LUPUS NEPHRITIS and PREGNANCY

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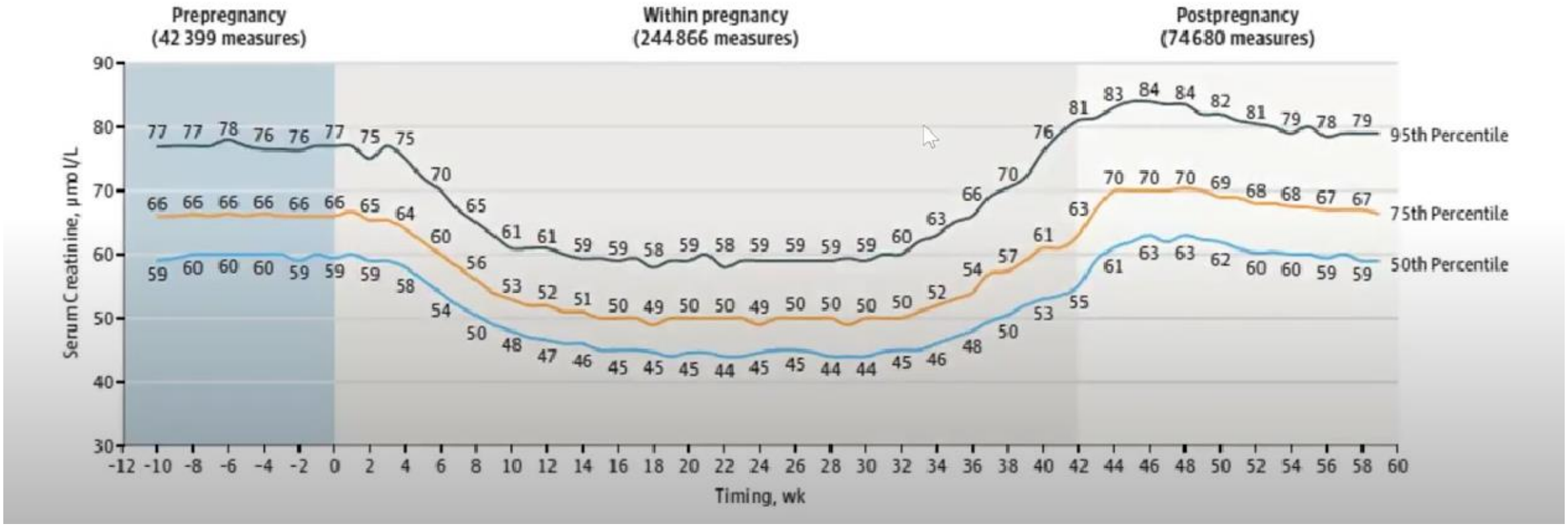
Introduction

Lupus nephritis (LN) :

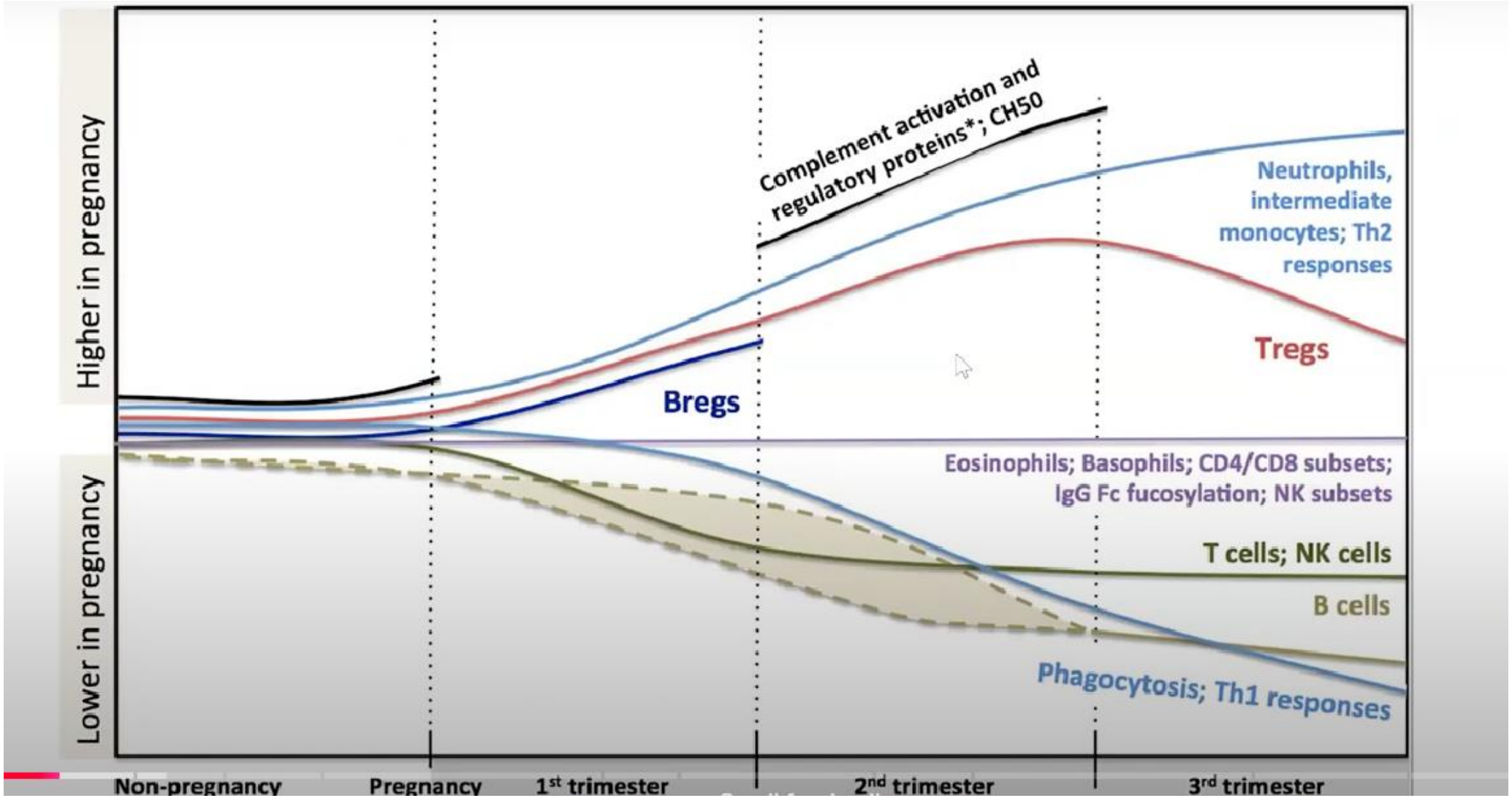
- severe manifestation of SLE
- Prevalence rates in SLE patients : 20% to 65%
- associated with higher mortality
- Pregnant women with LN are at increased risk for complications

Kidney Changes During Pregnancy



Serum Cr: 10- 20% drop
GFR:~505 increase

Pregnancy Immunological Changes



Normal Pregnancy Immunological Changes

- Increase in CD41/CD251 regulatory T cells (Tregs)
- Shift from Th1 (proinflammatory) mediated to Th2 (anti-inflammatory) antibody-mediated response.
- This Th1 to Th2 shift can increase the activity of Th2-mediated diseases like SLE
- Hormonal changes affect lupus activity: estrogen accelerates glomerulonephritis, lymphoproliferation, and mortality

New EULAR/ACR criteria for the classification of SLE

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

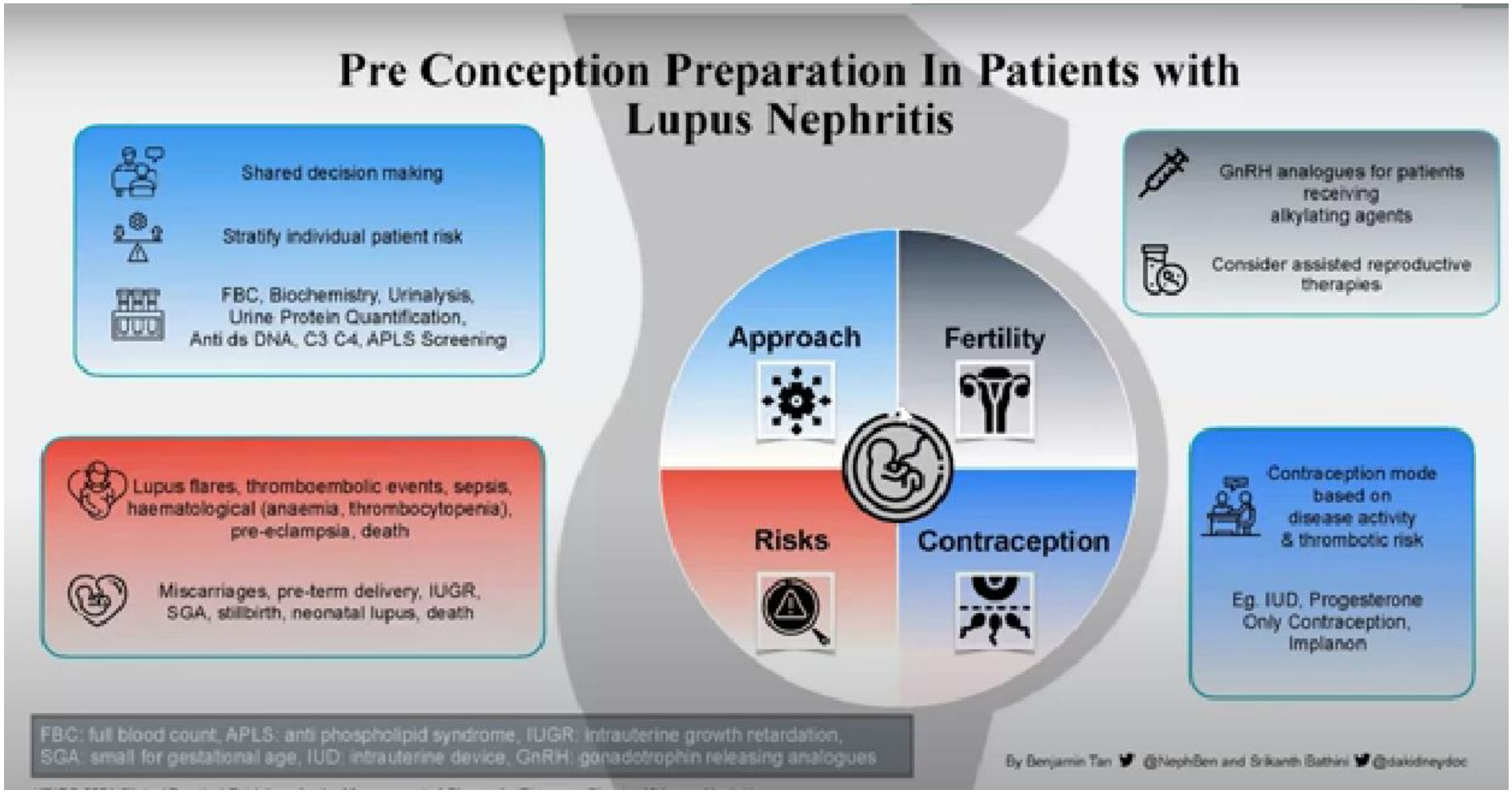
Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference

Pre Conception Preparation In Patients with Lupus Nephritis



FERTILITY

- No direct impact
- Both treatment (eg, cyclophosphamide) and consequences (eg, advanced chronic kidney disease) decrease fertility.
- **cyclophosphamide Premature ovarian failure**: 12%-39% in various studies
- Higher IN:

  total cumulative dose

  women over age 31 at the time of treatment

  after oral administration

Pregnancy Risks for LN patients

LN Flare

Drug complication

What are the maternal outcomes in women with stable lupus nephritis?

Methods

- Prospective study
- Multicenter
- **61** women with lupus nephritis
- **71** pregnancies
- 2006 - 2013
- Complete renal remission before pregnancy in **78.9%**

Intervention

Counselled within 3 months before pregnancy

Tested at

- ✓ Pre-pregnancy screening visit
- ✓ Every trimester &
- ✓ 1 year post delivery

For

Complete blood count
Urine analysis
Lupus anticoagulant
C3, C4 fractions
Anti-DNA Abs
Anti-C1q Abs
Anti-cardiolipin Abs
Anti-beta2 Abs

Results

Adverse maternal outcomes

- Renal flare during or after pregnancy **19.7%**
- All flares responded to treatment
- Pre-eclampsia **8.4%**
- HELLP syndrome **2.8%**
- Manifestations reversible

Predicted by

- History of renal flare
- Arterial hypertension
- Longer duration

Predictors of renal flares

All flares

- ↓ C3
- ↑ anti-DNA Abs

Early flares

- ↓ C4
- ↑ anti-C1q Abs

Late flares

- ↑ BMI

Conclusion: In pregnant women with lupus nephritis adverse maternal outcomes were relatively common but proved to be reversible when promptly diagnosed and treated. Immunological activity, arterial hypertension and BMI may predispose to maternal complications

References: Moroni et al. *Maternal outcome in pregnant women with lupus nephritis – A prospective multicenter study.* 2016. 10.1016/j.jaut.2016.06.012.

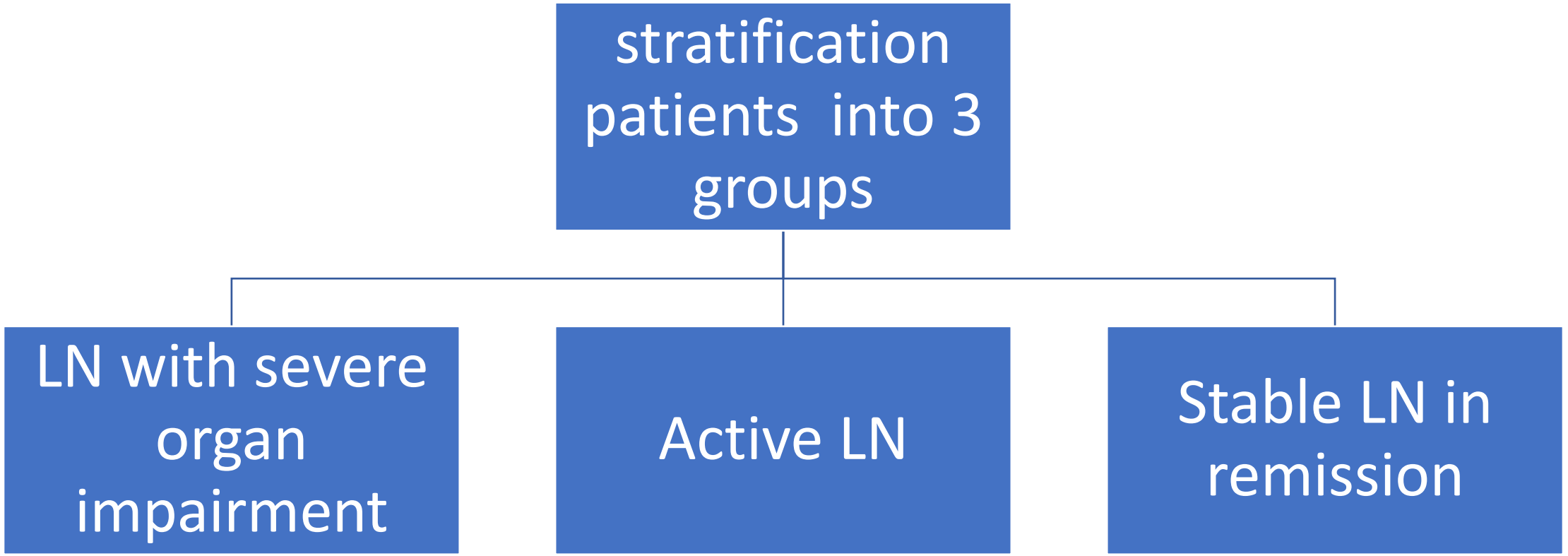
Visual abstract by Krithika Mohan MD DNB

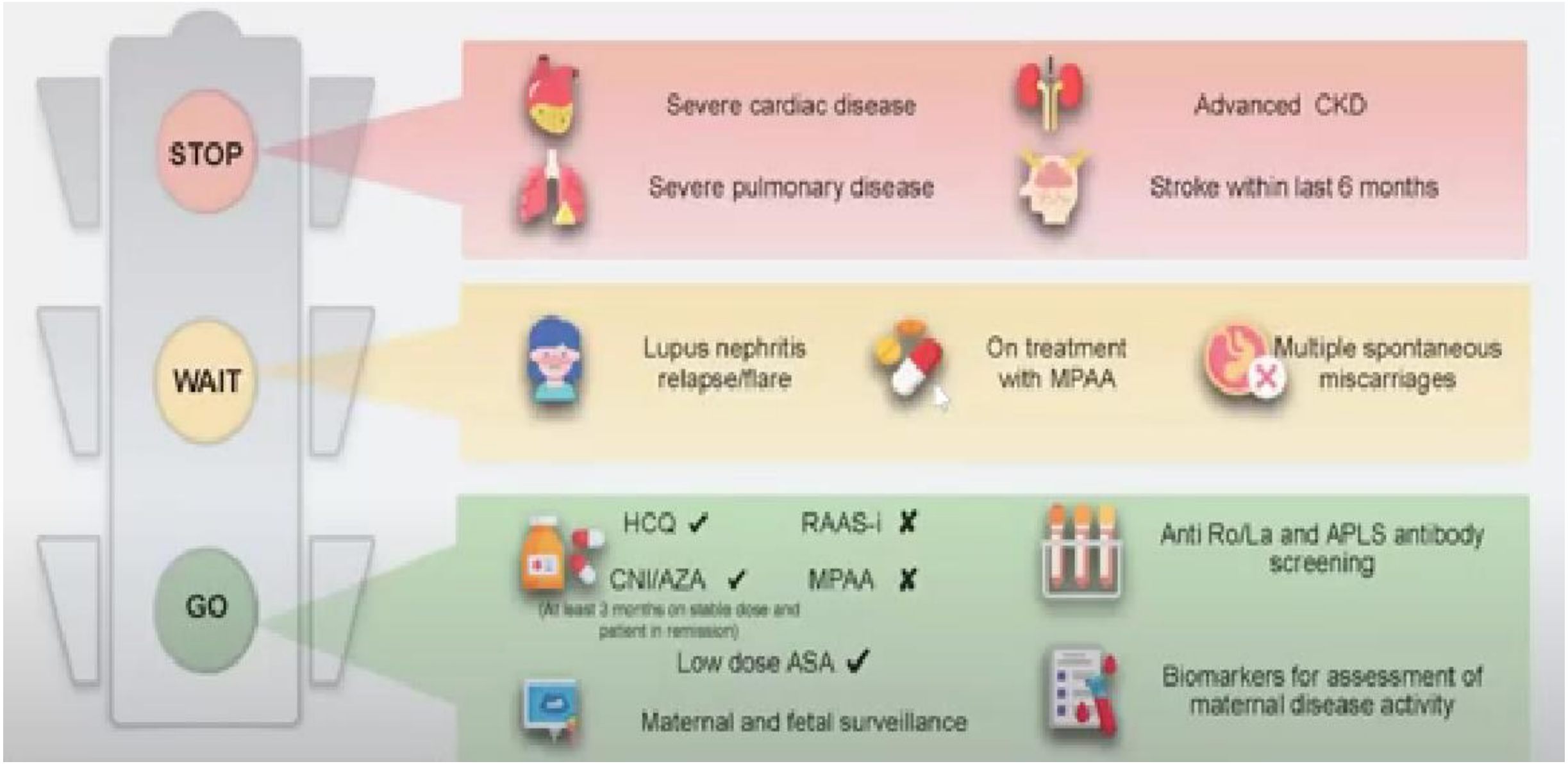
@krithicism

POOR OUTCOME RISK FACTORS

- Active disease
- Recent AKI
- Presence of SS-A and SS-B
- Presence of antiphospholipid antibody
- On pregnancy-incompatible medication
- BP control & level of proteinuria
- Creatinine level

Risk Stratification




STOP
WAIT
GO
Severe cardiac disease
Advanced CKD
Severe pulmonary disease
Stroke within last 6 months
Lupus nephritis relapse/flare
On treatment with MPAA
Multiple spontaneous miscarriages
HCQ ✓
RAAS-i ✘
CNI/AZA ✓
MPAA ✘
(At least 3 months on stable dose and patient in remission)
Low dose ASA ✓
Maternal and fetal surveillance
Anti Ro/La and APLS antibody screening
Biomarkers for assessment of maternal disease activity

Management of Lupus Nephritis (LN) in Pregnancy

- **Severe Organ Impairment (Group 3):**
  - High risk of disease progression and pregnancy complications (e.g., heart failure, kidney disease). Consider alternatives like adoption or surrogacy.
- **Active LN (Group 2):**
- Wait 6 months after remission before pregnancy
- **Stable LN in Remission (Group 1):**
  - Optimal time for pregnancy.
  - Discontinue teratogenic medications 3 months prior, switch to safe alternatives (azathioprine, calcineurin inhibitors).
  - Monitor kidney function, blood pressure, and proteinuria.
- **General Recommendations:**
  - **Hydroxychloroquine (HCQ):** Safe in pregnancy, reduces flare risk, slight increased risk of congenital malformations at high doses.
  - **Low-dose Aspirin & Calcium:** Prevent preeclampsia.
  - **Multidisciplinary Care:** Regular maternal & fetal monitoring, including ultrasounds and kidney function tests.

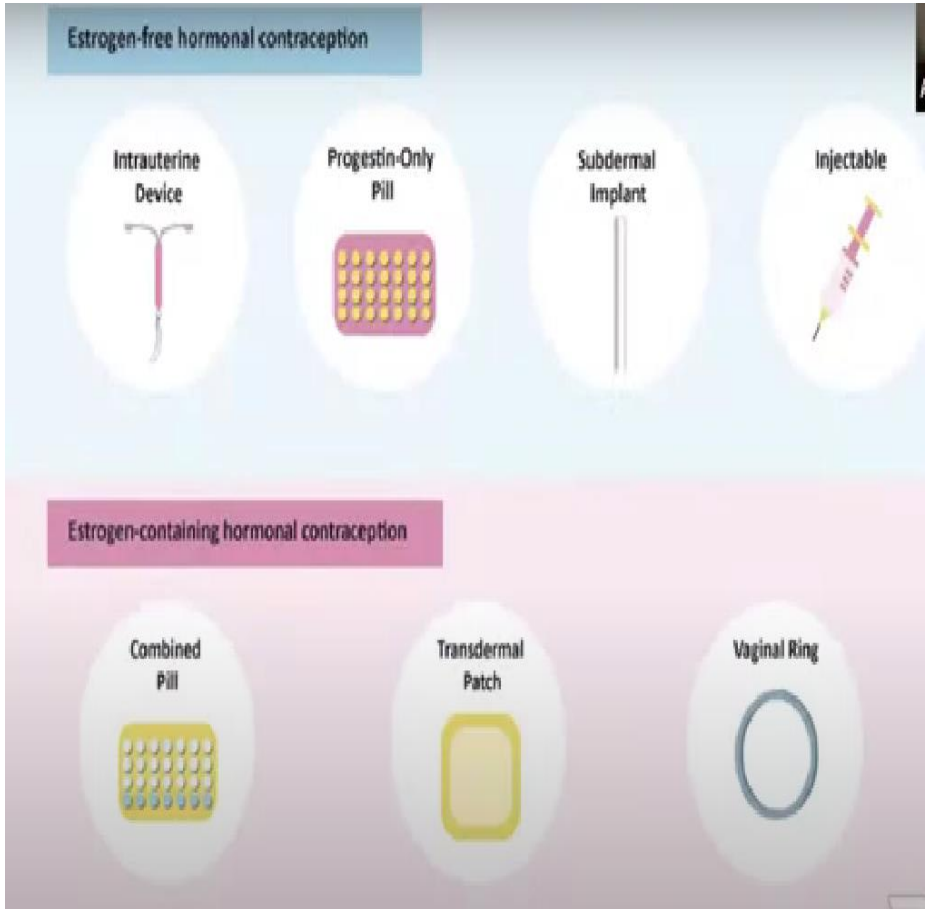
Contraception

- **Preferred Methods:**
- **Intrauterine Device (IUD):**
  - Copper IUD safe for most LN patients.
  - Levonorgestrel-based IUD is an option if benefits outweigh thrombotic risks.
- **Progestin-Only Contraception (POC):**
  - Options include pills, depot injections, or subdermal implants.
  - Suitable for those with positive APS antibodies or thrombotic risks.

Lower thromboembolism risk compared to estrogen-based options

Avoid:

- Estrogen-based contraception, barrier methods, and withdrawal due to higher failure rates.



Lupus Nephritis vs Preeclampsia

	Preeclampsia	Lupus nephritis
Clinical		
Blood pressure: hypertension	After 20 weeks of gestation	Any time during pregnancy
Other organ affection	Occasionally CNS	Evidence of non-renal active SLE
Laboratory investigations		
Standard blood testing		
Platelets	Low–normal	Low–normal
Creatinine	Normal–raised	Normal to raised
Uric acid	Elevated	Normal
Immunology testing		
Complements	Normal–low	Low
Anti-dsDNA	Absent or unchanged	Rising titers
Urine testing		
Urinary sediment	Inactive (uniform pattern, reflect renal damage, no correlation with clinical course)	Active (urine sediment reflect lupus nephritis histopathology)
24-h urine calcium	< 195 mg/dl	> 195 mg/dl
Management:		
response to steroid therapy	No response	Good response

J Obstet Gynaecol Res. 2021 Jul;47(7):2318-2323. doi: 10.1111/jog.14815. Epub 2021 May 10.

sFlt-1/PlGF ratio as a predictive and prognostic marker for preeclampsia

Hae Rin Jeon [1], Da Hoe Jeong [1], Jin Young Lee [1], Eun Young Woo [1], Gwi Taek Shin [1], Suk-Young Kim [1]

Am J Perinatol. 2021 Aug;38(S 01):e292-e298. doi: 10.1055/s-0040-1709696. Epub 2020 May 23.

Evaluation of the Prognostic Value of the sFlt-1/PlGF Ratio in Early-Onset Preeclampsia

Oriane Tasta [1], Olivier Parant [1], Safouane M Hamdi [2], Mickael Allouche [1], Christophe Vayssiere [1], Paul Guerby [1 3]

Department of Obstetrics and Gynecology, Paule de Viguier Maternity, CHU Toulouse, Tc

MATERNAL-FETAL MONITORING

1. First Trimester:

Ultrasound to estimate delivery date.

2. Second Trimester:

Fetal anatomic survey (~18 weeks).

3. Third Trimester:

1. Regular ultrasounds (~every 4 weeks) to evaluate fetal growth and placental sufficiency.
2. Increased frequency with doppler velocimetry for suspected growth restriction or placental insufficiency.

Fetal Monitoring (Last 4–6 Weeks):

1. Nonstress tests and biophysical profiles.
2. Customized surveillance based on maternal-fetal health assessments.

Anti-Ro/SSA or Anti-La/SSB Antibodies:

1. Risk: Neonatal lupus, congenital heart block (0.7%–2%).
2. Recommendations:
    1. Fetal echocardiography for dysrhythmia or myocarditis.
    2. Continuous monitoring for signs of congenital heart block.

Recommended Medications During Pregnancy

- **Hydroxychloroquine (HCQ):**
- **Benefits:**
  - Reduces lupus flares and Increases complete remission rates, especially in Class V nephritis.
  - Reduces preterm birth risk and improves neonatal outcomes.
- **Safety:**
  - Generally safe but doses >400 mg/day in the first trimester may increase the risk of congenital anomalies.
  - May reduce the risk of congenital heart block in at-risk fetuses.
- **Low-Dose Aspirin:**
- **Indication:** Recommended from 12 weeks gestation to reduce preeclampsia risk.
  - Helps lower preeclampsia incidence in SLE patients and improves pregnancy outcomes when combined with HCQ.

Medications Selectively Allowed During Pregnancy

1. **NSAIDs:**
    1. Safe in early pregnancy but avoid beyond 30 weeks (risk of ductus arteriosus closure).
    2. FDA advises the lowest dose between 20–30 weeks.
2. **Glucocorticoid:** Low doses (<6.5 mg/day) may still pose risks, emphasizing careful management.
3. **Azathioprine (AZA):** Compatible with pregnancy if doses are ≤2 mg/kg/day.
4. **Cyclosporine:** Limited use; safe if maternal benefits outweigh fetal risks.
5. **Tacrolimus:**

   Effective for LN management; no established link to congenital anomalies.

1. **Antihypertensive Medications:**

   Safe: Methyldopa, nifedipine, labetalol.
   Contraindicated: ACE inhibitors, ARBs.

Rituximab in Pregnancy?

Rituximab before and during pregnancy: A systematic review, and a case series in MS and NMOSD

Gitanjali Das [1], Vincent Damotte [1], Jeffrey M Gelfand [1], Carolyn Bevan [1], Bruce A C Cree [1], Lynn Do [1], Ari J Green [1], Stephen L Hauser [1], Riley Bove [1]

Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development

D T Klink [1], R M van Elburg, M W J Schreurs, G T J van Well

Affiliations + expand

PMID: 18596903 PMCID: PMC2438602 DOI: 10.1155/2008/271363

Medications to Use with Caution

Biologic Medications:

1. **Rituximab:**

   Safe before conception or in early pregnancy but avoid in the third trimester (risk of neonatal B cell depletion).

2. **Belimumab:**

   Limited data but no increased risk of anomalies

Cyclophosphamide in Pregnancy

Management of breast cancer during pregnancy using a standardized protocol

D L Berry [1], R L Theriault, F A Holmes, V M Parisi, D J Booser, S E Singletary, A U Buzdar, G N Hortobagyi

Affiliations + expand

PMID: 10071276 DOI: 10.1200/JCO.1999.17.3.855

Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals

Alistair E Ring [1], Ian E Smith, Alison Jones, Catherine Shannon, Eleni Galani, Paul A Ellis

Affiliations + expand

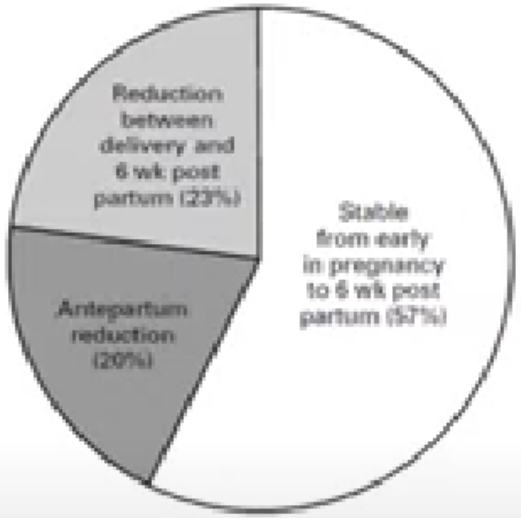
Contraindicated Medications in Pregnancy

1. **Cyclophosphamide:** Avoid during the first 10 weeks of gestation; may be considered later in life-threatening scenarios.
2. **Mycophenolate Mofetil:**
   - Associated with congenital anomalies and first-trimester pregnancy loss.
   - Discontinue at least 6 weeks before conception; substitute with AZA or tacrolimus.
3. **Methotrexate:**
   - Cease 1–3 months before conception due to fetal growth risks.
4. **Leflunomide:**
   - Use cholestyramine washout before conception to eliminate residues.

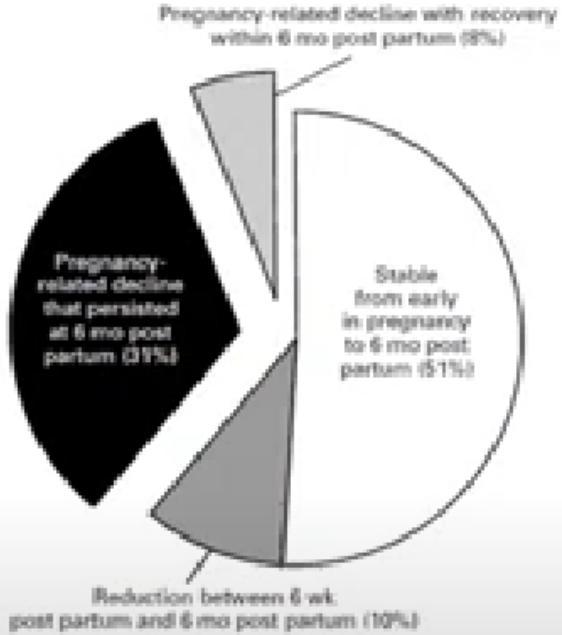
Thromboprophylaxis

Obesity (BMI >30)
Age >35
Parity >= 3
Smoker
Gross varicose vein
Current pre-eclampsia
Immobility
Low-risk thrombophilia
Multiple pregnancy
IVF/ART
Sub-nephrotic proteinuria

Post Partum Period



- In patients with moderate kidney function (>creatinine 124 umol/L), about 40% may deteriorates during peri-partum.



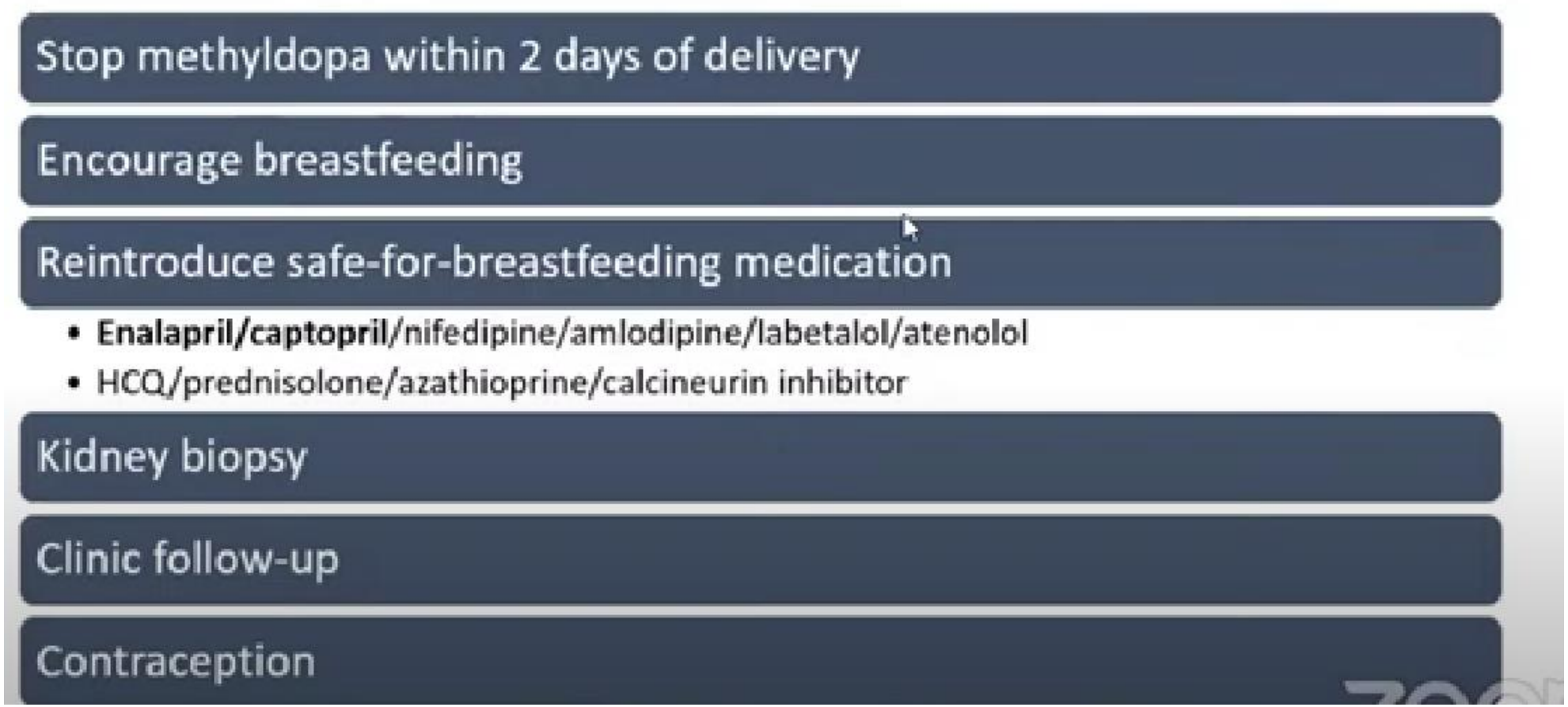
- Only 8% recovered to baseline if kidney function deteriorates during pregnancy

Delivery and Postpartum Care

Key Considerations:

- Timing of Delivery: Based on maternal-fetal well-being
- Nephritis flare not a trigger for delivery.
- Breastfeeding:
  - Safe drugs: Hydroxychloroquine, prednisone, azathioprine, tacrolimus.
  - Unsafe drugs: Mycophenolate, methotrexate, cyclophosphamide.

Issues During post Partum Period



Pregnancy Post-Kidney Transplant

- Requires stable kidney function (1-2 years post-transplant).
- Higher risks: Preeclampsia, miscarriages.
- Preparatory Steps:
  - Adjust immunosuppressants (e.g., switch from mycophenolate to azathioprine).
  - Monitor for LN recurrence, hypertension, or graft issues.

Renal Replacement Therapy

Hemodialysis:

- Increase frequency/intensity: 5–7 sessions per week, at least 24 hours total per week.
- Target: Pre-dialysis urea levels <20 mmol/L to reduce uremic risks.

Anemia Management:

- Use erythropoiesis-stimulating agents to maintain adequate hemoglobin levels.
- Benefits: Supports fetal growth and reduces risks of low birth weight/prematurity.

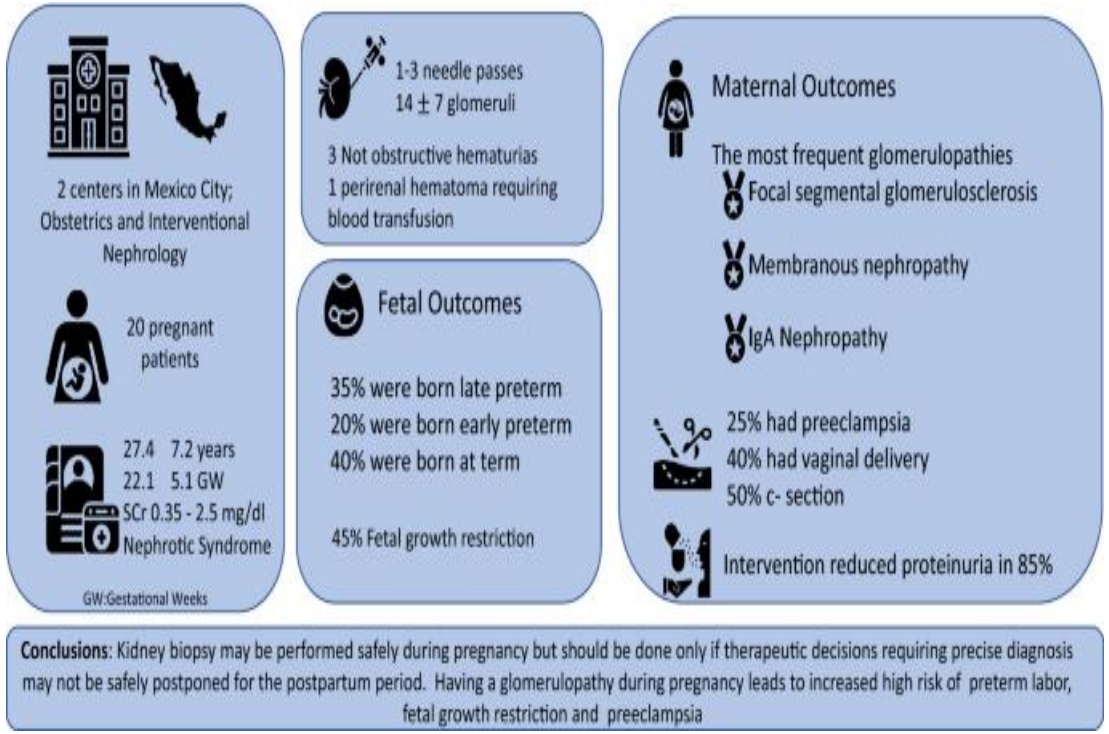
Nutritional Management:

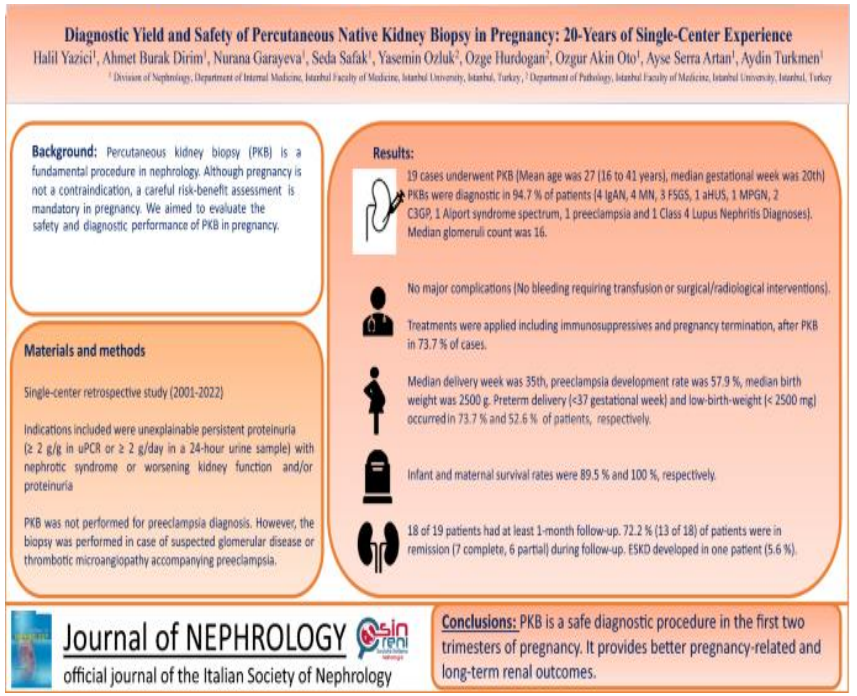
- High-protein diet tailored to pregnancy and renal needs.
- Adjust vitamins/minerals (e.g., calcium, phosphate).
- Safe phosphate binders: Calcium carbonate.

Fluid & Electrolyte Monitoring:

- Daily adjustments to manage fluid balance and prevent complications like hypercalcemia or alkalosis

KIDNEY BIOPSY





Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review

GB Piccoli, G Daidola, R Attini, S Parisi, F Fassio, C Naretto, MC Deagostini, N Castelluccia, M Ferraresi, D Roccatello, T Todros

First published: 15 January 2013 | https://doi.org/10.1111/1471-0528.12111 | Citations: 86

Systematic review: In 197 kidney biopsies performed during gestation there were **4/197 or 2% major complication rate** and **5% minor complication rate.**

KIDNEY CARE IN PREGNACY

Lupus in pregnancy- expect the unexpected

Outcomes

Maternal

Higher risk of:

- flare (26%)
- hypertension (16%)
- preeclampsia (7.6%)
- lupus nephritis (16.1%)

Mortality x 20

Fetal

Higher risk of:

- intra-uterine growth restriction (12%)
- spontaneous abortion (16%)
- premature delivery (35%)
- neonatal death (2.5%)

Anti-phospholipid antibody syndrome

lupus anticoagulant + -> more adverse outcomes

early treatment -> up to 85% live-birth rate

Planning

SLE activity evaluation

No flare 6 months before conception

IMMUNOSUPPRESION

Safe

- Hydroxycloroquine
- Azathyoprine
- CNI
- PDN <20 mg/day

Unsafe

- Mycophenolate
- Cyclophosphamide
- Methotrexate

Flare

- **Hydroxycloroquine** - for all
- **No 1. choice**- steroids
- **Azathyoprine** - 2mg/kg/day
- **AVOID** Cyclophosphamide, Rituximab

References:
Cristina Popa & Anoushka Krishnan, **My patient with lupus wants to get pregnant- what should I know?**, NSMC2022 blog
PMID: 20688887, PMID: 17499705, PMID: 30772493, PMID: 32090480

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