LUPUS et GROSSESSE

Lupus et grossesse

50% des grossesses ne sont pas planifiées

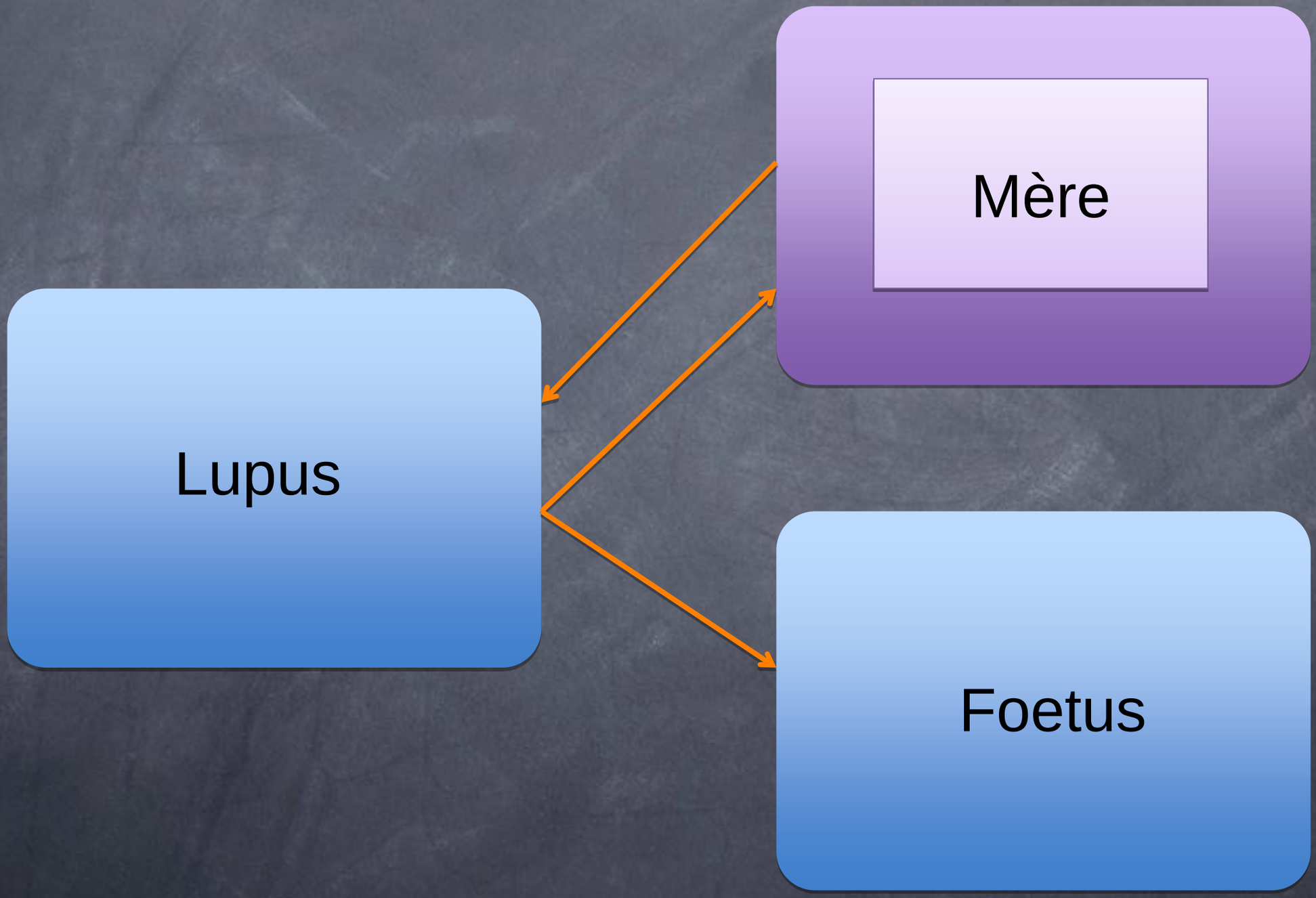
En parler avec les patientes jeunes.

Leur prescrire de l’acide folique (0.8mg/j).

Lupus et grossesse: Key issues

- Risque de récurrence
- Devenir obstétrical
- Tératovigilance; quelle médication

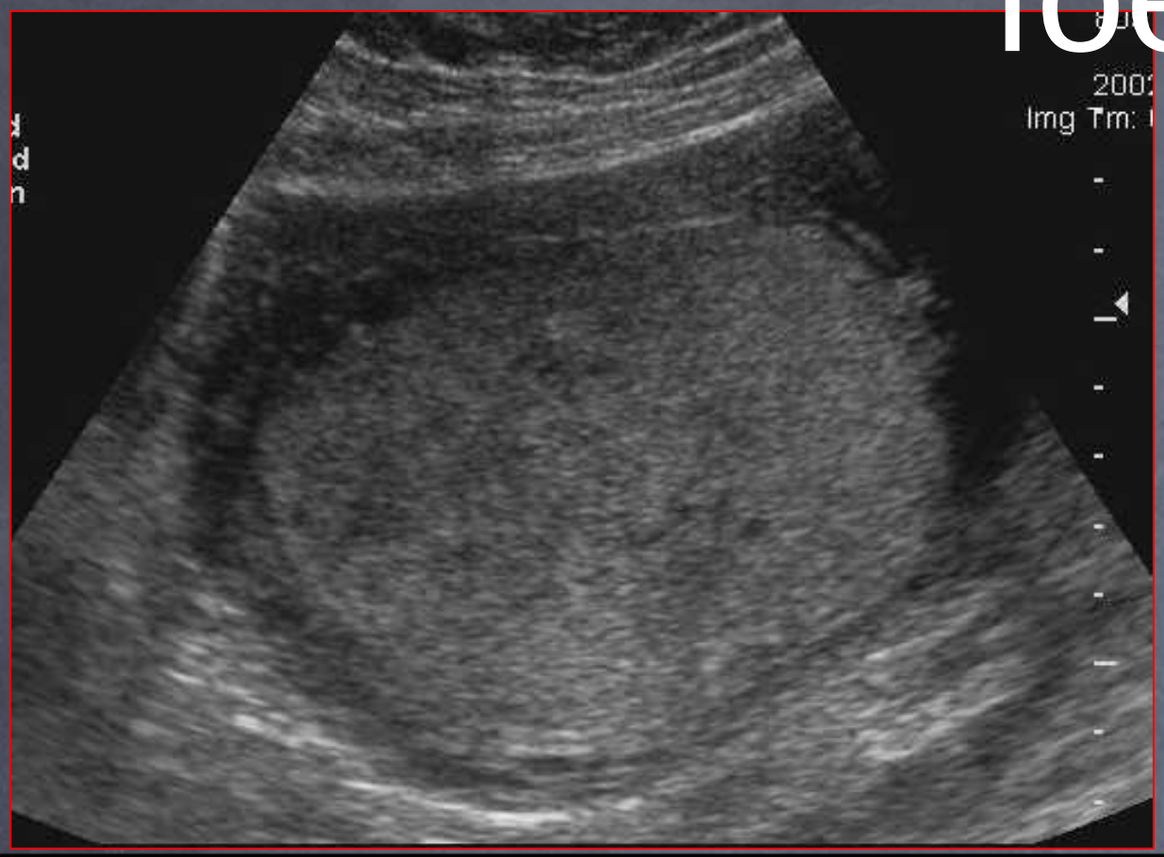
Lupus et grossesse

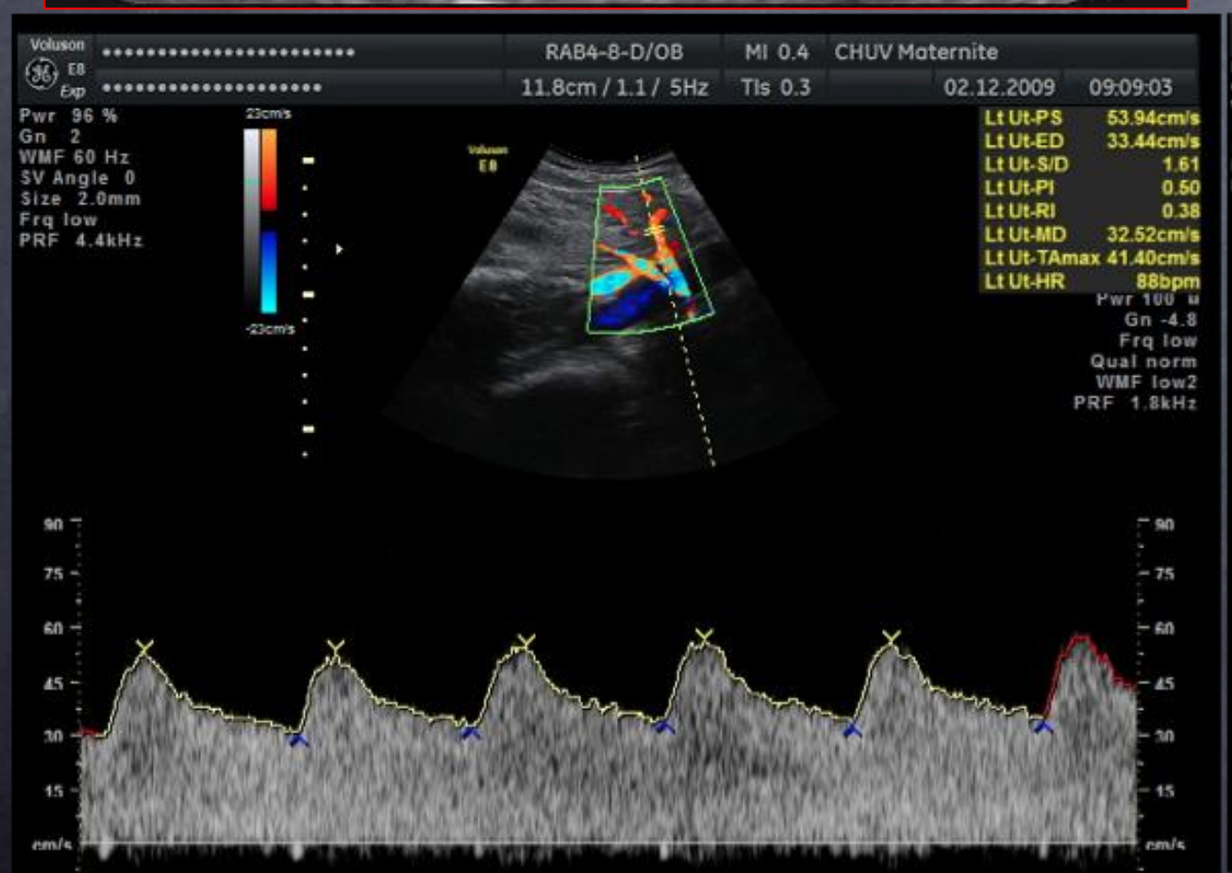


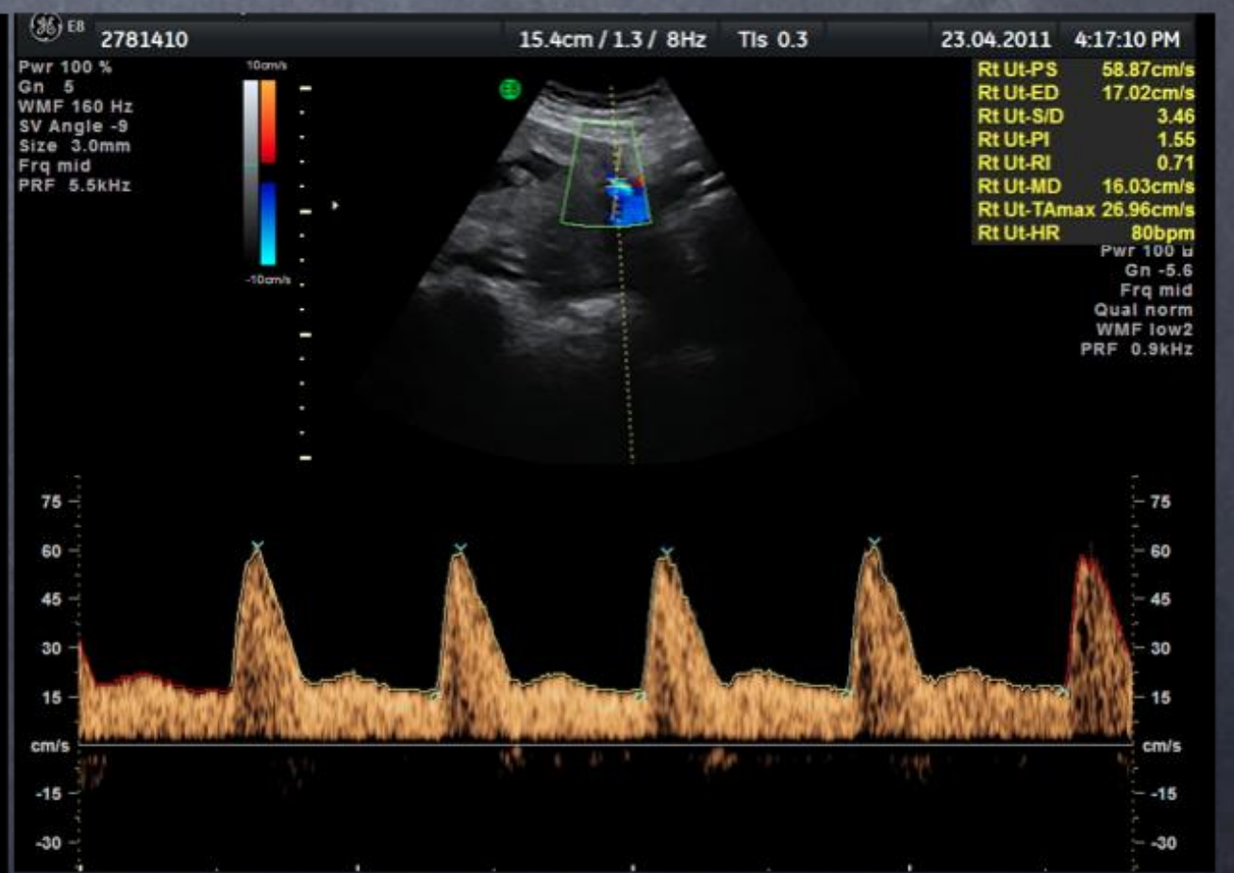
Effet de la Grossesse => le Lupus

- 25% des lupus sont diagnostiqués pendant la grossess
- 25% de risque de récurrence
- ↑ du risque de dialyse post-partum
- ↑ du nombre de thromboses veineuses profondes
- ↑ de l’hypertension

Placenta et doppler et devenir foetal







Effet du Lupus => la Grossesse

Complications in patients active and inactive at conception in the Hospital Clínic of Barcelona experience (103 pregnancies in 76 SLE patients)

Complication	Active (7)	Inactive (78)	*P*
Preeclampsia	2 (28.5%)	5 (6.4%)	<0.05
Flare	3 (42.8%)	16 (20.5%)	NS
Premature rupture of membranes	2 (28.5%)	5 (6.4%)	<0.05
Intrauterine growth retardation	2 (28.5%)	6 (7.6%)	NS
Pre-term delivery	2 (28.5%)	18 (23%)	NS
Low birthweight	3 (42.8%)	16 (20.5%)	NS
Perinatal mortality	0	5 (6.4%)	NS

Cervera et al., Autoimm Rev 2002;1:354-9,

Prééclampsie

- Incidence globale: 30%

- <u>Augmentation du risque</u>

1. lors de néphrite lupique (37%) versus(14%) en absence de néphrite
2. lors d'hypertension associée
3. en présence d'un syndrome des AC anti-phospholipides
4. lors de ttt avec des hautes doses de stéroïdes

Effet du Lupus => la Grossesse

- ↑ des fausses couches 20 - 30%
- ↑ mort in utero 10%
- ↑ Prématurité
- ↑ des ruptures prématurée des membranes
- ↑ des risque de prééclampsie
- ↑ IUGR

Effet du Lupus => la Grossesse

- La présence d'une protéinurie, d'un syndrome des anticorps antiphospholipides, d'une thrombocytopénie et d'une hypertension

Facteurs de mauvais pronostic obstétrical

CONSENSUS

pas de poussée depuis 6 mois avant la conception.

Quand concevoir?

Plus la rémission est de longue durée, mieux c’est!

Risque de récurrence - maladie en activité/néphrite

Qu’est-ce qu’une rémission

- stabilisation de la fonction rénale
- normalisation du urinaire sédiment
- protéinurie < 1 g/jour

Récurrence en cours de grossesse

Effect of pregnancy on SLE in the Hospital Clínic of Barcelona experience (103 pregnancies in 76 SLE patients)

Type of flare	Number	Percentage
Cutaneous	13	54.1%
Thrombocytopenia	8	33.3%
Pericarditis	5	20.8%
Arthritis	5	20.8%
Renal	4	16.6%
Any flare	24	23.3%

Cervera et al., Autoimm Rev 2002;1:354-9,

Diagnostic différentiel
Poussée lupus avec néphrite et Prééclampsie

	Prééclampsie	Poussée lupique
Complément abaissé	+	+++
Anti-DNA élevés	-	+++
Déficit en Anti-thrombine 3	++	+-

	Prééclampsie	Poussée lupique
anémie hémolytique	++	-
thrombocytopénie	++	++
leucopénie	-	++

Diagnostic différentiel
Poussée lupus avec néphrite et Prééclampsie

	Prééclampsie	Poussée lupique
Hématurie	+	+++
cylindres	-	+++
élévation de la créatinine	+-	++
hypocalciurie	++	+_
Transaminases	++	+-

Preconception counselling

- Delay pregnancy until remission
  evaluate lupus activity
  OCP's safe
- Discuss complications-
  PET
  miscarriage
  PTL
  IUGR
  IUFD
  neonatal lupus
- Delineate end organ damage-
  nephritis
  Haematological
  HTN
  APA
- Discontinue???
  NSAIDS and cytotoxic agents

Effects of SLE on fetus

IUGR

Fetal loss

Preterm delivery

Effects of SLE on fetus

IUGR

Fetal loss

- Abortion - 6-35%
- Stillbirth - 0-22%
  - Risk factors
    - active nephritis
    - previous IUD
    - aPL Ab.

Preterm delivery

Effects of SLE on fetus

IUGR

Fetal loss

- 17-49%
- Active disease
- HTN
- Treatment with prednisone

Preterm delivery

Transplacental effects on fetus

- Neonatal lupus
  - presence of anti-Ro (SSA)/anti-La (SSB)
  - congenital heart block or cutaneous lupus
- Caused by transplacental passage of these antibodies
  - persist in fetal circulation for few weeks after delivery

Congenital heart block

- Permanent immune-mediated damage to conductive pathways in heart (in 2nd trim.)
- Myocarditis, pericardial effusion, valvular regurgitation -> cardiac failure
- Significant morbidity and mortality (20-30%)
  - 1:20,000 live births
  - 0.6% in SLE
  - 7% in presence of anti-Ro
  - 2X higher in female fetus
  - 12-16% recurrence risk

Congenital heart block

- Prevention

– steroids, IVIg, plasmapheresis

– ? success

- Anti-Ro/La present

– need fetal echo./serial US

– cardiac failure/hydrops

– dexamethasone

Cutaneous lupus

- Appears days-weeks after birth
- Transient
- Resolves in a few weeks after delivery
- No increased risk of SLE in future life

– genetic predisposition

– increased risk ?

Other manifestations of neonatal lupus

- Thrombocytopenia
  - 10-20%, transient
  - usually benign, GI hemorrhage
- Hepatomegaly
  - 20-40%
  - cardiac failure
  - extramedullary hematopoiesis
- Less common –
  - neurological abnormalities
  - anemia

Management of SLE in pregnancy

- All pregnancies – considered high risk
- Team approach
  - obstetrician, internist, rheumatologist, hematologist and neonatologist
- Monitor maternal disease
- Monitor fetal growth and well being
- Mid-trim. evaluation of placental function

When to treat?

- No symptoms, no treatment
  - monitor anti-dsDNA, complement levels
  - exceptions: proteinuria, hematuria or severe thrombocytopenia (<50 K)
- Symptomatic patient - treat

Medications for SLE

- **NSAIDs**
  - Useful for symptom control esp. arthritis
  - No terratogenic effects
  - LDA is safe
  - High dose - avoid after 30-32 wks
    - closure of ductus
    - oligohydramnios

Medications for SLE

- **Steroids**
  - No terratogenic effects
    - cleft palate in animal studies
  - Avoid fluorinated steroids – cross placenta
  - Prolonged use
    - maternal side effects – GDM, HTN, osteoporosis, avascular bone necrosis
    - PPROM
    - IUGR

Medications for SLE

- **Hydroxychloroquin (Plaquenil)**
  - Safe and effective
  - No terratogenic effects
  - Withdrawal associated with flares
    - Avoid stopping in pregnancy

Medications for SLE

- **Azathioprine (Imuran)**
  - No terratogenic effects
    - ? inadequate study population, ? IUGR/SGA
  - Used in cases with severe disease
  - **Cyclophosphamide**
    - terratogenic
    - effects on future fertility
  - **Methotrexate** – contraindicated
  - **Cyclosporin A** – safe alternative, ? SGA

Other treatments for SLE

- Sunscreens
  - SPF 15+
  - avoid excessive exposure to sunlight
  - prevent cutaneous manifestation
  - systemic disease triggered by sunlight
- Calcium + vit. D
  - pts on steroids
  - osteoporosis prevention
- IVIg
  - role in management of flares in presence of infection

Pharmacotherapy for concurrent APAS

- Heparin + LDA
  - better than LDA – Kutteh et al)
- Prednisone
  - Cowchock et al. – similar outcome with heparin + LDA vs. prednisone + LDA
  - increased risk of pre-eclampsia, PPROM and preterm delivery with prednisone

Pharmacotherapy for concurrent APAS

- SLE (no aPL Abs, no previous loss)
  - no treatment
- SLE + aPL Abs
  - LDA
- SLE + APAS/recurrent loss
  - LDA + heparin

SLE and breastfeeding ?

- Hyperprolactinemia
  - ? cause flares
  - role of estrogen/progesterone levels
- Breastfeeding is OK

Medications for SLE and breastfeeding

- NSAIDS
  - safe
  - avoid if jaundiced neonate
  - avoid high dose aspirin (increased secretion)
- Steroids and hydroxychloroquin
  - safe
- Immunosuppressants
  - avoid breastfeeding

Postpartum contraception?

- Oral contraceptives
  - ? cause flares
  - risks versus effectiveness of birth control
  - low dose pills likely to be safe
  - avoid in presence of aPL Abs – DVT/PE risk
- Alternatives – barrier methods, progesterone
- IUCD – increased infection risk

Management of Ms. MM

- Worsening butterfly rash + fatigue
- Dx- Likely a flare
- Referred to rheumatologist for evaluation the next day
- Obstetric care
  - FTS/MSS (placental function)
  - anatomy scan at 19 wks
  - placental evaluation at 22 wks
    - morphology/Ut A Dopplers
  - anti-Ro/La Ab.
  - anticardiolipin Ab. / lupus anticoagulant

Summary

- SLE no longer a contraindication for pregnancy
- Improved understanding of disease
- Judicious use of medications
- Better disease control and good pregnancy outcomes

Summary

- ® Patients should not be deprived of childbearing
- ® Need for team approach!

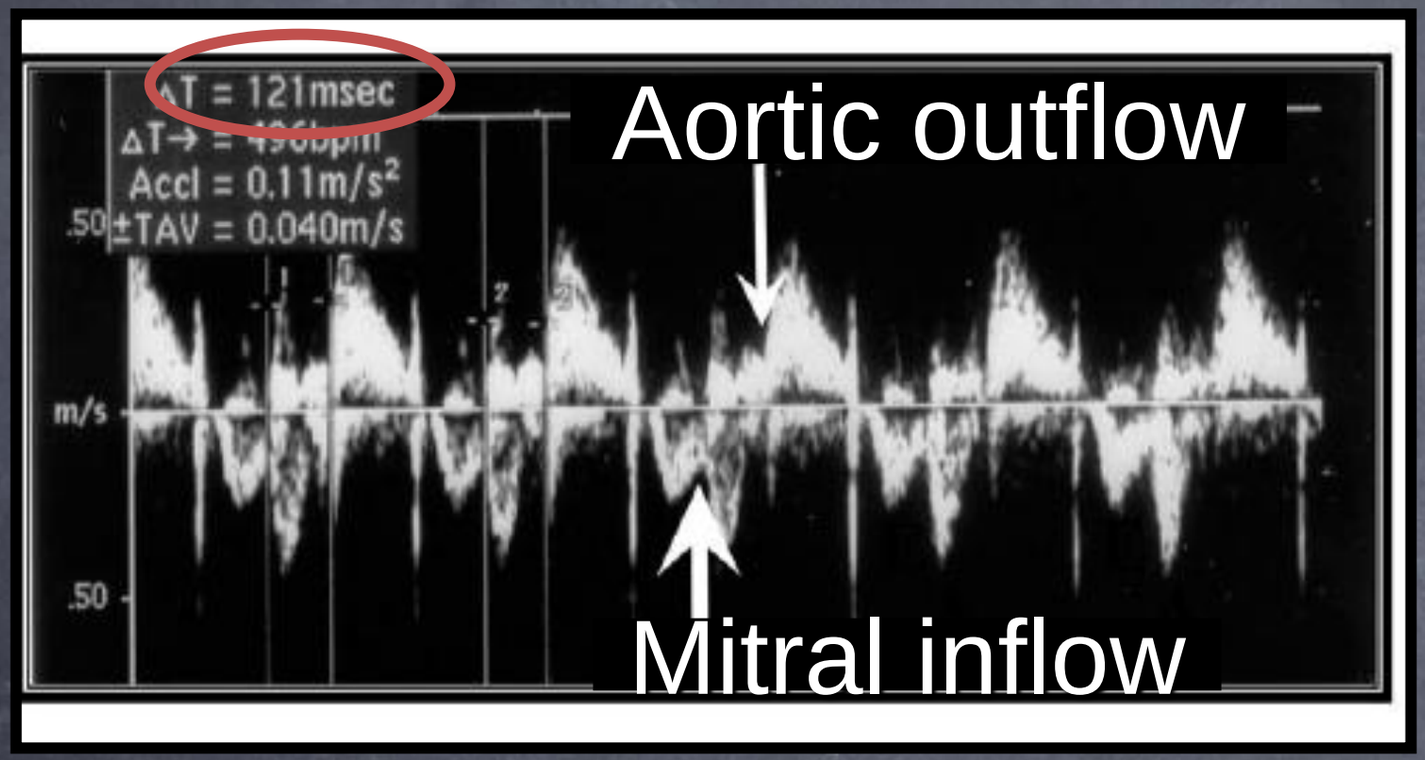
Complete Heart Block

- In 30% patients with structural heart disease
  - More likely if noted in first trimester
  - Heterotaxy syndrome, transposition
- If no structural heart disease, most common cause is maternal SLE
- 5% of fetuses with maternal lupus
  - 53% in 16-24 wks
  - 24% in 25-30 wks
  - 11% in 31-37 wks
  - 7% in 38-40 wks

Complete Heart Block

- Risk factors for mortality
  - Ventricular rate <55bpm in early pregnancy
  - Rapid decrease in ventricular rate in the pregnancy
  - Development of hydrops
  - Structural heart disease
  - Atrial rate < 120 bpm (?)

- Measurement of mechanical PR interval by pulsed doppler echocardiography
- > 150 msec = Primary AVB
- Alternative method – AV time interval
  - simultaneous doppler of SVC and ascending aorta



Effets du Lupus => Foetus manifestations non cardiaque

- Cutaneous neonatal lupus 15 - 25%
  - 4-6 weeks after birth, but may be present at birth.
  - Duration 15-20 weeks ␣
  - 95% of mothers have Anti-Ro␣
  - Liver disease ␣ 15-25% asymptomatic transient ↑ LFT & Hepatomegaly␣
  - Haematological NLE ␣ 15%
  - Thrombopenia & leucopenia in Anti-Ro mothers␣
  - Neurologic ␣ 8% Hydrocephalus in Anti-Ro mothers␣

Effets du Lupus => Foetusmanifestations cardiaques

- Période à risque 16 – 26 sem
- Associé au passage transplacentaire des IgG maternels contre:
  - Ac anti-SSB/La 48 kD
  - Ac anti-SSA/Ro 52 kD
  - Ac anti-SSA/Ro 60 kD

L’inflammation ainsi induite conduit à la fibrose du système de conduction

Effets du Lupus => Foetus atteintes cardiaques

- 1-3% of positive mothers will develop fetal AV-Block ␣
  - 30% of mother have symptomatic lupus ␣
  - 70% of mother are asymptomatic=>
    - antibodies only identified after the diagnosis of AV-Block ␣
- Recurrence in subsequent pregnancy = 18%

- Le cœur fœtal maintient son débit
  - En augmentant son volume d’éjection
  - En augmentant sa précharge
  - Cardiomégalie
  - Hypertrophie ventriculaire

- 20% des enfants atteints ont une atteinte cardiaque diffuse
- 16 – 42% ont CIA, CIV, ductus persistant, valves A-V dysplasique

- Risk of AVB :␣
- 2% ␣for an anti-Ro+ mother
- 3.1% ␣if the woman is also anti-La+
- 0.9% if the woman is anti-La-␣

Significant differences between groups (p = 0.001)

Take home message

- Mothers with anti-Ro face a 2% risk of having a child with AV-Block ⌴
- Normal sinus rhythm can progress to complete AV-block in < 7 days=> Weekly monitoring !⌴
- An AV-time >150 ms warrants an immediate discussion regarding the use of a Dexamethasone to potentially reverse the situation.(!! Side effects !!)⌴
- Iv Ig is currently being evaluated as a prophylactic therapy. (PITCH-study)

Risque de péjoration de la néphrite lupique au cours de la grossesse.

- créatinine sérique > 132 mmol/l
- clearance à la créatinine < 50ml
- Protéinurie > 3g/24h

Détérioration indépendante de la forme histologique

Retard de croissance intrautérin

- Incidence 12-32 %
- Facteurs de risque:
  1. atteinte rénale
  2. prééclampsie
  3. syndrome des Ac antiphospholipides

Accouchement prématuré

- Incidence 3-73 %
- Facteurs de risque:
  - maladie en activité
  - hypertension
  - syndrome des Ac anti-phospholipides
  - prééclampsie
  - retard de croissance intra-utérin
  - souffrance foetale
  - rupture prématurée des membranes

Lupus néonatal

- Incidence: 1/20.000 naissances
- Bloc atrioventriculaire foetal/néonatal
- Lésions cutanées

- Thrombocytopénie
- Anémie
- Hépatite
- SSA-Ro et SSB La

Quelle médication pendant la grossesse

- Cyclophosphamide et méthotrexate-

1. Tératogène
2. devrait être évité

- Azathioprine-

1. Généralement admis comme sûr
2. discussion sur son association avec des retards de croissance
3. induit des cassures chromosomiques, disparraissent avec la croissance

Quelle médication pendant la grossesse

- Prednisone-

1. sûr
2. augmente le risque de diabète gestationnel
3. fentes décrites dans les études animales

- Hydroxychloroquine-

1. relativement sûre , pas d'effet néfaste à long terme
2. ! à ne pas l'arrêter en début de grossesse, augmente le risque de poussée récurrente

Auto-anticorps et lupus

auto-anticorps	fréquence %	clinique
antinucléaires	95	non spécifique
anti-DNA	70	rénal, récurrence
anti-Sm	30	spécifique
anti-SSA	30	lupus néonatal
anti-SSB	10	bloc atrioventriculaire
Anticardiolipine	50	thrombose
lupus anticoagulant	26	RCIU, prééclampsie

Suivi de la grossesse

Obstétricien
Immunologue

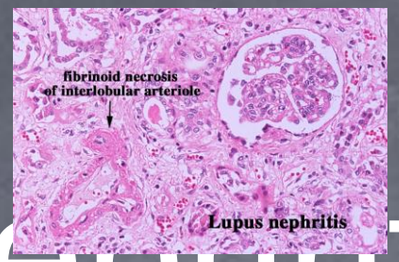
Visite en alternance toutes les 2 semaines

Tests de la fonction placentaire 1x/mois

Laboratoire 1x/mois

test de l’activité

Lupus nephritis



- 50 % patients with lupus will have renal disease
- potential for permanent decrease in renal function and maternal mortality - active lupus nephritis(8-30%)
- 50%-HTN

Factors influencing flares

- Active disease at conception
- Active nephritis- risk of flare of over 50% -

  Bobrie g et al Am J Kid Disease 1987
- systemic lupus erythematosus activity Index score of 5 or more
- Abrupt stoppage of therapy

Treatment of flares

90%
Mild/moderate

4-20 mg
prednisone

10%
severe

>= 20 mg prednisone
Imuran, plaque nil

Very severe
renal
CNS

Hospitalization
Rheumatology
Iv steroids
Cyclophosphamide
plasmapheresis

SLE

- Multi systemic
- Chronic inflammatory
- Remissions and relapses
- Dramatic mortality change-
  1950- 5 yr survival- 50%
  1990s-10 yr survival- >90%

- Lifetime risk for a white woman is 1:700

Buchanan NM, A study of 100 high risk lupus pregnancies. Am J Reprod Immunol 1992; 28(3-4):192-194

SLE

- Female: male 7:1
- Age 15-50
- Genetics Non definite
- 50% twins concordance

ACR criteria

Malar rash	Fixed erythema over malar areas, sparing nasolabial folds
Discoid rash	Erythematous raised patches with keratotic scaling / follicular plugging
Photosensitivity	Skin rash after exposure to sunlight, history or physical exam
Oral ulcers	Oral or nasopharyngeal, painless, by physical exam
Nonerosive arthritis	Tenderness, swelling, effusion in 2 or more peripheral joints
Pleuritis or pericarditis	Convincing history or physical exam or ECG or other evidence
Renal disorder	>0.5g protein/d or 3+ or cellular casts
Seizures, psychosis	Not due to drugs, metabolic derangement, etc.
Hematologic disorder	Hemolytic anemia or leukopenia (<4000 twice) or lymphopenia (<1500 twice) or thromobocytopenia (<100,000) without other causes
Immunologic disorder	Anti-dsDNA or anti-Sm or antiphospholipid antibodies (anticardiolipin, lupus anticoagulant, or false positive test for syphilis)
Positive ANA	Not drug-induced

Diagnosis

- 4+ criteria for diagnosis
  - for classification in studies
- ACR criteria should not be used for confirmation or exclusion of diagnosis
  - ANA + renal biopsy positive = SLE
  - Pt with RA (ANA + hemolytic anemia/thrombocytopenia + proteinuria + pleurisy) $\overline{\quad}$ SLE

Other forms of lupus

- **Discoid lupus** – only skin, 5% of cases have/develop SLE
- **Subacute cutaneous lupus –** rash predominates, indicators in the blood are strongly positive, mild involvement of other organs
- **Drug-induced lupus** – rare, drugs such as hydralazine, procainamide; antihistone antibody positive; no renal/CNS involvement
- **Neonatal lupus** – transplacental passage of maternal auto-antibodies (Anti-Ro/La)

Differential Diagnosis

- Inf. mononucleosis
- HIV
- Endocarditis
- Streptococcal sequelae (rheumatic fever and PSGN)
- Malignancy - lymphoma and leukemia
- Rosacea
- Antibiotic-induced photosensitivity

Overlap forms

- Rheumatoid arthritis
- Scleroderma
- Dermatomyositis
- Sjogren's syndrome
- Systemic vasculitis
- Diagnostic label is less important than the symptoms and organ systems involved
- Treatment is directed to specific abnormalities of specific organ systems

Diagnosis of sle-(4/11-serially/simultaneously)
98% sensitivity, 97% specificity

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis
- Renal
- Neurological disorder psychoses or seizure
- Haematological disorder
- Immunologic disorder (anti-DNA, anti Sm, positive LE CELL, false positive serologic test for syphilis)
- Anti nuclear antibody

Ten et al Arth rheum 1982