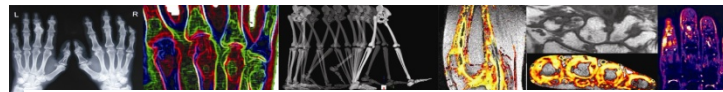


Pregnancy and rheumatology: What you might see and what to look out for

Shouvik Dass

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Leeds Teaching Hospitals NHS Trust**



Overview

Pre-pregnancy:

- Disease control
- Drug management – what to withdraw and when?

Pregnancy:

- Drug choices
- Disease management: mother & baby

Post natal



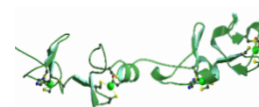
SLE & pregnancy

- SLE
- Anti-phospholipid syndrome
- Anti-Ro antibodies



Case 1

- 34 year old female
- SLE – skin, joints, renal (Grade III lupus nephritis); anti-cardiolipin antibody +ve
- 1 child, age 7
- Azathioprine, Hydroxychloroquine, aspirin
- 2nd pregnancy – stopped AZA, HCQ (?whose advice)



Case 1

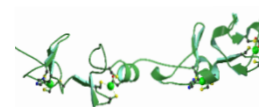
- 20/40 – admission with fever, rash, arthritis
- PV bleed
- Hypertension
- Fetal loss
- ?placental insufficiency ?maternal haemorrhage ?infection



Case 1

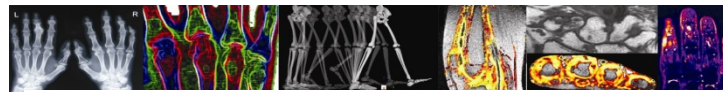
- Then flare of nephritis – commence mycophenolate
- Continued 9 months – not tolerating well
- Raised PCR
- Treated rituximab

- Became pregnant 7/12 later
- Continued HCQ, Aspirin, prophylactic heparin
- Healthy term delivery



SLE & pregnancy

- Preparing for pregnancy
- Medication use
- Maternal & fetal complications



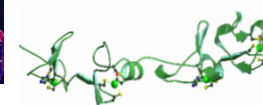
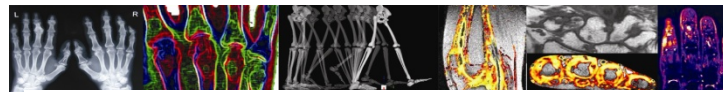
SLE – preparing for pregnancy

- Pregnancy planning should be part of evaluation in women of childbearing age
- Contraceptive advice including emergency
- Overall health of mother – and impact on caring for child
- Risk of preterm baby
- Specific risk factors
- Avoid in severe lung disease, heart disease, CVA



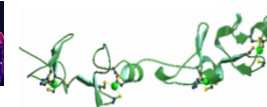
SLE – preparing for pregnancy

- Outcomes have improved significantly
- Majority result in normal fetal outcomes
- Annual mortality rate of pregnant SLE vs non-pregnant SLE is same
- 17% pregnancy loss rate quoted (2005)



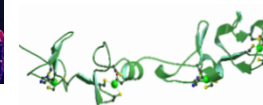
Predictors of high risk pregnancy in SLE

- History of preg complications & poor outcome
- Presence of antiphospholipid antibodies
- Presence of anti-Ro, anti-la antibodies
- Current/previous lupus nephritis, ongoing severe renal impairment
- Maternal age >40
- Multiple pregnancies
- Use of cytotoxics at conception inc high dose steroids
- Active flare at or within 6 months of conception



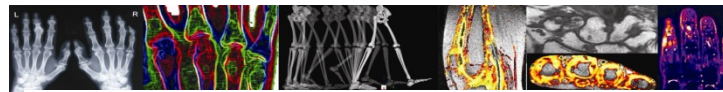
SLE – pregnancy – maternal complications

- Thrombosis
- Infection
- Thrombocytopenia
- Caesarean section
- Preterm birth
- Pre-eclampsia



Normal pregnancy vs SLE Flare

- Skin – facial blush/plamar erythema/mild alopecia
- Arthralgia, myalgia, backache vs synovitis
- Mild anaemia/thrombocytopenia vs more severe/leucopenia



Lupus nephritis vs pre-eclampsia

| | Lupus nephritis | Pre-eclampsia |
|------------------|----------------------------------|--------------------------------------|
| Timing | Weeks- months | 3 rd trimester; hrs -days |
| Hypertension | sometimes | always |
| dsDNA | increased | normal |
| C3/C4 | Low/normal | normal |
| Uric acid | Normal | raised |
| Urinary sediment | Cellular/granular casts | normal |
| Delivery | Proteinuria/hypertension persist | Rapid resolution |

Use prophylactic low dose aspirin in all SLE cases in pregnancy
Can HELLP syndrome be seen in both? Overlap pathology?



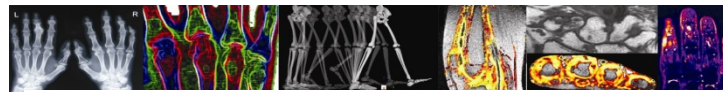
Lupus nephritis

- There may be a large increase in proteinuria without nephritis
- But beware rising Cr
- 64% nephritis (history of) pts experienced pre-eclampsia vs 14% of non-nephritis (Askie, Lancet, 2007)



Antiphospholipid antibodies

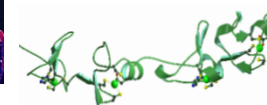
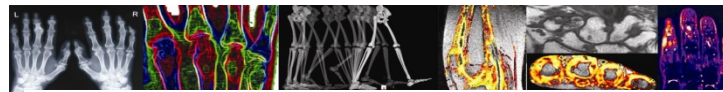
- Anti-cardiolipin (IgG, IgM), β 2microglobulin, lupus anticoagulant
- “Syndrome” – if there has been recurrent pregnancy loss or thrombosis
- Placental insufficiency
- ?complement activation due to antibody and thus inflammatory burst, oxidative stresses, tissue death
- Possible antibody binding to trophoblasts
- Pregnancy loss, reduced amniotic fluid, growth



Antiphospholipid antibodies

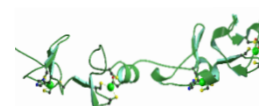
Treatment:

- Antibody +ve but no events: none/low dose aspirin
- Recurrent pregnancy loss/thrombosis: prophylactic vs full dose heparin
(depends partly on warfarin status)
- Combined heparin and aspirin most effective in high risk group
- May need adjustment at delivery
- Continue for 6/52 after delivery



Neonatal lupus

- Rash – 4 to 6 weeks after birth, most common in anti-Ro mothers, 20%, often self limiting
- Most commonly as scarring large macules
- 10-15% of babies reported haematological/LFT abnormalities – dissipate as maternal Ab's diminish



Anti-Ro related fetal heart block

- Congenital heart block – 2% of anti-Ro; 20% of subsequent pregnancies
 - 18-24 weeks' gestation
 - More frequent scans
 - Premature atrial contractions, moderate pericardial effusions may occur
 - Dexamethasone can be given if cardiac abnormality detected
 - 80% survive but need pacemaker



SLE in pregnancy – drug therapy

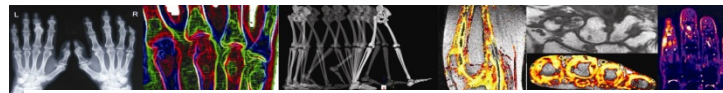
- HCQ – should be continued
- AZA – safe in pregnancy
- Steroids – need not be given prophylactically but generally safe (prednisolone)
- Antihypertensives (not ACE-I)
- Cyclophosphamide, mycophenolate, warfarin contraindicated



Cyclophosphamide – (in)fertility effect

Rates of amenorrhoea (Boumpas et al 1993)

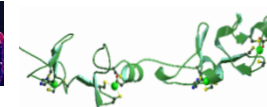
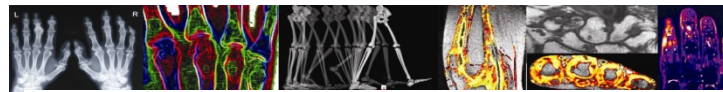
| Age of patient | <7 pulses | >15 pulses |
|----------------|-----------|------------|
| <25 yrs | 0% | 17% |
| 26-30 yrs | 12% | 43% |
| >31 yrs | 25% | 100% |



Biologics in lupus & pregnancy

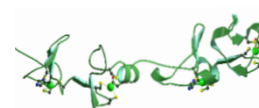
Rituximab:

- $T_{1/2}$ is 21 days
- Response varies: shorter in RA, may be long lived in SLE
- Want to encourage pregnancy before flare
- 6/12 post RTX can be regarded as safe
- RTX has been used in pregnancy – did lead to temporary neonatal B cell depletion but little ill effect (fetal protection from maternal Ig in first 6 months)



Drugs in pregnancy

| Safe in pregnancy: | Breastfeeding |
|------------------------|---------------|
| Azathioprine | √ |
| Corticosteroids | √ |
| Heparin | √ |
| Hydroxychloroquine | √ |
| Sulfasalazine | √ |
| Not Safe in pregnancy: | |
| Methotrexate | X |
| Leflunomide | X |
| Cyclophosphamide | X |
| Mycophenolate | X |
| Warfarin | √ |



Case 2

- SS diagnosed RA age 26
- Started Methotrexate
- Got married
- Disease quite well controlled – DAS28 3.1

- Stopped MTX to try to conceive
- Flared after 2/12



Case 2

- Started Sulfasalazine and HCQ
- Moderate response DAS28 3.9

- Became pregnant
- Stopped all DMARDs

- Seen combined clinic 12/40
- Flare: DAS28 5.2

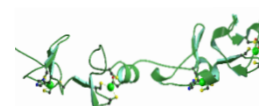


Case 2

- Restarted SSZ and HCQ
- IM Depo

- Disease better controlled throughout pregnancy

- Healthy baby with delivery at term



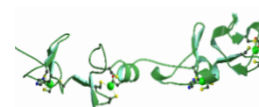
Case 2

- Review 4/52 post natal in combined clinic
- Flare: DAS28 4.5
- Breastfeeding
- Started oral prednisolone (reducing course)



Case 2 - issues

- RA in pregnancy
 - The disease course
- DMARDs in pregnancy
 - What to stop and when



RA in pregnancy

- Conventional wisdom: 70% remission rate
- More recent data suggest 50% remission

- Flare certainly recognised in early post partum stages

- Down regulation of TNF and other inflammatory cytokines



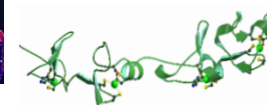
Methotrexate

- Folate antagonist
- Profoundly abortigenic – can be used for management of ectopic pregnancy
- Severe teratogenicity – craniofacial abnormalities and mental retardation
- Most toxicity at 6-8/40 and at >10mg/week
- No safe window – 25% foetal abnormality rate if 1st trimester exposure
- Stop 3 months pre conception
- Not compatible with breastfeeding



Sulfasalazine

- Large meta-analysis showed no significantly increased risk of congenital abnormalities
- Can be used in breastfeeding
- Does interfere with spermatogenesis and motility
– males should stop for 3 months



Hydroxychloroquine

- Several series with no fetal abnormalities
- May improve control of SLE
- Can be used in breast feeding



Glucocorticoids

Fetal effects?

- Prednisone/prednisolone not readily metabolised by placenta
- Asthma study – 8mg/day – no increased rate of abnormalities
- Possible first trimester risk of cleft palate
- Small babies/prematurity - not seen with occasional IM depo and pred < 10-15mg/day



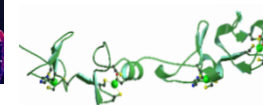
Glucocorticoids

Maternal effects:

Risks:

- Diabetes, hypertension, osteoporosis
- If steroids throughout, then need iv steroids at delivery

Breastfeeding ok if $<20\text{mg/day}$



Case 3

- EF – Rheumatoid Arthritis
- Failed Infliximab (secondary non-response)
- Doing well on Adalimumab and MTX



Case 3

Pre-pregnancy:

- Stopped MTX
- Continue IFX

Pregnancy

- Stop IFX on confirmation
- Initially stable but flare of oligoarthritis
- Persisted despite po steroids and repeated IAI's



Case 3

Anti-TNF in pregnancy:

- Increasingly used by Gastro throughout
- Some registry data in rheumatology - ?higher rate of miscarriage but not of anomalies
- Human data from 152 pregnancies with certolizumab (pegylated anti-TNF - does not cross placenta – no increased rate of abnormalities or complications)
- Certolizumab now licensed throughout pregnancy



Case 3

- Introduced certolizumab at week 30
- Good response in 3/52
- Healthy normal delivery
- Maintained certolizumab after pregnancy (remained off MTX)



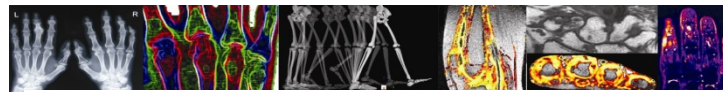
Principles

- Disease should be in remission or good control at conception
- Medications can be minimised/discontinued as appropriate – but in some circs, some agents should definitely be continued
- Treat disease manifestations individually/pragmatically



Role of combined clinic

- Monthly at St James's – Dr Shillito (Obstetrician)
- Combined care before and during pregnancy often very helpful
- Monitoring disease activity
- Advising re maternal medications
- Advising re risk of specific complications
- Fetal assessment
- Holistic approach



Thank you

- Any questions?

With thanks to Jayne Shillito

