Lupus and pregnant? We can help you.

QUESTIONS ABOUT MATERNAL AND FETAL OUTCOME:
- MATERNAL RISK
- FETAL RISK
- FETAL HEART BLOCK
- MEDICATION SAFETY

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Objectives
- Review how pregnancy affects SLE
  - Prognostic factors
  - Contra-indication to become pregnant because of SLE
  - Diagnosis of flares during pregnancy
- Review how SLE affects the pregnancy
  - Fetal heart block
  - Antiphospholipid antibodies
- Drugs safety
- Global Management
Pregnancy affecting SLE

- Multiple series across time but SLE seems to increase flares
  - Mostly mild (cutaneous, MSK)
  - Up to 30%
  - Maybe more in 2nd trimester and postpartum but really at any time

- Risks:
  - Lupus flare within 6 months
  - Use of prednisone and HCQ during pregnancy
    - Associated with use but...
    - Also more flares if stopped
    - Likely simply a marker of disease activity

High-risk pregnancy

- Previous poor obstetrical history
- Lupus nephritis
  - Esp. active proteinuria
- Cardiac involvement
- Pulmonary involvement
  - Especially pHTN and ILD
- Active disease
  - Elevated anti-double-stranded DNA antibody
  - High-dose steroids
- Anti-phospholipid antibody or syndrome
- Anti-RO, Anti-LA
- Multiple pregnancy
### Contra-indication to pregnancy

- **Severe pHTN**
  - SPAP > 50 mm Hg or symptomatic
  - 30% mortality peripartum
- **Severe restrictive lung disease**
  - FVC < 1 l
- **CHF**
- **CRF**
  - > 250 mmol / l
- **Previous pre-eclampsia or HELLP**
  - Despite ASA and heparin
- **Severe lupus flare within 6 months**
  - Including stroke
- **APS with thrombosis within 6 months**
  - E.g. arterial bed

### Diagnosis of flare during pregnancy

- **Quite a challenge**
  - Need to decipher between normal pregnancy changes, hypertensive complications/HELLP and lupus flares
  - PE and eclampsia increased in Lupus but might be due to high prevalence of aPS
- **Hypertension**
  - Lupus nephritis, pre-existing hypertension and PE
- **Dyspnea**
  - Progesterone, pHTN
- **Seizures**
  - Eclampsia vs lupus cerebritis
Diagnosis ...

- **Proteinuria**
  - PE, lupus nephritis or even resolved proteinuria re-appearing due to increased GFR

- **Anemia**
  - Dilutional vs lupus

- **Thrombocytopenia**
  - Pregnancy associated, lupus, ITP...

- **Complement**
  - Increase in pregnancy
  - Might be normal even during a flare

Clues to lupus

- Malar rash but raised or with scaly areas
- Synovitis as opposed to arthralgia only
- Edema with nephrotic range proteinuria
- Red blood cell casts in urine
- Decreasing trend of complements, even in normal range
- Rising titers of Anti-DNA antibody
- Positive direct Coombs
- Antiplatelet antibody

- Rising uric acid points AGAINST lupus

- Art of medicine: clinical acumen
Fetal risk: disease activity

- SLE associated with IUGR
  - Although hypertension might be a confounder to a certain extent
  - Can appear even before symptoms in mother
- Up to 20% of preterm birth, esp. with
  - Hypertensive and corticosteroids Rx at conception
  - Severe flare during pregnancy
  - Nephrotic range proteinuria
- Lupus nephritis
  - High risk
  - Increases various risks independently

Fetal risk: heart block

- Associated with anti-Ro and anti-La antibodies
- Affects about 2% of pregnancies
- Caries a high morbidity
- Irreversible when established 3rd degree AVB
  - Some might try dexamethasone but no clear benefit demonstrated
  - Often mandates a pacemaker insertion

- New study brings interesting details
  - The Importance of the Level of Maternal Anti-Ro/SSA Antibodies as a Prognostic Marker of the Development of Cardiac Neonatal Lupus Erythematosus: A Prospective Study of 186 Antibody-Exposed Fetuses and Infants
  - Edgar Jaeggi, Carl Laskin, Robert Hamilton, John Kingdom, Earl Silverman,
  - Journal of the American College of Cardiology, Volume 55, Issue 24, 15 June 2010, Pages 2778-2784
Study NLE

- From Toronto
- All cases referred since 2000 for serial fetal echocardiography or cardiac complications related to maternal anti-bodies were included...
  - Patients without cardiac NLE (group 1)
  - and with cardiac NLE (group 2)
- ...were compared. Antibody levels were measured by enzyme-linked immunosorbent assay with a cutoff value of 8 U/ml for a positive test result.

Table 1

<table>
<thead>
<tr>
<th>Antibody-Related Cardiac Symptoms</th>
<th>Yes</th>
<th>No</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>6 (11%)</td>
<td>125</td>
<td>NS</td>
</tr>
<tr>
<td>Median maternal age (range)</td>
<td>32.3 (19.4–40.3)</td>
<td>33 (17.7–43.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of pregnancies (offspring)</td>
<td>39 (40)</td>
<td>144 (146)</td>
<td>NS</td>
</tr>
<tr>
<td>Prolonged aesthetic</td>
<td>8 (21%)</td>
<td>54 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous live births</td>
<td>28 (72%)</td>
<td>67 (47%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous child with heart block</td>
<td>1 (3%)</td>
<td>8 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive antibody tests</td>
<td>39 (100%)</td>
<td>144 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cases with plasma level measurements</td>
<td>39 (100%)</td>
<td>129 (90%)</td>
<td>NS</td>
</tr>
<tr>
<td>Negative anti-Ro, &lt; 8 U/ml</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Low positive anti-Ro, 8–49 U/ml</td>
<td>0 (0%)</td>
<td>72 (57%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate positive anti-Ro, 50–99 U/ml</td>
<td>6 (15%)</td>
<td>6 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>High positive anti-Ro, ≥100 U/ml</td>
<td>33 (86%)</td>
<td>50 (36%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Negative anti-La, &lt; 8 U/ml</td>
<td>26 (67%)</td>
<td>63 (54%)</td>
<td>NS</td>
</tr>
<tr>
<td>Low positive anti-La, 8–49 U/ml</td>
<td>5 (13%)</td>
<td>14 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate positive anti-La, 50–99 U/ml</td>
<td>1 (3%)</td>
<td>5 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>High positive anti-La, ≥100 U/ml</td>
<td>7 (18%)</td>
<td>27 (21%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Results: NLE

- All cardiac complications were associated with
  - moderate (>50 U/ml; 15%) or
  - high (>100 U/ml; 85%) maternal anti-Ro levels, independently of anti-La antibody titres.
- Most cases of cardiac NLE are detected in asymptomatic women without connective tissue disease (85%) and without a history of a previous child with heart block (98%).

Results NLE

- Average risk of an antibody-positive woman for fetal CAVB is perhaps only about 0.2%, serial fetal echocardiography appears not indicated for many antibody-positive woman.

- Nearly 60% of serially screened mothers in this study had Ro-titres <50 U/ml with, in hindsight, no risk of major antibody-related cardiac complications.
**Conclusion**

- General anti-Ro titres for all pregnant women might help screen detect more affected patients by
  - Targeting high risk patients and re-directing resources to their care
  - Identify patients not routinely sent for cardiac ultrasound given their lack of symptoms or connective tissue history
- It might also relieve anxiety in patients currently identify as “at risk” with the yes/no paradigm if their titre is low
- A larger prospective study is required to confirm these findings.

**NLE and hypothyroidism in the mother**

- 87 women anti-Ro +, 102 infants
- 9 women had hypothyroidism and 78 had normal thyroid function.
- Complete congenital heart block (CCHB) in
  - 5/9 (55%) in the hypothyroid group
  - 10/78 (13%) of the normal thyroid function group
  - $p < 0.005$
- Conclusion: screen mother with hypothyroid for anti-Ro
  - A bit of a stretch since the cohort was defined with anti-Ro and not the other way
Preeclampsia

- Risk increased with SLE
  - APS
  - History of preeclampsia
  - SLE itself
  - Hypertension
  - Lupus nephritis

- Treatment
  - No clear trend of solid evidence
  - Low dose ASA
    - Found to have a small but significant reduction

Anti-phospholipid antibody

- aPL is main predictor in SLE (and non SLE) patients
  - Miscarriage
  - Fetal death
  - Prematurity
  - Still birth
  - Preeclampsia

- Stronger association seems to be with lupus anticoagulant
- Anticardiolopin, esp. IgG are also associated with RFL

aPL and pregnancy loss


- Interesting literature on role of complement activation
  - Esp. C3
- Heparin does inhibit C3 activation
- Trials with Fondaparinux were NOT positive to reduce pregnancy losses in aPL patients
- Coming up:
  - We have initiated the PROMISSE Study (Predictors of Pregnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus), a prospective, multi-center observational study to translate our findings in mice to humans and evaluate the role of complement in aPL antibody-induced pregnancy loss in women.
  - The PROMISSE Study will test the hypothesis that classical, alternative and terminal complement pathway activation will be detected in the circulation and placentas of patients with aPL antibodies and will be associated with poor pregnancy outcomes.

SLE medication and pregnancy

- Very useful paper:

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Yes (avoid after 32 weeks)</td>
<td>Yes</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Yes</td>
<td>Yes?</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Yes</td>
<td>Yes?</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Warfarin</td>
<td>No (with caution after first trimester)</td>
<td>Yes</td>
</tr>
<tr>
<td>Heparin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AAS (low dose)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NSAIDs, non-steroidal anti-inflammatory drugs; AAS, aspirin.
Medication Safety: European workgroup

- Prednisolone and other non-fluorinated glucocorticoids, azathioprine, ciclosporin A and low-dose aspirin have been used in lupus pregnancy, but their efficacy and safety have not been demonstrated in randomised trials.

- The efficacy and safety of hydroxychloroquine in lupus pregnancy have been evaluated in one RCT.

- These recommendations may differ from the ratings of the United States Food & Drug Administration which, in their current form, are often not helpful for the clinician treating patients with chronic disease during pregnancy and lactation.

- There is no evidence to support the use of mycophenolate mofetil or CY, and methotrexate and these agents must be avoided during pregnancy.


The longer version: pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>PDA risk</th>
<th>Transplacental passage</th>
<th>Human teratogenicity</th>
<th>Fetal/neonatal adverse effects</th>
<th>Long-term effects in offspring</th>
<th>Impairment of fertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>G/C</td>
<td>Yes</td>
<td>No</td>
<td>Not at recommended doses</td>
<td>No impairment of growth or hearing</td>
<td>Not studied</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>B</td>
<td>Fetal like</td>
<td>No</td>
<td>Case reports of aplastic anemia and microtubular DNA-like dosage</td>
<td>Not studied</td>
<td>In merothymocytes, decreased sperm motility, abnormal forms</td>
</tr>
<tr>
<td>Lufenamid</td>
<td>X</td>
<td>No data</td>
<td>Data not conclusive</td>
<td>None published</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>D/P</td>
<td>Yes</td>
<td>No</td>
<td>Sporadic congenital anomalies. Transient immune alterations in newborn infants</td>
<td>Normal immune responses in childhood. One case report of live development of autoimmunity</td>
<td>No</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>Methotrexate 4 polyglutamates</td>
<td>Yes</td>
<td>Cytopeps</td>
<td>None reported</td>
<td>Oligoanuromas at high doses</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>D</td>
<td>Yes - animal data</td>
<td>Yes</td>
<td>Osteoskeletal abnormalities,畸胎症</td>
<td>Anucleated</td>
<td>In males and females</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>C</td>
<td>1/50th of experimental human concentration</td>
<td>Yes</td>
<td>None reported</td>
<td>Transient immune alterations</td>
<td>None reported</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>G</td>
<td>Yes</td>
<td>Not reported</td>
<td>Hyperkalemia, renal impairment</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Mycophenolate sodium</td>
<td>G</td>
<td>Yes</td>
<td>3 reports of congenital abnormalities</td>
<td>Not reported</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Immunglobulin</td>
<td>C</td>
<td>Yes</td>
<td>Not reported</td>
<td>No fetal effects reported</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Dimethyl</td>
<td>B</td>
<td>Yes</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not studied</td>
<td>Not studied</td>
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<tr>
<td>Infliximab</td>
<td>B</td>
<td>Not reported</td>
<td>Data not compliant</td>
<td>Not reported</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
</tbody>
</table>
Good pre-conception counseling
- Discussion of risks and optimal conditions
  - Suggest birth control until then
- Ensure no major contra-indication
- Complete antibody panel
  - aPL (LA, aCL)
  - Anti-Ro, Anti-La – eventually titres
  - Anti-DNA titres
  - TSH screen
- Ideally no flare and no thrombosis in last 6 months
- Medication ok for pregnancy
  - Do NOT stop HCQ.
  - Prednisone ideally < 7.5 mg/day
SLE and Pregnancy: Global Management

- During pregnancy
  - High risk clinic
  - BP and dipstick at every visit to any specialist
  - Doppler studies, esp. with aPL, at 20 wks
  - Fetal heart US as soon as 16 wks (usually between 20 and 30 wks) for Anti-Ro or Anti-La + mothers
    - Although that might be adjusted given new evidence
  - Close monitoring post partum

aPL treatment

- ASA low dose before conception
- APS
  - Full dose anticoagulation with LMWH
- Poor obstetrical history
  - Prophylactic dose LMWH is consensual at this point but not supported by solid evidence
    - Empson MB et al. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database of Systematic Reviews 2005 Issue 2
- 4-6 weeks post partum
- Do not forget Vit D and calcium for longstanding heparin, especially if breastfeeding.
IVF

- High dose estrogen over short period
- Limited published evidence
  - No major complications reported
- Should ensure longstanding remission prior to IVF
- aPL patient should be prescribed prophylactic heparin and ASA during procedures

Key messages

- SLE requires a complex assessment and management plan from an experienced multi-disciplinary team.
  - Up to 20% preterm births, many other maternal and fetal complications
- Quiescent disease on medication acceptable during pregnancy for months before conception is recommended
  - HCQ should not be stopped, prednisone < 7.5 mg /day is ok
- Flares might be difficult to differentiate from normal pregnancy changes or other pregnancy associated complications
Key Messages

- aPL and lupus nephritis are important determinant for maternal and fetal outcome.
  - Relative risks ranging from 2.2 to 5.8
  - aPL needs careful follow-up and treatment with ASA and LMWH

- Anti-Ro titres might help discriminate risk level regarding fetal heart block
  - Hypothyroidism in the mother might be an additional contributor

- IVF seems to carry acceptable risk as far as we know
  - Consider ASA and LMWH, especially with aPL

References


- Petrie M, Inam, Min-Y Kim, Carola Linnos, Pia H Le, Marta M Guerra, Ace N Alkilani, June E Selkirk, Jill P Ryan. Evaluation of the risk of anti-SSA-Ro-SSB-La antibody-associated cardiac manifestations of maternal lupus in babies of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. Anti Rheum Dis. published online May 6, 2010 A


