SLE An Obstetricians View

Chris Tippett- March 2012
“the most difficult medical condition associated with pregnancy to predict outcome”

What will influence the pregnancy outcome for the mother and her fetus? What do I need to know?
What will influence the pregnancy outcome for the mother and her fetus? What do I need to know?

How is the disease manifest? endothelial damage?*
How active is the disease?*

Antiphospholipid status*
Antinuclear antibody status

Past pregnancy history*
Medications

* implications for placentation.
1. Will placentation be affected?

Defective deep placentation
pre-Eclampsia
IUGR
pre-term birth
pre-term PROM
late miscarriage
placental abruption

Inflammatory changes in the placenta give similar complications.
Fig. 1. Spiral artery remodelling steps: (a) unmodified spiral artery; (b) step one: decidua-associated remodelling with disorganization of vascular smooth muscle; (c) step two: interstitial trophoblast invasion enhances vascular smooth muscle disorganization; (d) endovascular trophoblast temporarily replaces the endothelium; (e) step 3: intramural incorporation of endovascular trophoblast and deposition of fibrinoid, replacing the vascular smooth muscle; (f) step 4: re-endothelialization and intimal thickening.

Endo, endothelium; ET, endovascular trophoblast; IT, interstitial trophoblast; INT, intimal thickening; VSM, vascular smooth muscle.

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Implantation, placentation and maternal vascular remodelling of spiral arteries

50-60mLs/min

- endometrium

700-900mLs/min

- Placenta/intervillous space
- decidua
- myometrium

200-400mLs/min

- Non-pregnant
- Normal pregnancy
- IUGR/PET

(after Moffett-King Nature Reviews Immunology 2002)
1. Will placentation be affected?

- Primigravidity
- Previous obstetric complications-PET/IUGR
- Other “diseases” also associated with endothelial damage- Hypertension, renal disease, diabetes

- Antiphospholipid syndrome?

• Increase the likelihood of pregnancy complications-influence advice & surveillance
Can Placentaion or placental function be modified? Aspirin

Prevention of Preeclampsia and Intrauterine Growth Restriction With Aspirin Started in Early Pregnancy: A Meta-Analysis.
Bujold, Emmanuel; MD, MSc; Roberge, Stephanie; Lacasse, Yves; MD, MSc; Bureau, Marc; Audibert, Francois; MD, MSc; Marcoux, Sylvie; MD, PhD; Forest, Jean-Claude; MD, PhD; Giguere, Yves; MD, PhD

DOI: 10.1097/AOG.0b013e3181e9322a

Fig. 3. Forest plot of trials studying intrauterine growth restriction. Aspirin treatment to prevent intrauterine growth restriction according to gestational age at the initiation of intervention. CI, confidence interval; M-H, Mantel-Haenszel. Bujold. Preeclampsia and IUGR Prevention With Aspirin. Obstet Gynecol 2010.
Can Placentation or placental function be modified?  
Anticoagulants  
a) Heparin to promote successful implantation!  

Low-molecular-weight heparin in the treatment of recurrent IVF–ET failure and thrombophilia: A prospective randomized placebo-controlled trial Qublan et al  
Fertility Sterility 2008, Vol. 11, No. 4, Pages 246-253  
(doi:10.1080/14647270801995431)  

83 women daily 40mg heparin or placebo from day of ET  
Heparin cf Placebo implantation 20.9% vs 6.1%  
ongoing pregnancy 31% vs 9.6%  
live birth 23.8% vs 2.8%  
In women without a hereditary or acquired defect no benefit
Can Placentation or placental function be modified? Anticoagulants

b) Heparin to prevent recurrent !st/2\textsuperscript{nd} TM loses

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Thrombophilia status</th>
<th>Intervention</th>
<th>Live birth rate Treatment arm</th>
<th>Live birth rate Control arm</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Dolitzky et al. (2006)\textsuperscript{45}</td>
<td>Multicentre RCT of women with 3 or more consecutive first trimester losses or 2 or more consecutive second trimester losses</td>
<td>Negative for hereditary thrombophilias</td>
<td>Treatment: LMWH (enoxaparin; 40 mg/day) Control: Aspirin (100 mg/day)</td>
<td>82%</td>
<td>84%</td>
<td>LMWH does not result in better outcomes compared to women receiving ASA</td>
</tr>
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<td>Kaandorp et al. (2009)\textsuperscript{46}</td>
<td>Multicentre RCT of women with a history of 2 or more losses at \leq 20 wks</td>
<td>Negative for antiphospholipid syndrome, no history of thromboembolism</td>
<td>Treatment: LMWH (nadroparin; 2850 IU/day) + ASA (80 mg/day) Controls: 1) ASA alone (80 mg/day) 2) Placebo</td>
<td>71.4%</td>
<td>67.4% (ASA) 70.5% (placebo)</td>
<td>Neither LMWH combined with ASA or ASA alone confers benefit to women in this population</td>
</tr>
<tr>
<td>Laskin et al. (2009)\textsuperscript{44}</td>
<td>RCT of women with a history of 2 or more losses prior to 32 wks</td>
<td>Positive for either autoantibodies or a coagulation abnormality</td>
<td>Treatment: LMWH (Fragmin 5000 IU/day) + ASA (81 mg/day) Control: ASA alone</td>
<td>77.1%</td>
<td>79.1%</td>
<td>LMWH does not confer additional benefit in women receiving ASA</td>
</tr>
<tr>
<td>Clark et al. (2010)\textsuperscript{50}</td>
<td>RCT of women with 2 or more consecutive losses at \leq 24 wks</td>
<td>Negative for all thrombophilias (hereditary and acquired)</td>
<td>Treatment: LMWH (Enoxaparin 40 mg/day) + ASA (75 mg/day) Control: No treatment</td>
<td>78%</td>
<td>80%</td>
<td>LMWH plus ASA does not confer any benefit to women in this population</td>
</tr>
</tbody>
</table>
Can Placentation or placental function be modified? Anticoagulants
Heparin to prevent perinatal complications in pregnancy

Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction (Review)

Dodd JM, McLeod A, Windrim RC, Kingdom J

THE COCHRANE COLLABORATION®
Can Placentation or placental function be modified?

Anticoagulants

c) Heparin to prevent perinatal complications in pregnancy

Although combination aspirin and heparin is considered standard care for women with APS and embryo fetal loss there is a paucity of good data.
Can Placentation or placental function be modified?  
Anticoagulants  

Heparin _Non-Anticoagulant actions on the placenta.  

Probably diverse mechanisms of action of heparin  
1. on the placental surface, may include some antiiflammoatory effects  
2. on the villous cytrophoblast: promoting proliferation.  
Effects may be dose related with adverse effects at higher dose  

Wide spread use to prevent a variety of placental complications requires better evidence.
Assessment of placentation
1st and 2nd trimester bloods

- **1st Trimester** Association with adverse outcome
  - PAPP-A < 0.3 MoM (Syncitiotrophoblast)

- **2nd Trimester** Association with adverse outcome
  - Alpha fetoprotein > 2 MoM
Assessment of placentation
Uterine Artery Dopplers

- Normal wave forms-”normal placentation”
Uterine Artery Dopplers

- Abnormal wave forms
Assessment of placentation

Predictive tests/"combined screening"

- First/second trimester tests for Down syndrome and spina bifida
- Uterine artery Dopplers
- Placental morphology.
What will influence the pregnancy outcome for the mother and her fetus? What do I need to know?

How is the disease manifest? endothelial damage?*
How active is the disease?*
History of previous thrombosis

Antiphospholipid status* LA/aCL/antiβ2GPI
Autoantibody status antiRo/SSA  antiLa/SSB

Past pregnancy history*
Medications

* implications for placentation.
Autoantibodies and AV block

Congenital Heart block in structurally normal heart is rare 1/15,000 1/20,000 newborns.

- anti-SSA/Ro anti-SSB/La risk of CHB 2-5%
- Risk of two children with CHB 12-25%
- Anti-Ro 52kd may have higher risk
Diagnosis and Treatment of CHB

• Two stage process
  – Antibodies bind to developing heart-1st degree block
  – Inflammatory reaction results in fibrosis

• Suggested echocardiography every 2 weeks from 16 weeks-26 weeks-to identify fetuses with 1st degree heart block. Treat

• Suggested that fetuses with CHB II treated with fluorinated steroids

• CHB III considered irreversible
Measured PR time interval >2SD above mean +ve
8/24 fetuses signs of 1\textsuperscript{st} degree heart block
  1 fetus-- Normal to Complete AVB in 1 week
  1 fetus-CHB II treated with betamethasone-normal
  6 fetuses spontaneously reverted 3 prior to delivery and 3 after delivery without treatment

22 fetuses had heart rates in normal range
Doppler flow echo is effective at identifying fetuses with CHB I - PPV 50%
• 95 subjects- PR interval >3SD above mean +ve
• weekly echo 16-24 weeks/biweekly 26-34 weeks
  – Prolongation of PR interval was uncommon and did not precede more advanced block which occurred in 3 fetuses.
  – One fetus normal PR interval to CHB III within a week
  – 2 fetuses PR interval >3SD above mean Betamethasone-reversal
    • ?curative or incidental
Sonesson and PRIDE studies

- What is clinical significance of prolonged PR interval?
- What is the biological implication with regard to tissue injury of a prolonged PR interval?
- Identification of the fetus at risk not yet achieved
- Regular echocardiography-research tool
<table>
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<tr>
<th>Summary of outcomes</th>
<th>Initial detection</th>
<th>Birth</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Treated Group</td>
<td>22 (CHB III)</td>
<td>18 (CHB III)</td>
<td>1 Death 15/12</td>
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<tr>
<td></td>
<td>4 deaths in utero</td>
<td></td>
<td></td>
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<tr>
<td>Dex</td>
<td>6 (CHB II)</td>
<td>1 (CHB III)</td>
<td>1 death 2yrs</td>
</tr>
<tr>
<td></td>
<td>3 (CHB II)</td>
<td>2 (CHB III)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (NSR)</td>
<td></td>
<td>1 (CHB II P)</td>
</tr>
<tr>
<td></td>
<td>2 (CHB I)</td>
<td>2 (NSR)</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>9 CHB(III)</td>
<td>9 (CHB III)</td>
<td>(CHB III)</td>
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Treatment options

• Routine steroid prophylaxis not indicated.
• IVIG not effective
• The utility of serial echos unclear
• The efficacy of Dexamethasone and Betamethasone is unproven in management of CHB II
• Betamethasone may be “safer” than Dexamethasone for fetus.
What is common practise?

Listen with a doptone
Monitor closely if CHB detected