NUHS
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PREGNANCY AND RHEUMATIC DISEASES

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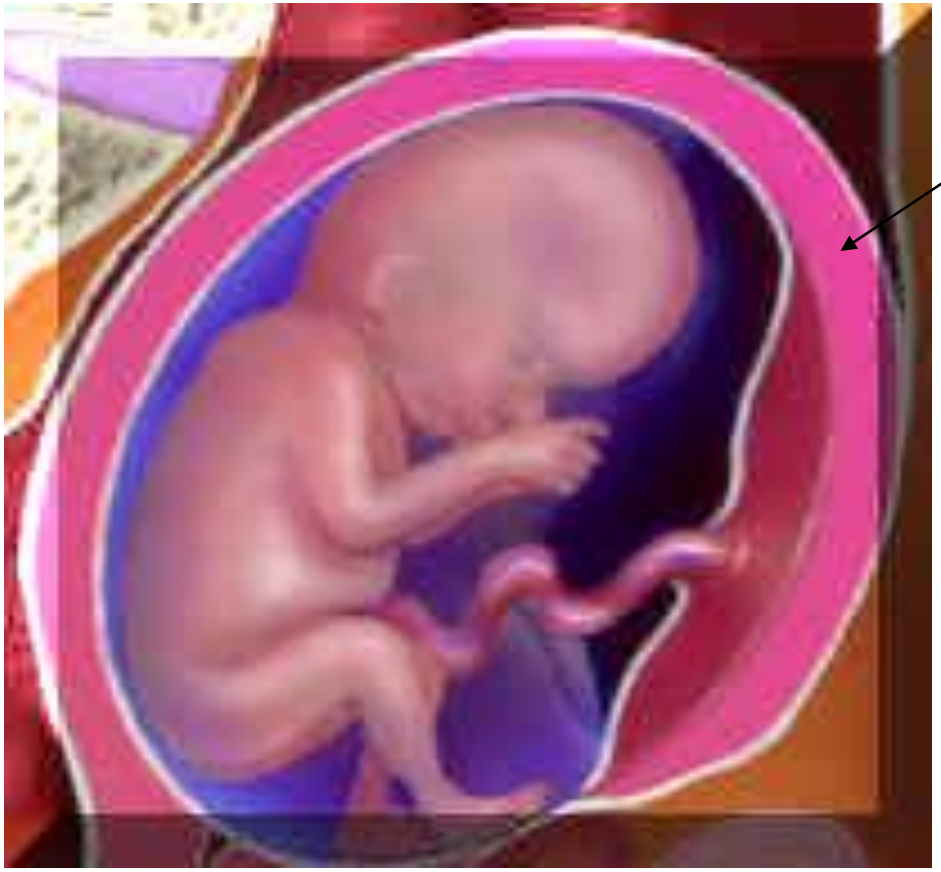
Outline

- 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

A Lateef, M Petri. Rheumatologic Disorders in Pregnancy. In: August P, Cohen WR (eds) Obstetric Medicine, 2013

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

Systemic Lupus Erythematosus

- 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)

- Urowitz MB et al. J Rheumatol 2008;35:2152–8
- Vinet E et al. Ann Rheum Dis 2012;71:557–559
- Clark CA et al. J Rheumatol 2005;32:1709–12

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

- *A Lateef, M Petri. In: August P, Cohen WR (eds) Obstetric Medicine, 2013*
- *A Lateef, M Petri. Best Practice & Research Clinical Rheumatology 27 (2013) 435–447*

Effect of SLE on pregnancy

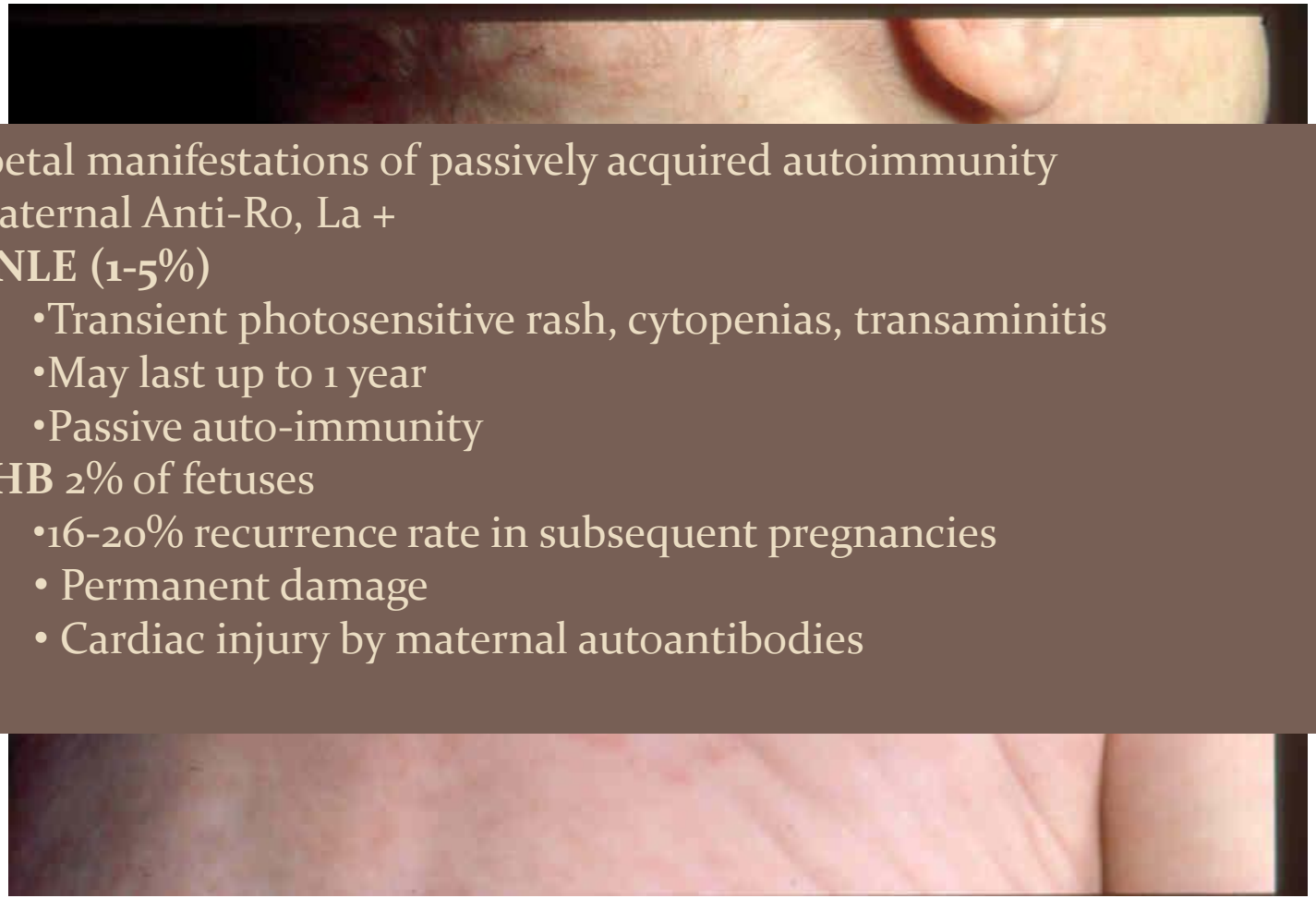
- Increased risk of maternal complications
  - Higher risk of hypertension, gestational diabetes, infections, thrombosis, and operative deliveries.
    - Caveat: Non-pregnant SLE patients have higher risk of medical complications
  - Pre-eclampsia : 16-35% (vs 5-7%)
    - SLE associated predictors:
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

Lateef A, Petri M. Best Practice & Research Clinical Rheumatology 27 (2013) 435–447

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 6months post delivery)
- **Effect of RA on Pregnancy**
  - Higher rates of prematurity, caesarean section and length of stay
  - Higher rates of IUGR and LBW

- De Man YA et al. Curr Opin Rheumatol. 2014 May;26(3):329-33
- Cush JJ, Kavanaugh A. Curr Opin Rheumatol 2014, 26 (3):299–301

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

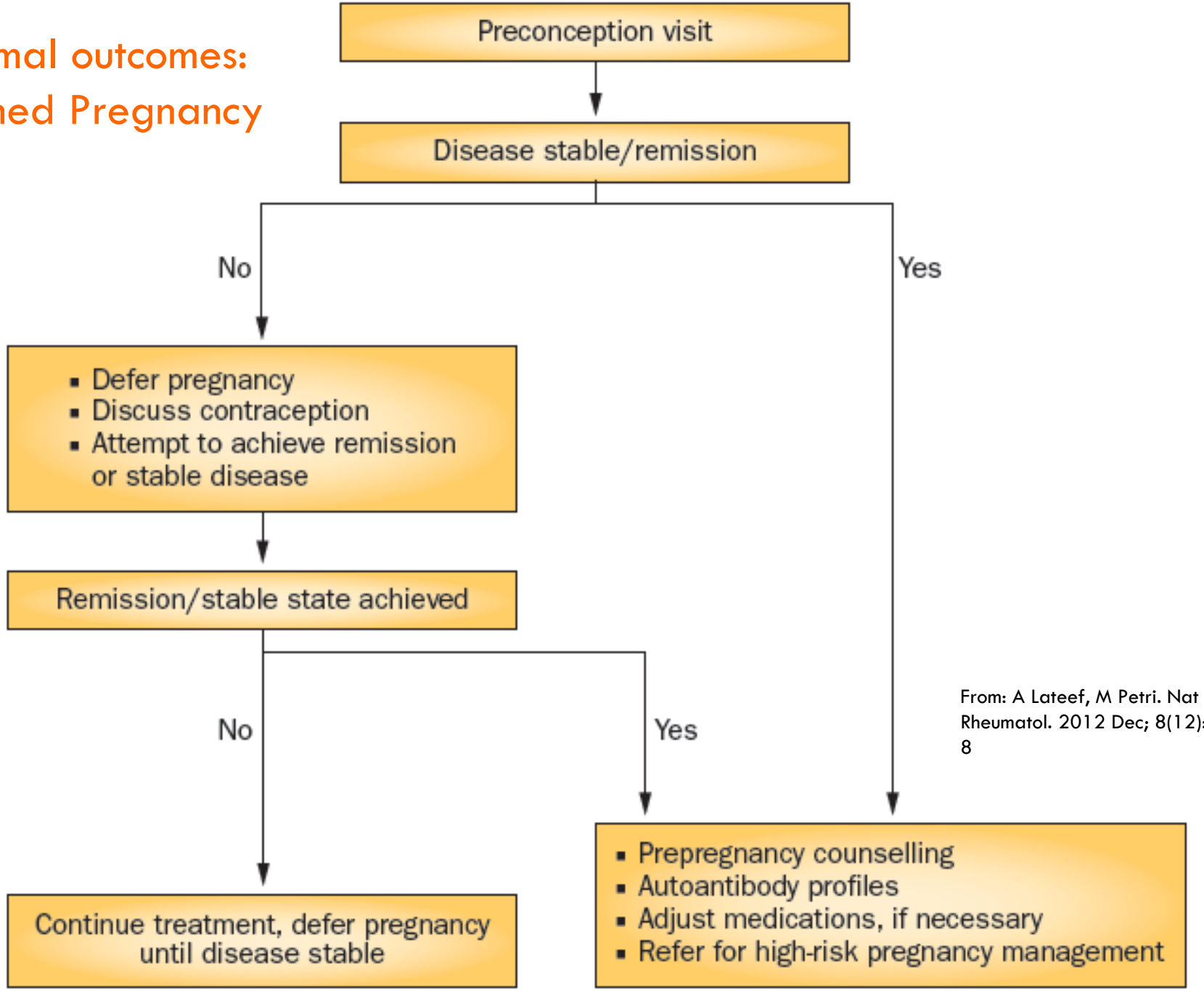
- Systemic Sclerosis (SSc) was previously considered a contra-indication for pregnancy
- Although still high risk, success can be achieved in the majority of cases
- Higher risk of materno-fetal complications
- Pregnancy does not affect SSc adversely
- No increase in risk of renal crisis
  - Caveat: 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



From: A Lateef, M Petri. Nat Rev Rheumatol. 2012 Dec; 8(12):710-8

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

Yazdany, J. et al. Arthritis Care Res (Hoboken) ***63****, 358-65 (2011)*

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

Clinical review	Investigations	Specific Monitoring
•Rheumatologist: 4–6 weekly, more frequent if active disease or flare	•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	• Poitive anti-Ro antibodies : Fetal echocardiography, weekly from week 16–26 and biweekly thereafter, continuing till delivery
•Obstetrician : Monthly till week 20, then 2 weekly till week 28, and weekly thereafter	•Ultrasound: early pregnancy for gestational dating, between week 16–20 to screen for fetal anomalies, 4 weekly thereafter to monitor growth	•Pre-eclampsia: Uterine artery Doppler study (week 20 and 4 weekly thereafter), Fetal umbilical artery Doppler velocimetry (weekly from week 26 onwards)
	•Fetal surveillance tests (FST): weekly from week 26	•IUGR: Increase frequency of growth monitoring by ultrasound and FST

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Medicines safe in pregnancy

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

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, trachea-esophageal, 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?

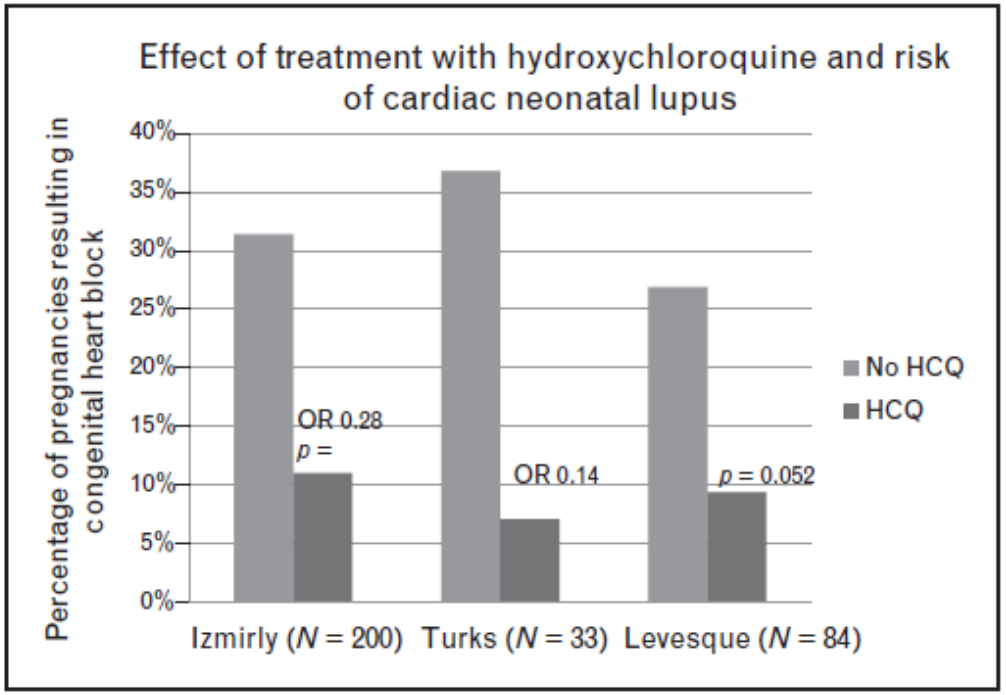
Your advice?

- 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
- Breur J et al. Ultrasound Obstet Gynecol 2004; 24: 467–472

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



- Izmirly PM et al. Arthritis Rheum 2010: 62 (4): 1153–1157
- Pisoni CN et al. . Arthritis Rheum 2010: 62 (4): 1147–1152
- 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

- 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

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

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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

Clinical and Laboratory Features	Pre-eclampsia	Lupus nephritis
Hypertension	After 20 weeks of gestation	Any time during the pregnancy
Platelets	Low - normal	Low - normal
Complements	Normal - low	Low
Anti dsDNA	Absent or unchanged	Rising titers
Creatinine	Normal - raised	Normal to raised
Serum Uric Acid	Elevated (>5.5mg/dl)	Normal
24 hour Urine Calcium	<195mg/dl	>195mg/dl
Urinary Sediment	Inactive	Active
Other Organs Involved	Occasionally CNS or HELLP	Evidence of active non-renal SLE
Response to steroids	No	Yes

Other tools?

- Abnormal uterine artery waveforms
- Biomarkers:
  - Placental growth factor (PlGF)
  - 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


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Questions?