Connective tissue disease in pregnancy

Professor Catherine Nelson-Piercy
Concerns in pregnancy

• Effect of CTD disease on pregnancy outcome
• Effect of pregnancy on CTD disease
• Drugs
  – In pregnancy
  – While breast feeding
Connective Tissue Disorders

- SLE
- Antiphospholipid syndrome
- RA
- Rheumatoid arthritis
- MCT
- Mixed Connective Tissue disease
- SS
- Systemic sclerosis/scleroderma

• Safety of Drugs
  – In pregnancy
  – While breast feeding
‘Contraindications’ to pregnancy

- Pulmonary hypertension
  - SLE / scleroderma
- CKD 4/5
- Active lupus nephritis
- Severe restrictive lung disease

- MMF
- Methotrexate
- Cyclophosphamide
- Warfarin / NOAC
Pregnancy outcome in SLE

- Disease activity
- Lupus nephritis
  - Hypertension
  - Renal impairment
- Anti Ro / La
- Antiphospholipid antibodies
- Cardiac / Lung involvement
SLE – Disease activity

• Active disease at conception or first presentation of SLE in pregnancy increases the risk of
  – pre-eclampsia
  – fetal growth restriction
  – preterm delivery
• Pregnancy increases the risk of disease flare
• Flares more difficult to diagnose
  – Hair fall facial erythema
  – Fatigue anaemia
  – Oedema raised ESR
  – Musculoskeletal pain
Fig. 2
Incidence of **pre-eclampsia** during pregnancy: comparison between the normal population and nephropathic women.

*Stratta et al, J Nephrol 2006*
Imbasciatti et al. Nephrol Dialysis Transplant 2009; 24: 519-25

- 113 pregnancies 81 women pre-existing biopsy-proven LN.
- Renal Bx performed 7.2 +/- 4.9 years before:
  - 6 class II,
  - 8 class III,
  - 48 class IV
  - 19 class V.

At conception, 49% in complete and 27% partial remission.

9 MC, 1 SB, 5 NNDs.

- 31 (30%) preterm.
- 34 (33%) BW <2500 g
• 34 (33%) renal flares (pregnancy & postpartum)
  – 20 were reversible
  – 3 progressive decline of GFR (1 on dialysis).

• Pregnancy outcome was predicted by
  - hypocomplementaemia at conception (RR 19.02; 90% CI 4.58-78.96)
  - aspirin during pregnancy (RR 0.11; 90% CI 0.03-0.38).

• Renal flare was predicted by renal status
  – partial remission RR 3.0; 90% CI 1.23-7.34,
  – Non remission RR 9.0; 90% CI 3.59-22.57.
### SLE with and without Lupus Nephritis

<table>
<thead>
<tr>
<th></th>
<th>SLE + Nephritis</th>
<th>SLE - Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>7 (20.6%)</td>
<td>10 (16.9%)</td>
</tr>
<tr>
<td>Thrombus</td>
<td>0</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Flare</td>
<td>14 (41.2%)</td>
<td>22 (37.3%)</td>
</tr>
<tr>
<td><strong>Neonatal Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUD</td>
<td>1 (2.9%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>NND</td>
<td>1 (2.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Gestation Mean±SD</td>
<td>36.7±4.2</td>
<td>38.2±3.0</td>
</tr>
<tr>
<td>% &lt;34/40</td>
<td>6 (17.6%)*</td>
<td>4 (6.8%)*</td>
</tr>
<tr>
<td>% &lt;37/40</td>
<td>10 (29.4%)</td>
<td>10 (16.9%)</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2715±862</td>
<td>2963±717</td>
</tr>
<tr>
<td>%&lt;10th Centile SGA</td>
<td>10 (29.4%)</td>
<td>14 (23.3%)</td>
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</tbody>
</table>

Bramham et al. J Rheumatol. 2011
### Systematic review and meta-analysis outcomes of pregnancy in patients with SLE and Lupus Nephritis

<table>
<thead>
<tr>
<th></th>
<th>Unsuccessful pregnancy</th>
<th>Premature Birth &lt;37/40</th>
<th>Still Birth and neonatal death</th>
<th>FGR</th>
<th>Maternal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23.4% (20-27)</td>
<td>39.4% (32-46)</td>
<td>3.6% and 2.5%</td>
<td>12.7%</td>
<td>Flare 25.6%</td>
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<tr>
<td></td>
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<td>Hypertension 16.3%</td>
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<td></td>
<td></td>
<td>Nephritis 16.1%</td>
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<td></td>
<td></td>
<td>Pre-eclampsia 7.6%</td>
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<td></td>
<td>Eclampsia, stroke and death &lt;1%</td>
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</tbody>
</table>

37 studies – 1842 patients, 2751 pregnancies
Explain the risks of prematurity
Infection or Inflammation?

**Infection**
- Raised CRP
- Raised / reduced WC
- Fever
- Response to antibiotics
- Raised procalcitonin (sensitivity 70%)

**Inflammation**
- Normal CRP (↑in pericarditis / lupus pneumonitis / arthritis)
- Reduced WC
- Fever
- Response to immunosuppression

**Remember:** most deaths in SLE are due to overwhelming sepsis
Anti Ro / La antibodies (ENA)

Mother
• 30% of women with SLE
• Associated with photosensitivity, subacute LE, Sjogren’s, Raynaud’s, ANA- negative SLE
• 50% have CTD within 15yrs of baby with CHB

Fetus / Neonate
• Risk of neonatal cutaneous lupus = 5%
• Risk of congenital heart block = 2%
• Offer fetal cardiology scan (18/20 and 28 weeks)
Neonatal cutaneous lupus

- Manifests age 2-3 weeks
- Geographical skin lesions (cf. Subacute cutaneous LE)
- Face, scalp
- After exposure to sun / UV light
- Disappears spontaneously within 6 months
- Residual hypopigmentation/telangiectasia for up to 2 yrs
- No scarring
Congenital Heart Block
(52Kd Ro, 60 Kd Ro, La)

- Appears in utero; 18-20 weeks
- Fetal bradycardia (1st or 2nd degree precede)
- Increased PNMR – 20%
- 50-60% of those who survive need pacemakers in early infancy (others in early teens)
- Pathogenesis; inflammation and fibrosis of conducting system; direct effect on myocytes
- Pancarditis and myocarditis associated
- 16% (10 fold) recurrence rate
  - No role for prophylactic steroids, IVIG, plasmapheresis
  (Brucato Rheumatology 2008)
Autoimmune Congenital Heart Block: A Systematic Review

Nat Rev Rheumatol 2014 In press

1416 cases from 9 retrospective case series

Overall incidence of CHB in Ro + ve mothers = 20/729 = 2.74%

54% diagnosed 20-24 weeks    75% 20-29 weeks
21% diagnosed 25-29 weeks

19% mortality (of which 70% = in utero)

64% required pacemaker (of which 80% within 1st year of life and 67% within 10 days of birth)

Recurrence in subsequent pregnancy (97/574 = 17%)
86% of women with babies with ACHB are anti-Ro +

Rest 14%:
- Others (ANA, FR, DNA...)
- Not tested for the 4 abs (Ro/SSA, La/SSB, Ro52, Ro60)
- Included some post-natal CHB

53% Asymptomatic

70% Systemic rheumatic disease

SS
SLE
3 databases (US, UK, France)
Analysis of pregnancies following a child with cardiac NL
HCQ (started < 10/40 and continued) reduced recurrence of CHB by 77% (OR, 0.23; 95% confidence interval, 0.06-0.92; P=0.037).

<table>
<thead>
<tr>
<th></th>
<th>+ HCQ (40)</th>
<th>-HCQ (217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>37</td>
<td>171</td>
</tr>
<tr>
<td>Cardiac NL</td>
<td>3 (7.5%)</td>
<td>46 (21.7%)</td>
</tr>
</tbody>
</table>

Izmirlı et al. Circulation 2012
Pregnancy complications by classification of APS STH cohort (n= 90)

Bramham et al. Lupus 2010
## RCTs Aspirin vs Aspirin + Heparin / LMWH

<table>
<thead>
<tr>
<th>Study</th>
<th>%Live births ASA</th>
<th>%LB ASA + Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowchock 1992</td>
<td>68</td>
<td>73</td>
</tr>
<tr>
<td>Kutteh 1996</td>
<td>44</td>
<td>80</td>
</tr>
<tr>
<td>Rai 1997</td>
<td>42</td>
<td>71</td>
</tr>
<tr>
<td>Pattison 2000</td>
<td>80</td>
<td>vs placebo</td>
</tr>
<tr>
<td>Farquarson 2002</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Laskin 2008</td>
<td>71</td>
<td>77</td>
</tr>
</tbody>
</table>
APS - Management Recommendations

- APL – no thrombosis or fetal loss  
  - Aspirin 75 mg/day or nothing

- Thrombosis  
  - LMWH (≥40 mg bd) + aspirin

- Recur misc < 10/40  
  - Aspirin (± LMWH)

- Fetal loss or severe PET/FGR/NND  
  - LMWH (40mg od) + aspirin
Antiphospholipid antibodies do not a syndrome make

  - History / circumstance of loss very important eg. Cervical problems


<table>
<thead>
<tr>
<th></th>
<th>Controls (n=292)</th>
<th>aPL (n=73)</th>
<th>APS (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART (%)</td>
<td>6</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Customized BW centile</td>
<td>44</td>
<td>51</td>
<td>29*</td>
</tr>
<tr>
<td>SGA (%)</td>
<td>11</td>
<td>6</td>
<td>27*</td>
</tr>
<tr>
<td>APS complications^</td>
<td>11</td>
<td>12 aOR^^ 1.3(0.6-2.9)</td>
<td>38*</td>
</tr>
</tbody>
</table>

^ Fetal loss>10/40, PET <34/40, SGA, IUD secondary to abruption
^^ adjusted for maternal age and comorbidities
Rheumatoid arthritis

Traditional teaching:

- Pregnancy shifts Th1 dominance to Th2 dominance.
- Th2 cells ↓ IL and TNF.
- Most improve in pregnancy (only 16% complete remission)
- If improves, 90% suffer postpartum exacerbation
- T-cell immunity reduced in pregnancy and returns in puerperium
- First presentation of RA increased in first puerperium

Prospective studies (UK, Netherlands):

- Only 40-66% improve in pregnancy
- < 25% achieve remission by the third trimester.
- Women without anti-cyclic citrullinated peptide (anti-CCP), or rheumatoid factor (RF) more likely to improve in pregnancy.
- Anti-CCP, IgM and IgA-RF fall in pregnancy.

Rheumatoid arthritis

- Medications
  - Continue Aza and HCQ
  - 5 mg folate if taking sulfasalazine
  - Oral or Intra-articular steroids
  - NSAIDs until 32 weeks
  - Biologics safe

- Refer obstetric anaesthetist
  - Atlanto-axial subluxation

- Limitation of hip abduction

- Flares post-partum are common
  - 33% flare within 1/12 post-partum and 98% by 4/12
  - despite an increase of medications post-partum.

Raynaud’s

• Usually improves in pregnancy (increased skin blood flow; vasodilation)
• Heated gloves
• Nifedipine (10 mg SR BD)
Sjogren’s

- Dry eyes/ dry mouth
- Primary /secondary (SLE)
- Check ENA (anti Ro/La)
- Artificial tears / saliva
Scleroderma

- Localized cutaneous
- Systemic sclerosis
- CREST (anticentromere Abs)
  - Calcinosis
  - Raynaud’s
  - E/Oesophageal involvement
  - Sclerodactaly
  - Telangiectasia
Systemic sclerosis

- Progressive fibrosis involving oesophagus, lungs, heart, kidneys
- High risk in pregnancy = early (< 4yrs) and renal involvement
- Check FVC
- Check echo (for pulmonary hypertension)
- U3RNP (PHT) + Scl70/Topo (lung) markers
- Check renal function
- Beware postpartum deterioration
Systemic sclerosis

- Do not stop ACE inhibitors
- Steroids (> 10 mg /day) can precipitate a renal crisis
- Refer obstetric anaesthetist
  - Difficulty monitoring BP
  - Difficulty monitoring oxygen saturation
  - Difficult venous access
  - Difficult airway
  - Lung function

Don’t give steroids for fetal lung maturation
Vasculitis

• Takayasu
  – Exclude PHT
  – Continue immunosuppression
  – Monitor with ESR / CRP
Medications

**YES**
- Steroids
- Azathioprine
- Cyclosporin / tacrolimus
- Hydroxychloroquine
- (Etanercept / infliximab) Adalimumab
- IVIG

**NO**
- NSAIDs (third trim)
- Cyclophosphamide (1st trim)
- Methotrexate, thalidomide
- Chlorambucil
- Gold, D-penicillamine
- Mycophenolate mofetil
- Leflunamide
- Rituximab / abatacept

*Ostensen M et al. Arthritis Research & Therapy 2006; 8: 209*

In pregnancy maternal antibodies are transported across placenta by the neonatal Fc receptor. Immunoglobulin concentrations increase in fetal blood from early second trimester until delivery. IgG1 is the most efficiently transported Ig subclass. Infliximab and adalimumab are IgG1 subclass anti TNFα antibodies that are actively transported across the placenta (cord blood levels ~150% of maternal). Etanercept soluble receptor fusion protein (murine Fc portion), much shorter half-life, less binding to placental Fc receptors; etanercept cord levels much lower at 3.5%-7.4%. Certolizumab pegol is pegylated Fab fragment of humanized anti TNFα monoclonal antibody without an Fc portion. Therefore any transport across the placenta is by passive diffusion.

Biologics in pregnancy

- Systematic review (for IBD)
- 58 studies; 33 case reports, 21 case series
- >1533 patients (1 study 289 pregnancies IBD + other indications)
- No increase in adverse outcome
- No increase in congenital malformations
- No increase in RR infections in first year of life
- Stop only in remission and use usual stopping criteria

MMF

- Teratogenic – suggested by animal studies
- Now FDA – D
- Cord blood levels therapeutic in pregnant women
- Constellation of structural abnormalities now being recognised
  - Microtia
  - External auditory canal atresia
  - Orofacial clefts
  - Cardiovascular malformations
  - Digital hypoplasia

Mycophenolate Mofetil and Pregnancy

• MMF not recommended
• MMF should be reserved for when no more suitable alternative is available
• MMF should be used in pregnancy only if potential benefit outweighs potential risk to the fetus
• Stop (switch to azathioprine) at least 6 weeks before planned pregnancy
  (long half life, enterohepatic recirculation)
Azathioprine and breast feeding

• 6MP undetectable in breast milk samples from 4 mothers taking azathioprine
• Used HPLC – limit of detection = 5ng/ml
• Relative infant dose < 0.09% of weight adjusted adult dose

• 10 mother–baby pairs. No adverse effects
• 31 breast milk samples from 10 women
• Low levels (2-10% therapeutic) of 6MP in 2 samples from 1 woman
• No detectable 6MP or 6TGN in any of the neonatal blood samples
Is Infliximab safe to use while breast feeding?

- *Stengel et Arnold. W J Gastroenterol 2008;14:3085*
- 22yo fistulizing ileocolonic CD
- 10mg/kg (1000mg) infliximab x 6 doses in pregnancy
- Last dose 2 weeks prior to delivery
- CS 39/40; BW 7lb 6 oz
- Fully breast fed
- Breast milk spiked with 40 ng/ml infliximab
- Infliximab detected in all spiked samples (1:2, 1:4, 1:8) but not her unspiked breast milk
- Usual dose (10mg/kg) of infliximab given, breast milk collected daily for 30 days. NO INFLIXIMAB DETECTED
Thank you for your attention!