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Diagnosis, treatment and prognosis of systemic Lupus and Lupus Nephritis, in Pregnancy

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Pregnancy in Patients with SLE/LN

- SLE: disease of young women of childbearing age
- Pregnancy affects immune system
  - Altered Th1/Th2 balance, with Th2 polarization
    - ↓ Cell-mediated immunity, which could be detrimental to the allogeneic fetus
    - ↑ Production of antibodies
      - ? Auto-antibodies

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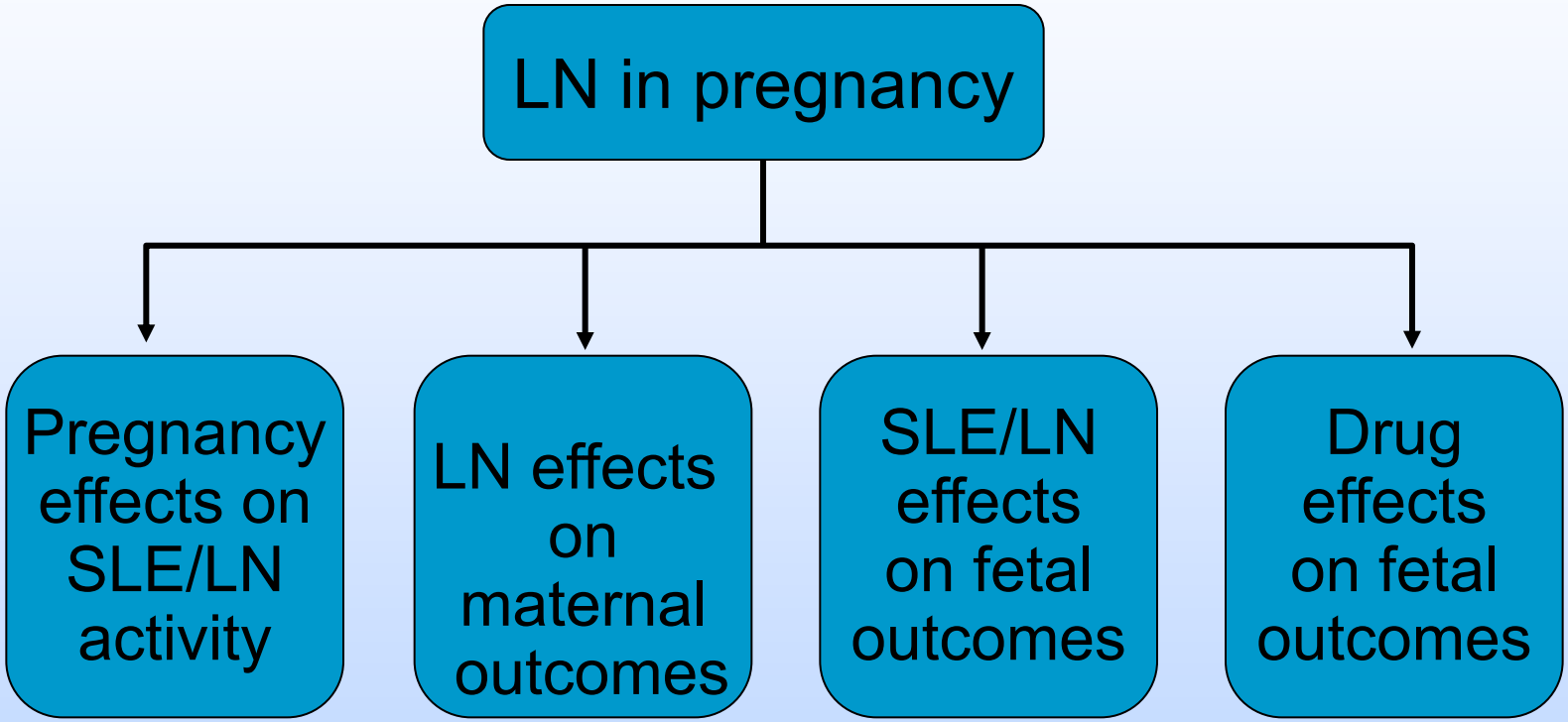
SLE/LN in Pregnancy
The Roadmap



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Pregnancy Effects on Preexisting Renal Disease

- Most important determinant of progression of renal insufficiency is renal function at the time of conception
- Possible contributing factors
  - Hypertension
  - ↑ Proteinuria during pregnancy
  - Urinary tract infections

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Pregnancy Effects on Preexisting Renal Disease

Progression of Renal Insufficiency

- No adverse effect with Cr<1.4 mg/dL (124 µmol/L) and normal BP
- ↑progression if Cr ≥1.4 mg/dL (124 µmol/L)
- Cr ≥3.0 mg/dL (265 µmol/L); pregnancy losses and maternal morbidity
- Role of underlying disease
  - SLE/LN
    - In remission for 6 months

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Pregnancy and Lupus Nephritis

- 31 year old with SLE for 10 years, 6 weeks pregnant
- History of 2 miscarriages, DVT x 2, stroke
- APS diagnosis
- Prior to pregnancy, maintained on Prednisone, Plaquenil, Coumadin

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Pregnancy and Lupus Nephritis

- d/c Coumadin, Plaquenil
- Start
  - Dalteparin 13,000 IU
  - Aspirin 81 mg QD
- Continue Labetalol for HTN
- 12 weeks of gestation: SOB, CP
- CT chest: old thrombus

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Pregnancy and Lupus Nephritis

- Negative Doppler US LE's
- Worsening proteinuria, HTN, Cr 1.6 from 1.0 mg/dL
- Nephrotic syndrome
- Kidney BX: membranous GN
- Prednisone to 60 mg, Plaquenil restarted 200 mg BID

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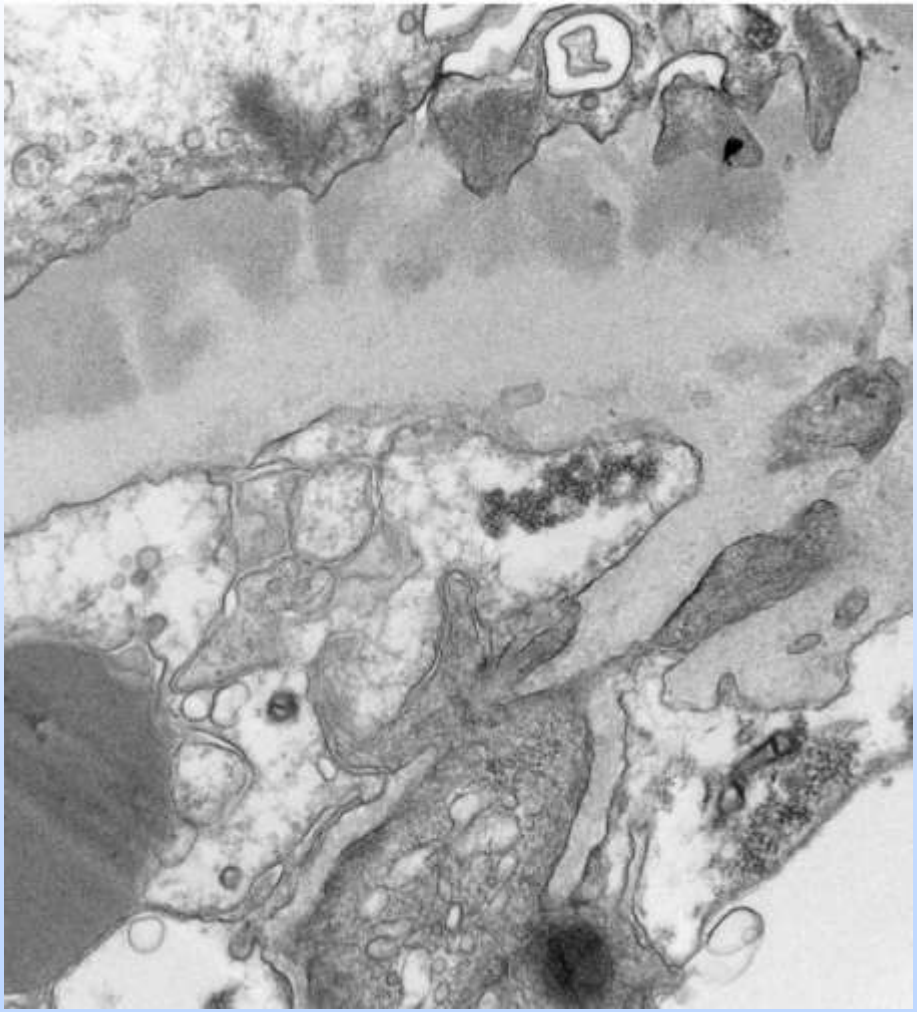
EM: SLE Membranous Nephropathy



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Pregnancy and Lupus Nephritis

- 3 weeks later: local ER evaluation for SOB
- Cardiorespiratory arrest, resuscitated, transferred to Mayo
- Intubated, sedated, oliguria develops – unresponsive to diuretics, volume overload
- Renal replacement required

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Pregnancy and Lupus Nephritis

- CRRT was initiated, pressors required, pulse steroids
- Fetal demise documented
- Apnea test positive, support withdrawn
- 2 major concerns
  - Risk for renal flare
  - Maternal mortality risk

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Pregnancy and Lupus Flare

- Case control studies
  - No difference between pregnant versus non pregnant matched women with SLE: 40% had increased activity; 20% deterioration in renal function

Tandon et al: Arthritis Rheum, 2004

- Prospective study
  - Controls: patients as their own controls and non-pregnant patients; increase in disease activity during pregnancy

Petri et al. Arthritis Rheum. 2004

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Pregnancy and SLE-Approach

Timing	Suggested Laboratory Investigations
Preconception Counseling and/or First Prenatal Visit	Urinalysis Determination of proteinuria (optimally 24 hour urine, or protein/creatinine ratio Complete blood count Serum creatinine Anti-phospholipid antibodies Anti-SSA/Ro and Anti-SSB (La) antibodies If positive, weekly fetal heart rate evaluation from weeks 16-24, and every other week from weeks 24-32 Anti-double stranded DNA antibodies Complement studies Liver function tests
Every month	Urinalysis & Measurement of Proteinuria Serum creatinine If any tests are abnormal, obtain lupus serologies, complement studies and consider renal biopsy before 32 weeks
Every trimester*	Complete blood count Anti-double stranded DNA antibody Complement studies Liver function tests (for patients on azathioprine)

Stanhope et al. cJASN, 2012

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Differential Diagnosis

SLE/LN flare vs. Preeclampsia/HELLP

Clinical features

	Preeclampsia	HELLP	Flare
Complement	Absent	Absent	Present
Thrombocytopenia	Absent	Present	Present
Neutropenia	Absent	Absent	Present
Active sediment (RBC casts)	Absent	Absent	Present
Other organ involvement	Absent	Absent	Present
Positive SLE serologies	Absent	Absent	Present
HTN>140/90 mm Hg	Present	Absent 10-15%	Variable
Cr>1.2 mg/dL	Absent	Up to 10%	Present
Abnormal LFT's	Absent	Present	Absent

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Differential Diagnosis
SLE/LN flare vs. Preeclampsia/HELLP
Rena biopsy

- If laboratory evaluation non-diagnostic
- Safe in patients with adequate BP control and normal coagulation
- Similar complication rates to those of non-pregnant patients

Day et al. NDT, 2007

- Not advisable >32 weeks of gestation
- Differentiation between PE/HELLP (treated with delivery) versus GN (immunosuppression)

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LN and Maternal Death

- Literature search from 1962 to 2009
- Maternal deaths in the 6 week postpartum period in patients with SLE and LN
- 17 deaths in 13 studies
  - Infection in 41.2%, n=7
  - Disease activity in 29.4%, n=5
  - Pulmonary embolus in 11.8%, n=2
  - Pregnancy associated cardiomyopathy, adrenal failure due to abrupt steroid withdrawal, and undefined, n=1 for each (5.9%)

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LN and Maternal Death

- All maternal deaths in patients with SLE and lupus nephritis occurred in those with active disease
- Disease activity/complications and opportunistic infections, such as CMV and Cryptococcus, being the two major causes
- Presented evidence further supports timing of pregnancy relative to SLE activity, and the judicious use of immunosuppressive agents in pregnant patients

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LN and Maternal Death

- Supports current recommendations that the disease should be quiescent for ≥6 months prior to conception
- This may decrease rates of complications, including maternal death, due to disease activity
- May lessen the use of aggressive immunosuppressive therapy, thus lowering rates of opportunistic infections and related deaths

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Pregnancy in Patients with Preexisting SLE/LN

- Pregnancy contraindicated for patients with secondary anti-phospholipid antibody syndrome with history of strokes
  - Surrogate mother?
- Relatively contraindicated for active LN
  - Remission for at least 6 months; >12 months
- Judicious use of immunosuppression

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SLE/Lupus Nephritis Effects on Maternal Outcomes

- 58 patients with SLE and 90 pregnancies
- No renal involvement (n=47)
- Quiescent LN (n=20)
  - Proteinuria <0.5 g/24 hr and inactive sediment
- Active LN (n=23)
  - Proteinuria >0.5 g/24 hr and/or active sediment
- LN biopsy confirmed in 19/26 patients
  - 1 Type II mesangial
  - 8 Type III focal segmental proliferative
  - 7 Type IV diffuse proliferative
  - 3 Type V membranous

Wagner et al: Lupus, 2009

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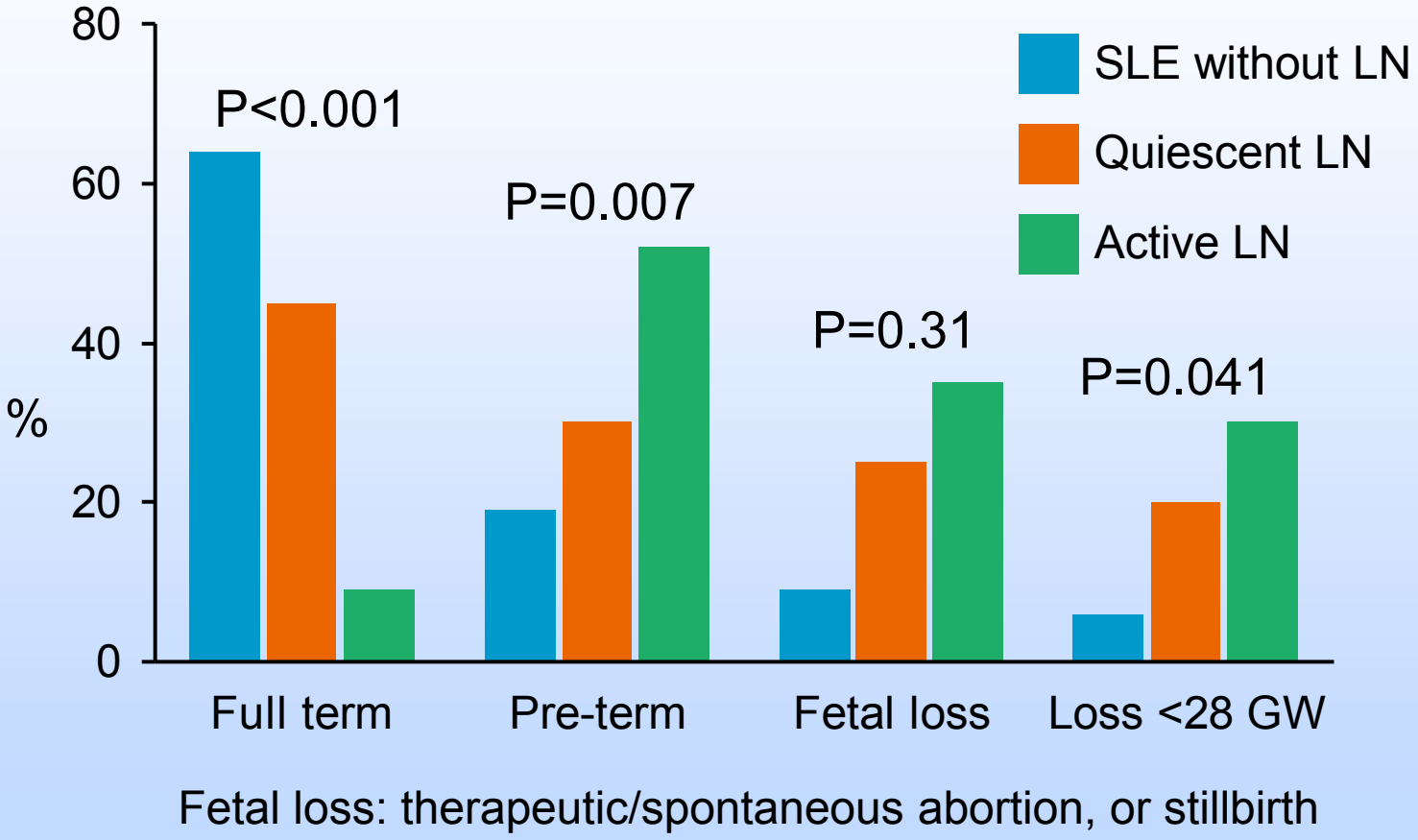
SLE/Lupus Nephritis Effects on Fetal Outcomes



Fetal loss: therapeutic/spontaneous abortion, or stillbirth

Wagner et al: Lupus, 2009

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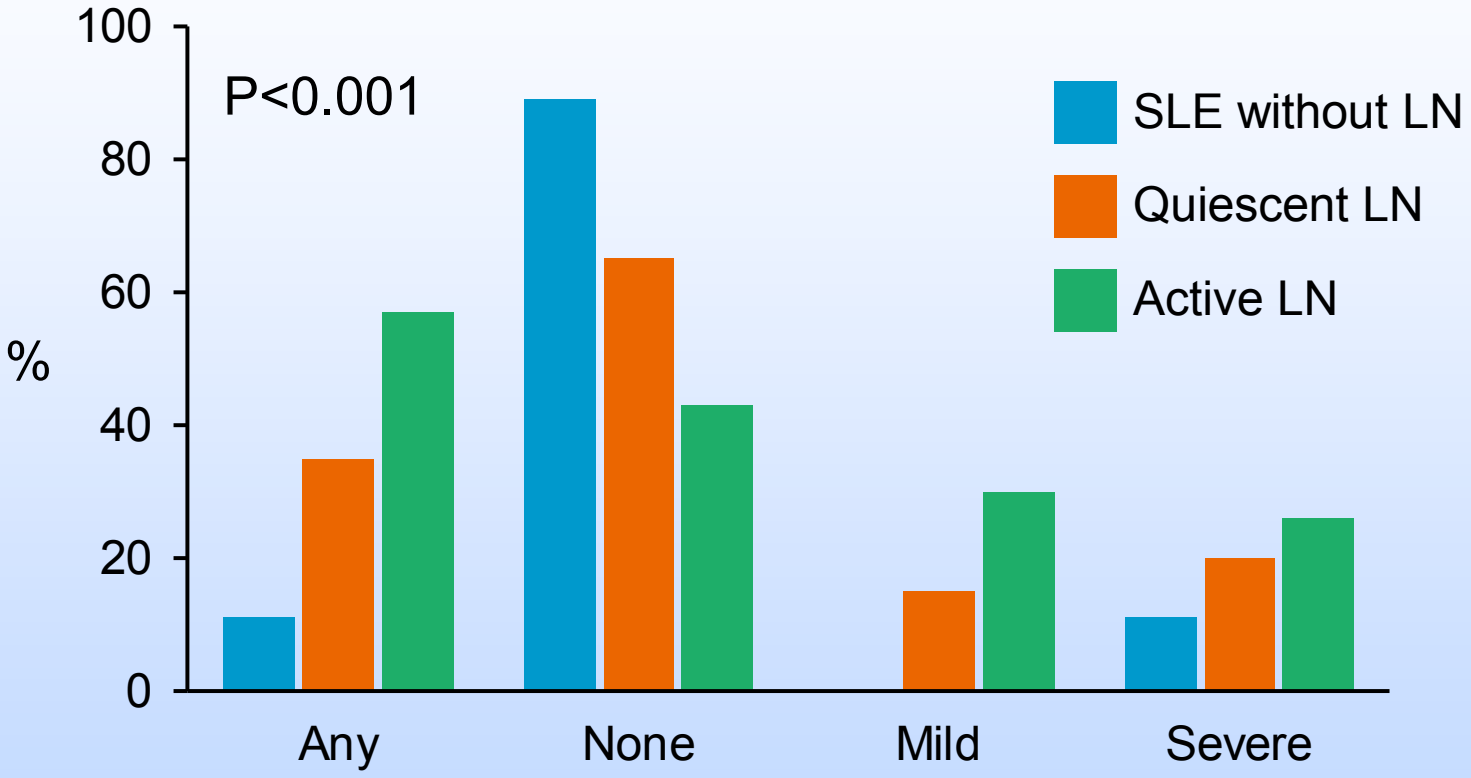
SLE/Lupus Nephritis Effects on Maternal Outcomes



Mild: HTN in pregnancy

Severe: preeclampsia, eclampsia, stroke, HELLP, and death

Wagner et al: Lupus, 2009

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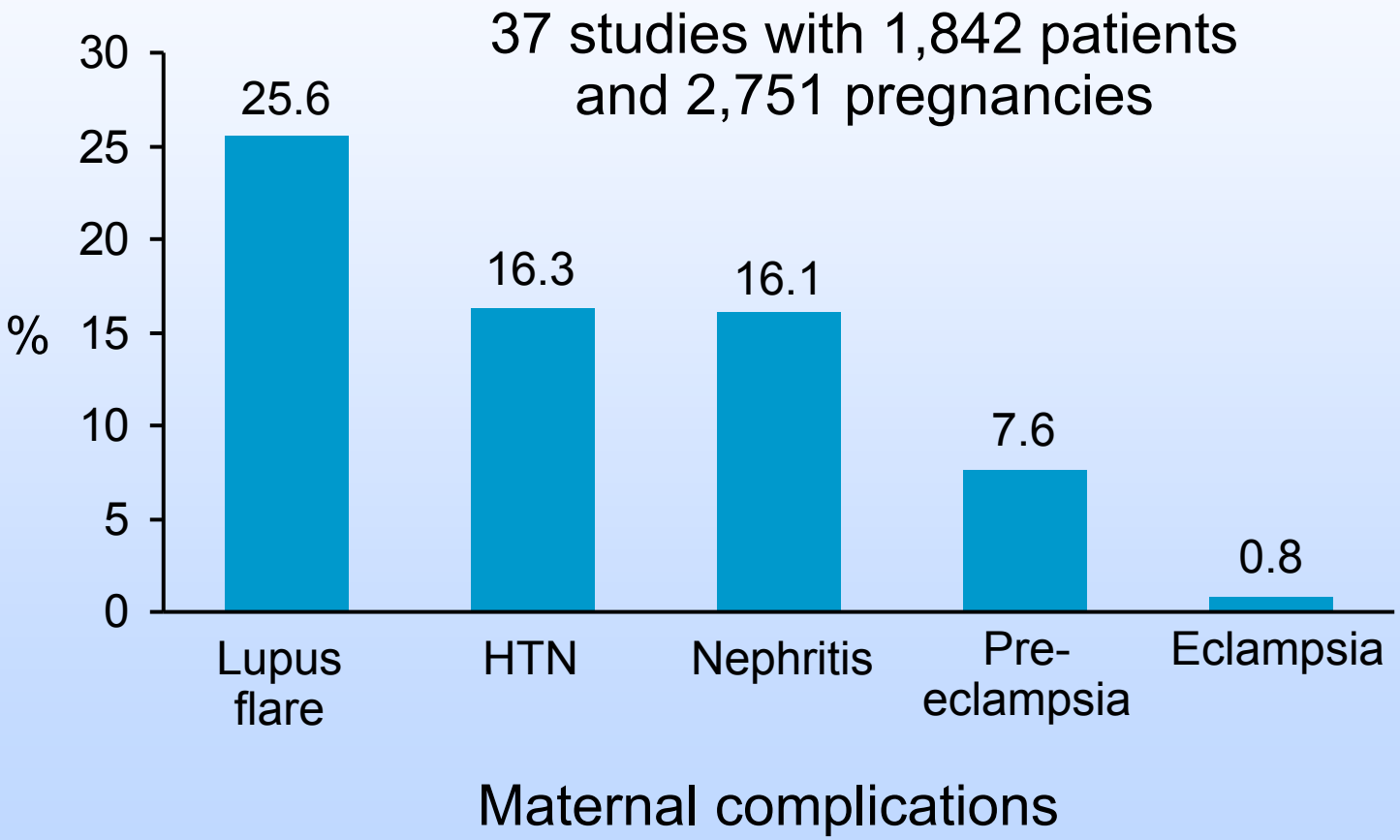
Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with SLE and LN



Smyth et al: cJASN, 2010

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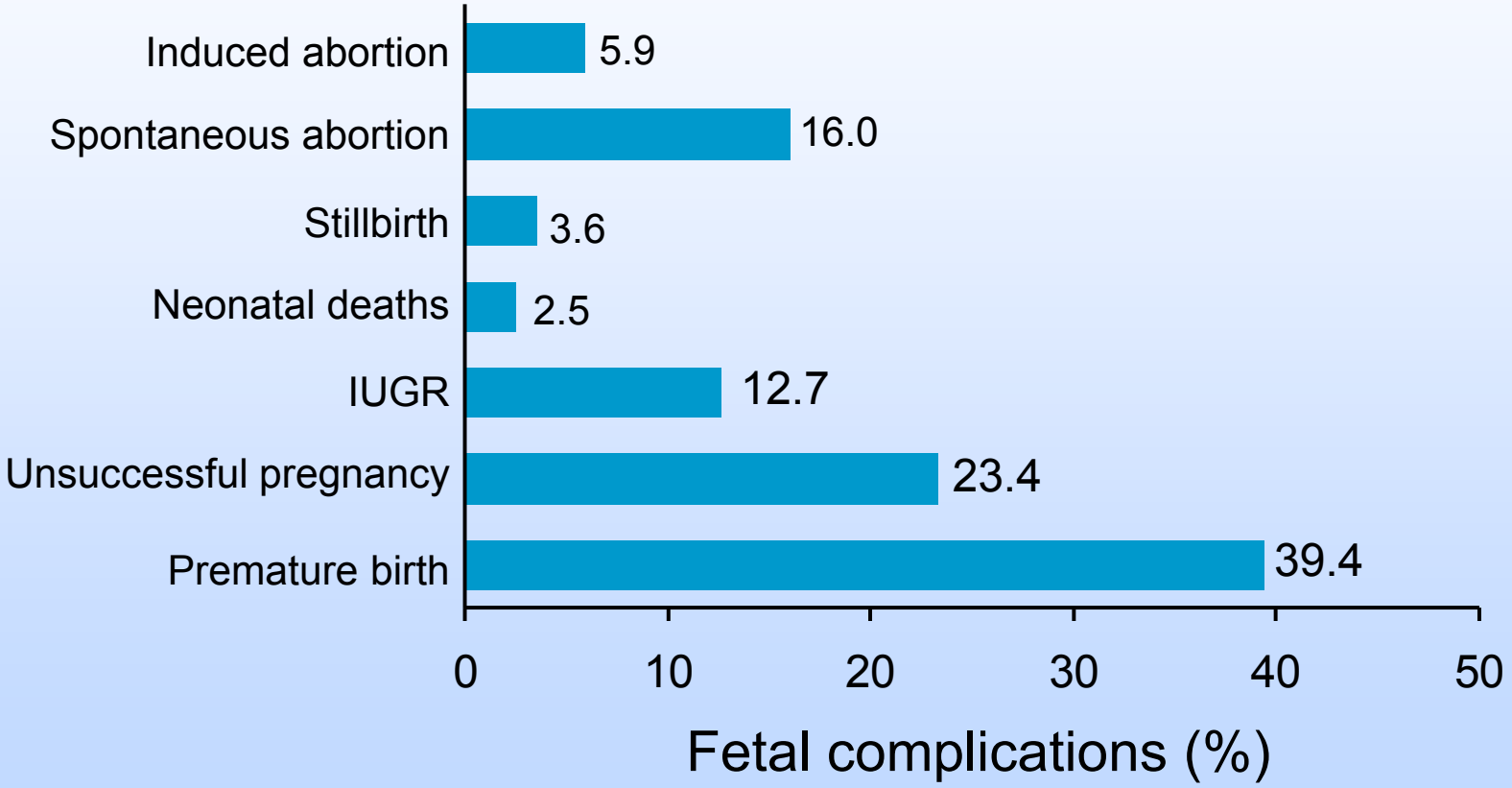
Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with SLE and LN



Smyth et al: cJASN, 2010

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Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with SLE and LN

Meta-Regression Analyses

- Positive associations between premature birth rate and active nephritis
- Increased hypertension rates in subjects with active nephritis or a history of nephritis
- History of nephritis was associated with pre-eclampsia
- Anti-phospholipid antibodies were associated with hypertension, premature birth, and an increased rate of induced abortion

Smyth et al: cJASN, 2010

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Treatment of Lupus Nephritis in Pregnancy

- Steroids
- Azathioprine, hydroxychloroquine
- Cytoxan, mycophenolate contraindicated
- Blood pressure control
  - ACE, ARB contraindicated, renal and skeletal abnormalities
  - Atenolol, IUGR

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Mycophenolate (Cellcept) in Pregnancy

Le Ray et al. Obstet Gynecol, 2004

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Pregnancy in Patients with SLE/LN
Summary

- Good prognosis: remission, no proteinuria or HTN (or controlled on meds)
- Risk factors for complications of pregnancy
  - ↓ GFR
  - Hypertension
  - Nephrotic range proteinuria
  - Active SLE/LN
  - Anti-phospholipid syndrome

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Pregnancy in Patients with SLE/LN
Summary

- Pregnancy contraindicated for patients with secondary anti-phospholipid antibody syndrome with history of strokes
  - Surrogate mother?
- Relatively contraindicated for active LN
  - Remission for at least 6 months; >12 months
- Judicious use of immunosuppression

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Case

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Thrombotic Microangiopathy and Pregnancy Case 1

- 43-year old, first, twin pregnancy (IVF) admitted at 33 weeks gestation for increasing edema and decreased urinary output
- Lab results: AST 636 u/l, ALT 398 u/l, LDH 1288 u/l, Cr 2.7 mg/dL, thrombocytopenia, low C3
- DX: HELLP syndrome Urgent C-section
  - Hemorrhagic shock, multiple transfusions, platelets, FFP, plasmapheresis
- Renal biopsy: TMA

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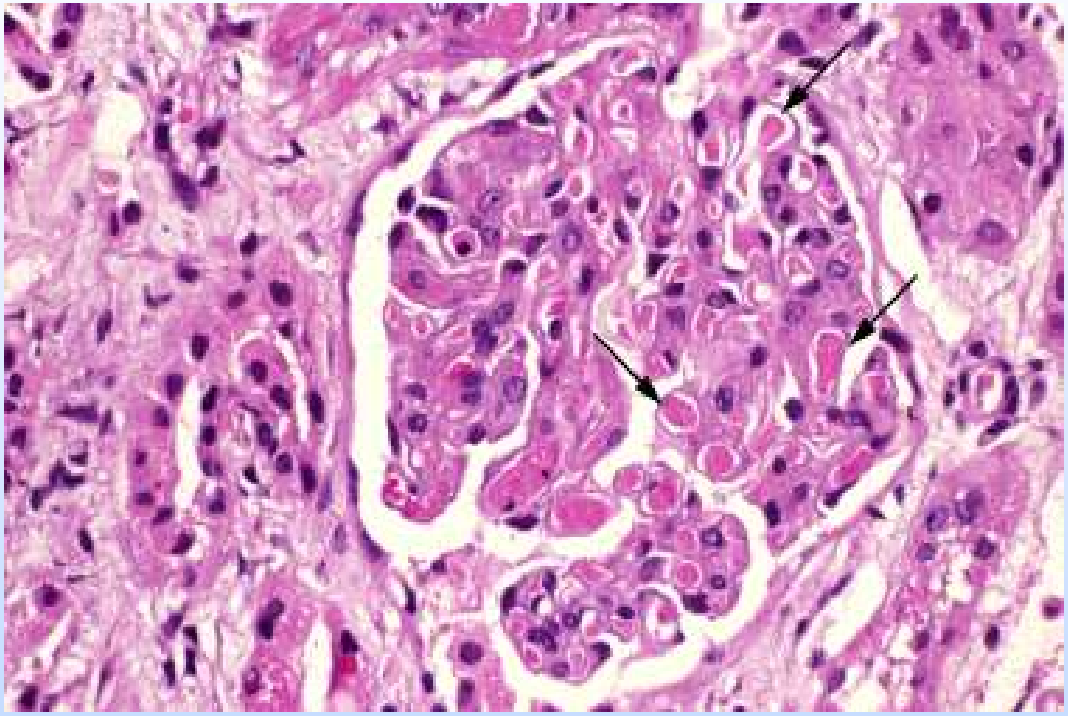
Thrombotic Microangiopathy and Pregnancy: Light Microscopy



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Thrombotic Microangiopathy and Pregnancy

- ADAMTS13 levels 45-68%, normal C3, C4, CH50, factors H and I, absent factor H antibody
- Negative mutation analyses
- Positive Lupus anticoagulant
- On chronic HD; evaluated for a RT

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Thrombotic Microangiopathy and Pregnancy

- She meets the diagnostic criteria of APS based on positive lupus anticoagulant and small vessel thrombosis
  - lupus anticoagulant can be seen in healthy individuals and could be a red herring
- Differentiation between APS and a HUS not feasible based on renal biopsy
- APS: a complement activating condition
- For complement activating conditions, primary treatment should focus on conditions per se
- ? Both APS **and** a HUS

Lupus Nephritis and Preeclampsia

- PROMISSE Study- Predictors of pRegnancy Outcome: bioMarkers In APLA Syndrome and Systemic lupus Erythematosus
- 250 pregnant patients with SLE and/or APL Ab
- 3 complement regulatory proteins – MCP, CFI, and CFH – in 40 preeclamptic patients
- Heterozygous mutations in seven (18%)
- Pregnancy promotes TMA in women at risk due to abnormalities of the complement system

Salmon et al: PLos Med, 2011

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Thrombotic Microangiopathy and Pregnancy

- One possible way to differentiate: complement studies
  - Atypical HUS ↓ C3, normal C4 (alternative)
  - APS: ↓C3, ↓ C4 (classical)
- APS: treat with anticoagulation +/- steroids or sometimes rituximab if a catastrophic event
- a HUS: PLEX and Eculizumab
- Future studies: define trajectory of CAP in APS and TMA
- a HUS should be used only in the context of AP complement abnormalities