**  Rheumatic heart disease of native valves in 39 pregnant women.

<table>
<thead>
<tr>
<th>Valvular disease observed</th>
<th>$n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single cardiac valve involvement (n = 12; 30.7%)</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>7 (18)</td>
</tr>
<tr>
<td>MR + MS</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>MR</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>AR</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Multiple cardiac valve involvement (n = 27; 69.3%)</td>
<td></td>
</tr>
<tr>
<td>MS + TR</td>
<td>9 (23)</td>
</tr>
<tr>
<td>MS + MR + TR</td>
<td>6 (15)</td>
</tr>
<tr>
<td>MR + TR</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>MS + MR + AR + TR</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>AR + MR</td>
<td>2 (5)</td>
</tr>
<tr>
<td>MS + AR</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>MS + AR + TR</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>MS + AS + AR</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>MR + AR + TR</td>
<td>1 (2.5)</td>
</tr>
</tbody>
</table>

AR: aortic regurgitation; AS: aortic stenosis; MR: mitral regurgitation; MS: mitral stenosis; TR: tricuspid regurgitation.
**Table 2** Predictors of adverse outcome (maternal death) in 46 pregnant women with rheumatic valvular disease.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adverse outcome (n=17)</th>
<th>Favourable outcome (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.1 (4.7)</td>
<td>28.8 (4.9)</td>
<td>0.79</td>
</tr>
<tr>
<td>Parity, n (%) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.52 (2.1)</td>
<td>1.7 (1.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Prior adverse cardiac events &lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (17.6)</td>
<td>22 (75.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior valvular intervention &lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 (0)</td>
<td>7 (24.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prosthetic valve &lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 (0)</td>
<td>7 (24.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitral stenosis &lt;sup&gt;b&lt;/sup&gt;</td>
<td>15 (88.2)</td>
<td>17 (58.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitral regurgitation &lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (41.1)</td>
<td>13 (44.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Aortic regurgitation &lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (17.6)</td>
<td>11 (37.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Severe tricuspid regurgitation &lt;sup&gt;b&lt;/sup&gt;</td>
<td>14 (82.3)</td>
<td>10 (34.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA functional class III or IV &lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (94.1)</td>
<td>14 (48.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation &lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (47.0)</td>
<td>8 (27.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Heart failure &lt;sup&gt;b&lt;/sup&gt;</td>
<td>17 (100)</td>
<td>7 (24.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anticoagulant therapy &lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 (70.5)</td>
<td>18 (62.0)</td>
<td>0.6</td>
</tr>
</tbody>
</table>


<sup>a</sup> Data are mean (standard deviation).

<sup>b</sup> Data are number (%).
Diagnosis of DVT and PE during pregnancy

1. Suspected DVT
2. CUS of proximal veins (Day 1)
   - Clearly abnormal: Treat
   - Normal: Isolated iliac DVT suspected
   - Equivocal: Venography
     - Normal: No treatment
     - Abnormal: Treat
3. Yes: Pulsed Doppler with direct visualization of iliac vein OR MRI
   - Normal: Serial CUS*
   - Abnormal: Treat OR No Treatment
4. No: Venography
   - Normal: No treatment
   - Abnormal: Treat
5. Serial CUS*
   - Repeat days 2-3 and 6-8
Diagnosis of DVT and PE during pregnancy

Management of venous thromboembolism during pregnancy

Suspected E

V/Q Scan*

High probability**

Non diagnostic***

Normal

Pre-test probability

CUS

Low

DVT present

Diagnose PE

DVT absent

Diagnose PE

Serial CUS

Pulmonary angiography

Negative

PE excluded

Positive

PE diagnosed

Negative

PE excluded

*Can substitute CUS and, if abnormal, diagnose PE; if normal, further testing is required
** At least one segmental perfusion mismatch
*** Neither normal nor high probability
Anticoagulants

MECHANISM OF ACTION

Rivaroxaban (Xarelto®)
Apixaban (Eliquis®)

Dabigatran (Pradaxa®)

Tissue factors

VIIa

Va

Fibrin

Xa

IIa

AT

Fondaparinux (Arixtra®)

HNF; HBPM et Danaparoide (Orgaran)
VKA: teratogenicity (6%) dose-dependent relationship between the 6th and 12th week of gestation: microcephaly, mental retardation, optic atrophy, nasal hypoplasia

Unintended pregnancy in a patient receiving VKA: amniocentesis

Coumadine® (warfarine) can be used in postpartum as it does not pass into the breast milk

Anticoagulant management according to risk

During cesarean: reducing or stopping IV heparin 2 hours before the incision to maintain aPTT between 1.5 and 2x the control

Vaginal delivery possible if moderate cardiac risk, NYHA I-II, Induction, strong patient desire. The reduction of anticoagulation may be only a few hours before expulsion, epidural analgesia is often not feasible
Pregnancy in a patient with a mechanical heart valve

**High risk**
Starr-Edwards valves, Bjork Shiley in mitral position, AF, known hemorrhage or thromboembolic events under anticoagulation

- **Coumadine®** (INR 2.5-3.5)
  - Until 35 GA and shift to IV heparine (aPTT 2.5-3.5)
  - + aspirine 80-100 mg po

- Non-fractionated heparin sc (aPTT >2.5) during 12 weeks GA or LMWH (anti Xa ~0.7)
- then
  - Coumadine® (INR 2.5-3.5) from 12 to 35 GA
  - then
  - Heparine IV (aPTT 2.5-3.5) or LMWH (anti Xa ~0.7)
  - + aspirine 80-100 mg

**Moderate risk**
2nd generation valve (St Jude, Medtronic-Hall), all mechanical valves in the aortic position

- Non-fractionated heparin sc (aPTT 2-3) or LMWH (anti Xa ~0.6)*

- Non-fractionated heparin sc (aPTT 2-3) during 12 weeks GA
- or LMWH (anti Xa ~0.6)
- then
  - Coumadine® (INR 2.5-3.0) de 12 to35 GA
  - then
  - Heparine IV (aPTT 2-3) or LMWH (anti Xa ~0.6)