PREGNANCY AND RHEUMATIC DISEASES

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Outline

- Consequences of pregnancy and rheumatic disease interaction
  - Effects of pregnancy on maternal disease
  - Effects of disease on maternal and fetal outcomes

- Planning and management of pregnancy in the setting of rheumatic diseases
The interaction and Consequences
Pregnancy Immunology

Tolerance at FMB
Immunological changes

- ↑ Complement inhibitors
- ↓ Classic HLA I Ag expression
- ↑ Non-Classic HLA I Ag expression
- ↑ Th2 polarization

- Hormonal Influences

JS Hunt. Immunological Reviews 2006 (213): 36–47
S Saito. J Reproductive Immunology 2000 (47): 87–103
Rheumatic Diseases

- **Alterations in cytokines**
  - Increased baseline IL-10, IL-17, TNF
  - Blunted IL-6 rise
  - Poor Th2 polarization

- **Hormonal changes**
  - Lower estrogen levels
  - Hormone-cytokine disassociation

- **Antibodies**
  - aCL, LAC

Consequences

- Effects of pregnancy on maternal disease
  - Disease activity

- Effects of disease on maternal and fetal outcomes
  - Pre-eclampsia
  - Intrauterine growth restriction
  - Fetal Loss
  - Prematurity
Pregnancy in the setting of Systemic Lupus Erythematosus (SLE) is increasingly common

- Disease of young women
- Improvement in survival and quality of life
- Women with SLE have comparable fertility to their normal counterparts (unless treated with agents with ovarian toxicity)

Effect of pregnancy on SLE

- Increased risk of disease flares
  - 23-65% pregnancies
  - Severity: mostly mild
  - Organs commonly affected
    - Renal
    - Haematological
- Predictors
  - Disease activity at conception
  - History of nephritis
  - HCQ discontinuation

Effect of SLE on pregnancy

- Increased risk of maternal complications
  - Higher risk of hypertension, gestational diabetes, infections, thrombosis, and operative deliveries.
    - Caveat: Non-pregnant SLE patients have higher risk of medical complications
  - Pre-eclampsia: 16-35% (vs 5-7%)
    - SLE associated predictors:
      - Lupus nephritis
      - Presence of aPLs
      - Thrombocytopenia
      - Genetic predisposition
Effect of SLE on pregnancy

- Sub-optimal obstetric outcomes
  - Pregnancy loss: 10-53%
    - Has decreased over the past few decades
  - Preterm birth: 16-58%
  - IUGR: 5-35%
  - Predictors:
    - Active disease
    - Nephritis
    - Presence of aPLs
    - Thrombocytopenia
    - Thyroid disease (pre-term birth)
Neonatal Lupus Syndromes

- Foetal manifestations of passively acquired autoimmunity
- Maternal Anti-Ro, La +
- NNLE (1-5%)
  - Transient photosensitive rash, cytopenias, transaminitis
  - May last up to 1 year
  - Passive auto-immunity
- CHB 2% of fetuses
  - 16-20% recurrence rate in subsequent pregnancies
  - Permanent damage
  - Cardiac injury by maternal autoantibodies
Rheumatoid Arthritis

- **Effect of Pregnancy on RA**
  - Improvement in the signs and symptoms (50-75%)
  - Relapse in the post-partum period (53-90% at 6 months post delivery)

- **Effect of RA on Pregnancy**
  - Higher rates of prematurity, caesarean section and length of stay
  - Higher rates of IUGR and LBW

Spondyloarthritides

- Limited data
- Disease activity: mostly stable, may remit
- Majority flare post-partum
- Pregnancy outcomes are not adversely affected by the disease
- May lead to difficult deliveries (pelvic and hip involvement)
Systemic Sclerosis

- Systemic Sclerosis (SSc) was previously considered a contra-indication for pregnancy
- Although still high risk, success can be achieved in the majority of cases
- Higher risk of materno-fetal complications
- Pregnancy does not affect SSc adversely
- No increase in risk of renal crisis
  - Caveat: Diagnosis of renal crisis may become difficult
  - Renal crisis during pregnancy: only indication for ACE inhibitors during pregnancy
Vasculitis and pregnancy

- Very limited data
- Successful pregnancies have been achieved
- Maternal and fetal morbidity is significantly increased

Special considerations:
- Takayasu’s arteritis: stenosis of large vessels
- Monitoring issues at the time of delivery
Pregnancy planning
Optimal outcomes: Planned Pregnancy

Preconception visit

Disease stable/remission

No
- Defer pregnancy
- Discuss contraception
- Attempt to achieve remission or stable disease

Remission/stable state achieved

No
- Continue treatment, defer pregnancy until disease stable

Yes
- Prepregnancy counselling
- Autoantibody profiles
- Adjust medications, if necessary
- Refer for high-risk pregnancy management

Contraception in rheumatic diseases

- Very important!!!
- But often over looked
- Study of 206 women with SLE
  - 59% - no counselling
  - 22% - inconsistent contraceptive use
  - Inappropriate use of contraceptives

Options

- Barrier methods
  - High failure rate of 15-32%
  - Unacceptable for women on teratogenic medicines and active disease

- Oral Contraceptives - safe in stable SLE
  - Safety not documented in severe active disease
  - Higher thrombotic risk, avoid in APS & aPL positive patient

- Progesterone only contraceptives - safe
  - ? Reduction in disease activity
  - Poor gynecologic tolerance, concerns about bone health

- IUD - safe
  - No evidence of increased risks
Pregnancy management
Learning from patients

- 35 year old female
- Lupus Nephritis, stable disease for 6 months
- Medications-
  - prednisolone 10mg/d
  - Azathioprine 100mg/d
  - Hydroxychloroquine 200mg/d
- Doctor, I missed my period and …UPT+!
- What is your response?
- Discuss the management plan!
Issues to be discussed

- Effects of SLE on pregnancy and vice versa
  - High risk pregnancy
- Importance of close monitoring
  - Multidisciplinary care
- Medication use
  - Safety and efficacy
- Risk stratification
  - Autoantibody profile
## Close monitoring

<table>
<thead>
<tr>
<th>Clinical review</th>
<th>Investigations</th>
<th>Specific Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rheumatologist: 4–6 weekly, more frequent if active disease or flare</td>
<td>• Each visit: Blood count, serum uric acid, urea, creatinine, electrolyte levels, liver function tests, urinalysis, spot urine protein/creatinine ratio, complement levels and dsDNA antibodies</td>
<td>• Positive anti-Ro antibodies: Fetal echocardiography, weekly from week 16–26 and biweekly thereafter, continuing till delivery</td>
</tr>
<tr>
<td>• Obstetrician: Monthly till week 20, then 2 weekly till week 28, and weekly thereafter</td>
<td>• Ultrasound: early pregnancy for gestational dating, between week 16–20 to screen for fetal anomalies, 4 weekly thereafter to monitor growth</td>
<td>• Pre-eclampsia: Uterine artery Doppler study (week 20 and 4 weekly thereafter), Fetal umbilical artery Doppler velocimetry (weekly from week 26 onwards)</td>
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<td></td>
<td>• Fetal surveillance tests (FST): weekly from week 26</td>
<td>• IUGR: Increase frequency of growth monitoring by ultrasound and FST</td>
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</table>
# Medicines safe in pregnancy

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Comments</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-steroidal anti-inflammatory drugs (NSAIDS)</strong></td>
<td>First trimester use may be associated with higher risk of congenital malformations, foetal renal impairment and premature closure of ductus arteriosus with use in last trimester</td>
<td>Use with caution during the first and second trimester. Discontinue during last trimester.</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>High doses can lead to higher maternal complications. Some association with impaired neuro-psychological development of the child.</td>
<td>Use lowest possible dose. Pulse therapy can be used for acute flares. Limit to one course, for foetal lung maturation.</td>
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<tr>
<td>• Prednisolone/Pulse methylprednisolone</td>
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<td>• Flourinated compounds (Betamethasone/dexamethasone)</td>
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<tr>
<td><strong>Antimalarials</strong></td>
<td>Reduced risk of disease flares, CHB and NLS</td>
<td>Should be continued in all SLE pregnancies.</td>
</tr>
<tr>
<td>• Hydroxychloroquine</td>
<td></td>
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<tr>
<td><strong>Immunosuppressants</strong></td>
<td>Used in large number of transplant recipients. Recent report of late developmental delays in offsprings with azathioprine</td>
<td>Limit azathioprine dose to 2 mg/kg/day. Explain the probability of late effects in the child to mother.</td>
</tr>
<tr>
<td>• Azathioprine</td>
<td></td>
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<tr>
<td>• Calcineurin inhibitors (cyclosporine/tacrolimus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-hypertensives</strong></td>
<td>Concerns about growth retardation with labetalol and impaired utero-placental blood flow with hydralazine</td>
<td>Generally safe and preferred drugs for hypertension during pregnancy.</td>
</tr>
<tr>
<td>• Methyldopa</td>
<td></td>
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<tr>
<td>• Labetalol</td>
<td></td>
<td></td>
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<tr>
<td>• Nifedipine</td>
<td></td>
<td></td>
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<tr>
<td>• Hydralazine</td>
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</tbody>
</table>
Hydroxychloroquine

- **SHOULD** be continued during pregnancy
  - Continued use leads to reduction in disease activity while discontinuation leads to flares
  - Improved maternal and fetal outcomes

- **SAFE** during pregnancy
  - No increase in congenital malformations

- Additional benefits in some situations
  - Reduces the risk of CHB in at risk fetuses.
What should not be used

- **Immunosuppressives**
  - Cyclophosphamide
  - Mycophenolate mofetil
  - Methotrexate
  - Leflunomide

- **Antihypertensives**
  - ACE inhibitors
  - ARBs
  - Diuretics (caution)

- **Antiplatelet agents other than aspirin**
Biologic Agents

- **TNF Inhibitors**
  - Report of higher incidence of VACTREL (vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities) in one study
  - Two prospective studies and multiple case series have not shown increase in major congenital malformations
  - Current consensus:
    - Discontinue if possible
    - Individualize therapy

- **Rituximab, belimumab, Abatacept, Tocilizumab**
  - limited data
  - Discontinue before conception
Other considerations

- Calcium and vitamin D supplementation
  - All pregnant women with SLE,
  - Especially those receiving corticosteroids and heparin
  - Should continue until the end of lactation

- Bisphosphonates
  - Careful consideration before starting therapy in pre-menopausal women
  - Discontinue 6–12 months prior to pregnancy
Risk Stratification: Autoantibody Profile

- Specific antibodies pose unique risks

- Anticardiolipin antibodies
  - Significant risk of pregnancy morbidity and loss

- Anti-Ro antibodies
  - Neonatal Lupus Syndromes
  - Most feared: Congenital heart block
Another Scenario

- 28 year old female
- Known to have SLE for 3 years
- Main manifestations: rashes, arthritis, alopecia
- Serologies: ANA, dsDNA, Sm, Ro
- Current medications:
  - Prednisolone 5mg/d
  - Hydroxychloroquine 400mg/d

- Her first baby died soon after birth due to some heart condition
- She wants to try again
- What will you advise her?
Your advice?

- Close monitoring

- Fetal echocardiography
  - Weekly between 16–26 weeks of gestation
  - Bi-weekly thereafter

- Rationale
  - Early treatment with fluorinated corticosteroids, dexamethasone and betamethasone may prevent progression to complete heart block
  - No benefit once complete block develops

- D. Hutter et al. Scandinavian Journal of Immunology 2010 (72): 235–241
- Friedman DM et al. Am J Cardiol. 2009 April 15; 103(8): 1102–1106
Is prevention possible?

- High risk of recurrence (~20%)
- Prophylactic treatment with IVIG
  - open label data suggested benefit
  - RCTs: no benefit, ?dose effect
- Hydroxychloroquine
  - Reduced recurrence

- Peart E, Clowse ME. Curr Opin Rheumatol 2014, 26:118–123
How will you manage her?

- 32 year old lady
- Arthralgias, livedo reticularis
- Investigations-
  - Mild thrombocytopenia
  - Positive ANA, dsDNA
  - aCL IgM & IgG, LAC present
- Treatment-HCQ
- Wants to plan her pregnancy
- What will you suggest?
Antiphospholipid antibodies are associated with higher rates of pregnancy loss and morbidity:

- Pre-eclampsia
- Placental insufficiency and IUGR
- Pre-term delivery

Pathogenesis:

- Placental thrombosis
- Complement activation
- Effects on trophoblast
Treatment Strategies

Based on risk profile of each pregnancy

- **Asymptomatic women**
  - Persistently positive aPLs but no prior event
  - Low dose aspirin throughout the pregnancy (limited data)

- **Obstetric APS**
  - Recurrent early losses or one late foetal loss
  - Aspirin, in combination with prophylactic dose of heparin
  - Heparin should be continued for 6 weeks post-partum

- **Systemic thrombosis**
  - Full therapeutic doses of heparin
  - Avoid warfarin, especially during period of organogenesis
Treatment Failures: What next?

- No consensus
- Individualized approach
- IVIG
  - Benefit in case reports and series
  - Controlled trials- No benefit
- Warfarin
- Steroids
- Plasmapheresis
How will you differentiate?

- 29 year old lady
- SLE 4 years: fatigue, arthritis, rashes, bicytopenia, dsDNA, low complements
- Stable disease for one year, current meds:
  - HCQ 300mg/day
  - Prednisolone 5mg/day
- 8 weeks pregnant, c/o joint pains and fatigue
- Investigations: Hb and albumin slightly low, complements normal, urine 1+ protein
- Is it flare or physiological changes of pregnancy?
## Differentiation of SLE flare

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnancy-related changes</th>
<th>SLE flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous</td>
<td>Facial flush</td>
<td>Photosensitive rash</td>
</tr>
<tr>
<td></td>
<td>Palmar erythema</td>
<td>Oral or nasal ulcers</td>
</tr>
<tr>
<td></td>
<td>Postpartum hair loss</td>
<td>Inflammatory arthritis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgias</td>
<td>Leucopenia, lymphopenia</td>
</tr>
<tr>
<td></td>
<td>Myalgias</td>
<td>Immune haemolytic anaemia</td>
</tr>
<tr>
<td>Haematologic</td>
<td>Mild anaemia,</td>
<td>Thrombocytopaenia</td>
</tr>
<tr>
<td></td>
<td>Mild thrombocytopaenia</td>
<td>Active urinary sediment</td>
</tr>
<tr>
<td>Renal</td>
<td>Physiologic proteinuria &lt;300 mg/day</td>
<td>Proteinuria &gt;300 mg/day</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Higher complement levels</td>
<td>Falling complement levels</td>
</tr>
<tr>
<td>Others</td>
<td>Fatigue</td>
<td>Rising anti DNA levels</td>
</tr>
<tr>
<td></td>
<td>Mild oedema</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Mild resting dyspnoea</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pleuritis</td>
</tr>
</tbody>
</table>

Another challenge

- 35 year old lady
- SLE for 10 years: nephritis, pancytopenia, arthritis, dsDNA
- Multiple nephritis flares, last flare 2 years back
- Current meds:
  - Azathioprine 150mg/day
  - HCQ 400mg/day
  - Prednisolone 10mg/day
Nephritis or pre-eclampsia?

- G2P1, 26 weeks gestation
- Previous pregnancy 6 years back, pregnancy induced hypertension, live birth at 35 weeks
- Presents with:
  - Increased leg swelling
  - BP: 150/95
  - Urine: protein 500mg/day
<table>
<thead>
<tr>
<th>Clinical and Laboratory Features</th>
<th>Pre-eclampsia</th>
<th>Lupus nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>After 20 weeks of gestation</td>
<td>Any time during the pregnancy</td>
</tr>
<tr>
<td>Platelets</td>
<td>Low - normal</td>
<td>Low - normal</td>
</tr>
<tr>
<td>Complements</td>
<td>Normal - low</td>
<td>Low</td>
</tr>
<tr>
<td>Anti dsDNA</td>
<td>Absent or unchanged</td>
<td>Rising titers</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal - raised</td>
<td>Normal to raised</td>
</tr>
<tr>
<td>Serum Uric Acid</td>
<td>Elevated (&gt;5.5mg/dl)</td>
<td>Normal</td>
</tr>
<tr>
<td>24 hour Urine Calcium</td>
<td>&lt;195mg/dl</td>
<td>&gt;195mg/dl</td>
</tr>
<tr>
<td>Urinary Sediment</td>
<td>Inactive</td>
<td>Active</td>
</tr>
<tr>
<td>Other Organs Involved</td>
<td>Occasionally CNS or HELLP</td>
<td>Evidence of active non-renal SLE</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Other tools?

- Abnormal uterine artery waveforms
- Biomarkers:
  - Placental growth factor (PIGF)
  - Vascular endothelial growth factor (VEGF)
  - Soluble fms-like tyrosine kinase-1 (sFLT1)
  - Soluble endoglin (sENG)
- Poor sensitivity and specificity
- Renal Biopsy: be aware of higher complication risk
- Delivery may be the only definitive answer
Can you help her?

- 38 year old lady
- Multisystem SLE for 15 years
  - Nephritis, class V
  - Pancytopenia
  - Serositis
- Multiple flares but stable for one year on:
  - Prednisolone 7.5mg/d
  - Azathioprine 150mg/d
  - Cyclosporine 150mg/d
  - Enalapril 10mg/d

- Told by her family doctor that she should forget about pregnancy as risk is unacceptably high
Contraindications for pregnancy in SLE

- Severe lupus flare within past 6 months
- Active lupus nephritis within past 6 months
- Stroke within past 6 months
- Previous severe pre-eclampsia or HELLP despite therapy
- Severe pulmonary hypertension (estimated systolic pulmonary artery pressure >50 mmHg or symptomatic)
- Severe restrictive lung disease (forced vital capacity <1l)
- Chronic renal failure (creatinine level >2.8 mg/dl)
- Advance heart failure
Questions?