Glomerular diseases in pregnancy

pragmatic recommendations for clinical management

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Glomerular diseases in pregnancy: pragmatic recommendations for clinical management

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Outline

- Epidemiology
- Tools for the diagnosis and monitoring
- Risk evaluation
- Diagnostic issues in de novo GD: kidney biopsy
- Management
- Conclusions

Epidemiology

- General population data of **CKD**
  - **3% to 6% of women of child-bearing age**
  - 3.3% of pregnant women have laboratory evidence of CKD.

- Australian study
  - 0.3% of pregnant women with CKD code
  - only 0.01% had an identified immunologic disease or GD

Epidemiology

- The most common GDs: **FSGS, IgA nephropathy** (IgAN), and **lupus nephritis** (LN)

- With history of **preterm birth or preeclampsia** had **higher rates** of FSGS, crescentic GN, or ANCA vasculitis.

Epidemiology

- **Preeclampsia** may be **the first sign of a GD,** usually diagnosed in the first few years postpartum, or it may represent one hit in a multiple-hit pathogenesis of a GD diagnosed later in life.

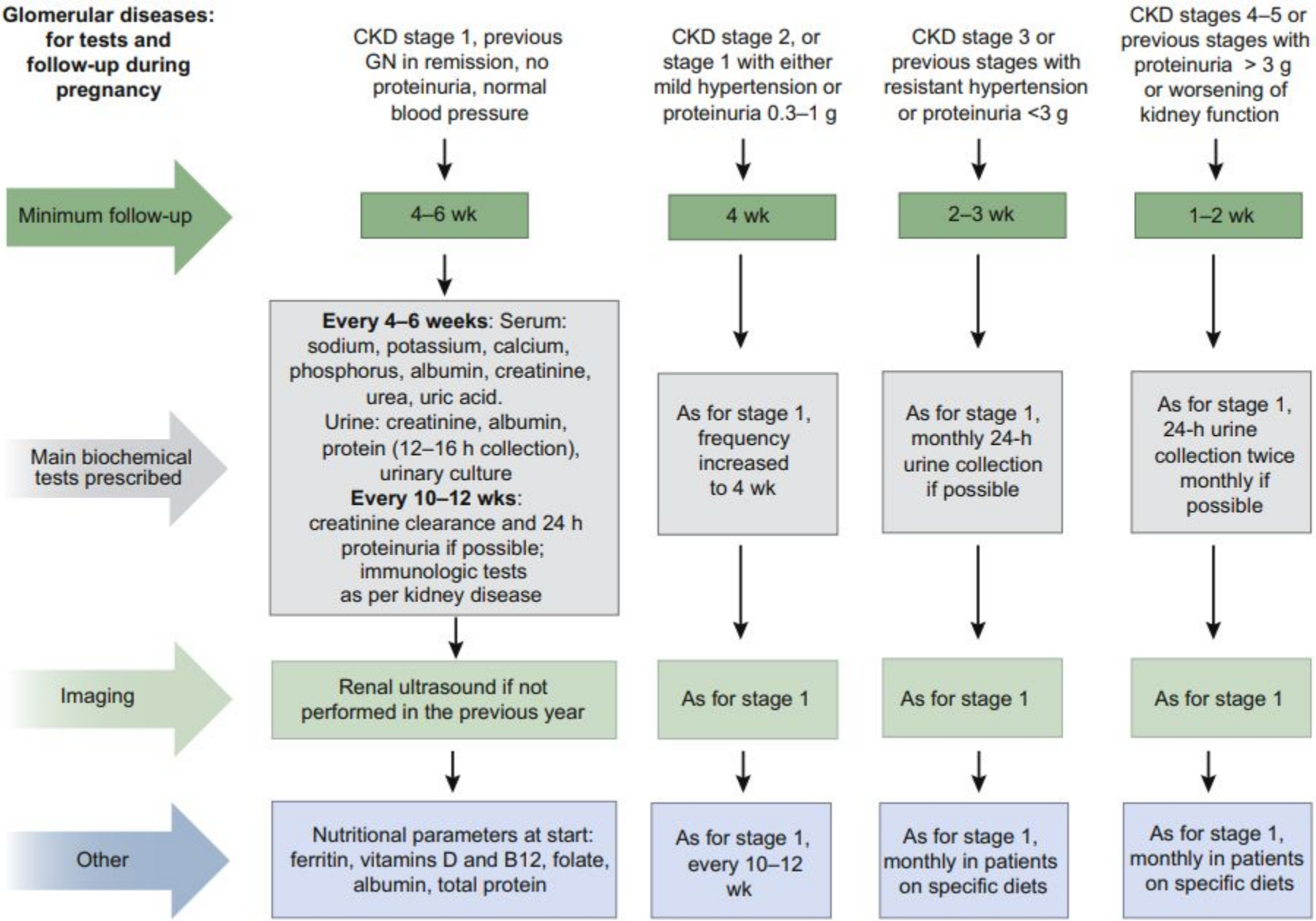
- **35% to 56%** of women on chronic dialysis or those having received a kidney transplant have a **GD as their primary renal disease**.

Tools for diagnosis and monitoring

- 38%–56% increase in CCr in first trimester
- Gold standard: **24 hrs-CCr + total protein**
- Serum Cre concentration: upper limit
  - first trimester: > 85% (76 μmol/L)
  - second trimester: > 80% (72 μmol/L)
  - third trimester: > 86% (77 μmol/L)

Tools for diagnosis and monitoring

- Staging of CKD in pregnant patients with a GD should be based on prepregnancy values.
-
- **UPCR**, for which new onset of proteinuria (UPCR >30 mg/mmol)


Glomerular diseases: for tests and follow-up during pregnancy
CKD stage 1, previous GN in remission, no proteinuria, normal blood pressure
CKD stage 2, or stage 1 with either mild hypertension or proteinuria 0.3–1 g
CKD stage 3 or previous stages with resistant hypertension or proteinuria <3 g
CKD stages 4–5 or previous stages with proteinuria > 3 g or worsening of kidney function
Minimum follow-up
4–6 wk
4 wk
2–3 wk
1–2 wk
Main biochemical tests prescribed
Every 4–6 weeks: Serum: sodium, potassium, calcium, phosphorus, albumin, creatinine, urea, uric acid.
Urine: creatinine, albumin, protein (12–16 h collection), urinary culture
Every 10–12 wks: creatinine clearance and 24 h proteinuria if possible; immunologic tests as per kidney disease
As for stage 1, frequency increased to 4 wk
As for stage 1, monthly 24-h urine collection if possible
As for stage 1, 24-h urine collection twice monthly if possible
Imaging
Renal ultrasound if not performed in the previous year
As for stage 1
As for stage 1
As for stage 1
Other
Nutritional parameters at start: ferritin, vitamins D and B12, folate, albumin, total protein
As for stage 1, every 10–12 wk
As for stage 1, monthly in patients on specific diets
As for stage 1, monthly in patients on specific diets

Risk evaluation

- Three major determinants of outcomes: **kidney function impairment**, proteinuria, and hypertension.
- GDs generally seem to be associated with a higher risk of adverse pregnancy events compared with patients with other types of kidney diseases.
- Women with a GD and normal kidney function before pregnancy do not have a clearly increased risk of kidney function impairment during or after pregnancy, even in the long-term, compared with nonpregnant women with a GD. --> **IgAN and LN**.

GD worsening VS preeclampsia

- Preeclampsia markers
  - **Soluble fms-like tyrosine kinase 1/placental growth factor ratio** → normal level in CKD even worsening
  - **Low placental growth factor** → higher threshold in women with CKD
  - Impaired **uteroplacental Doppler flows** and IUGR -> no IUGR in worsened GD/renal function
- If the persistence of proteinuria and hypertension **beyond 3 months postpartum** –> GD likely

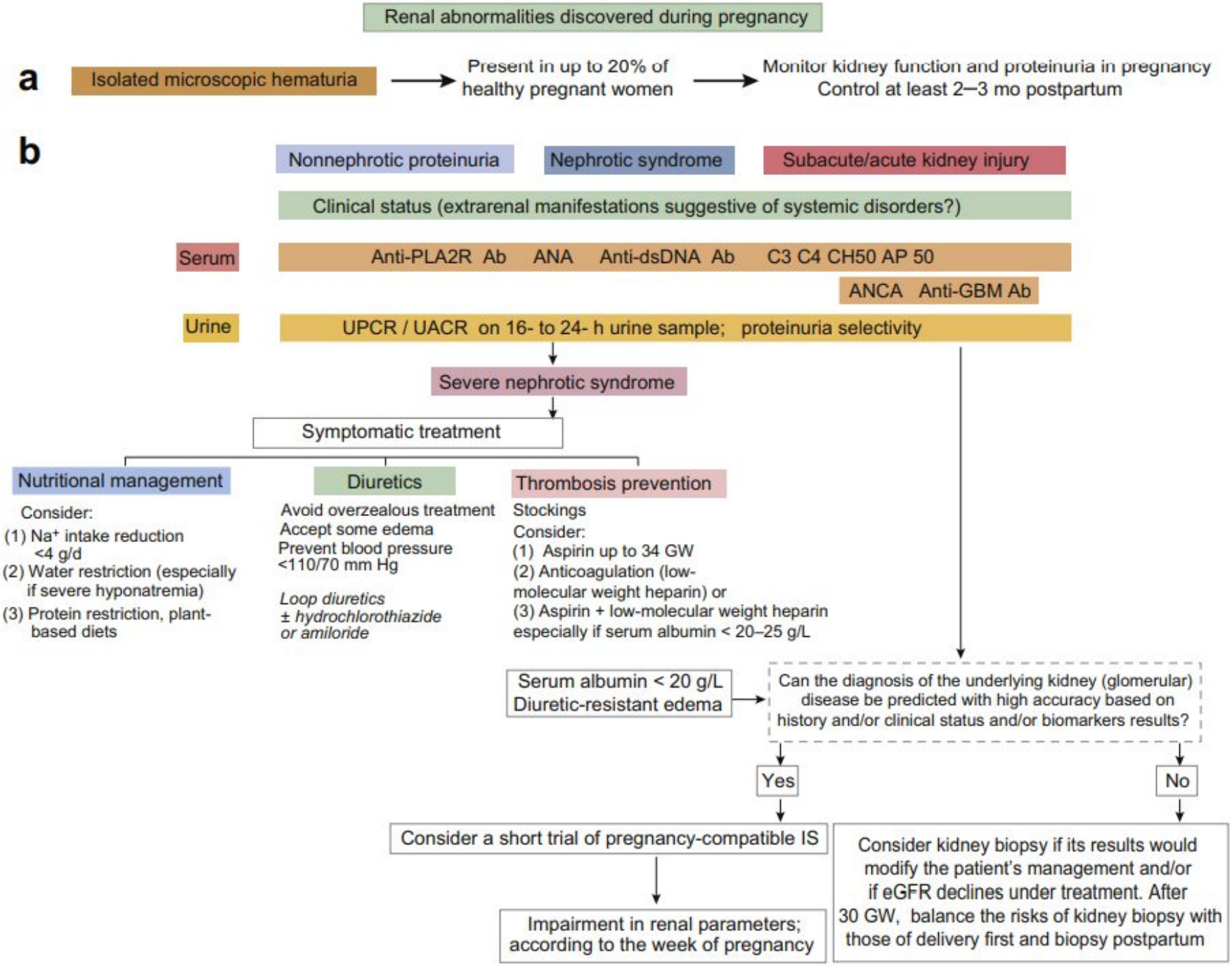
Diagnostic issues in de novo GD

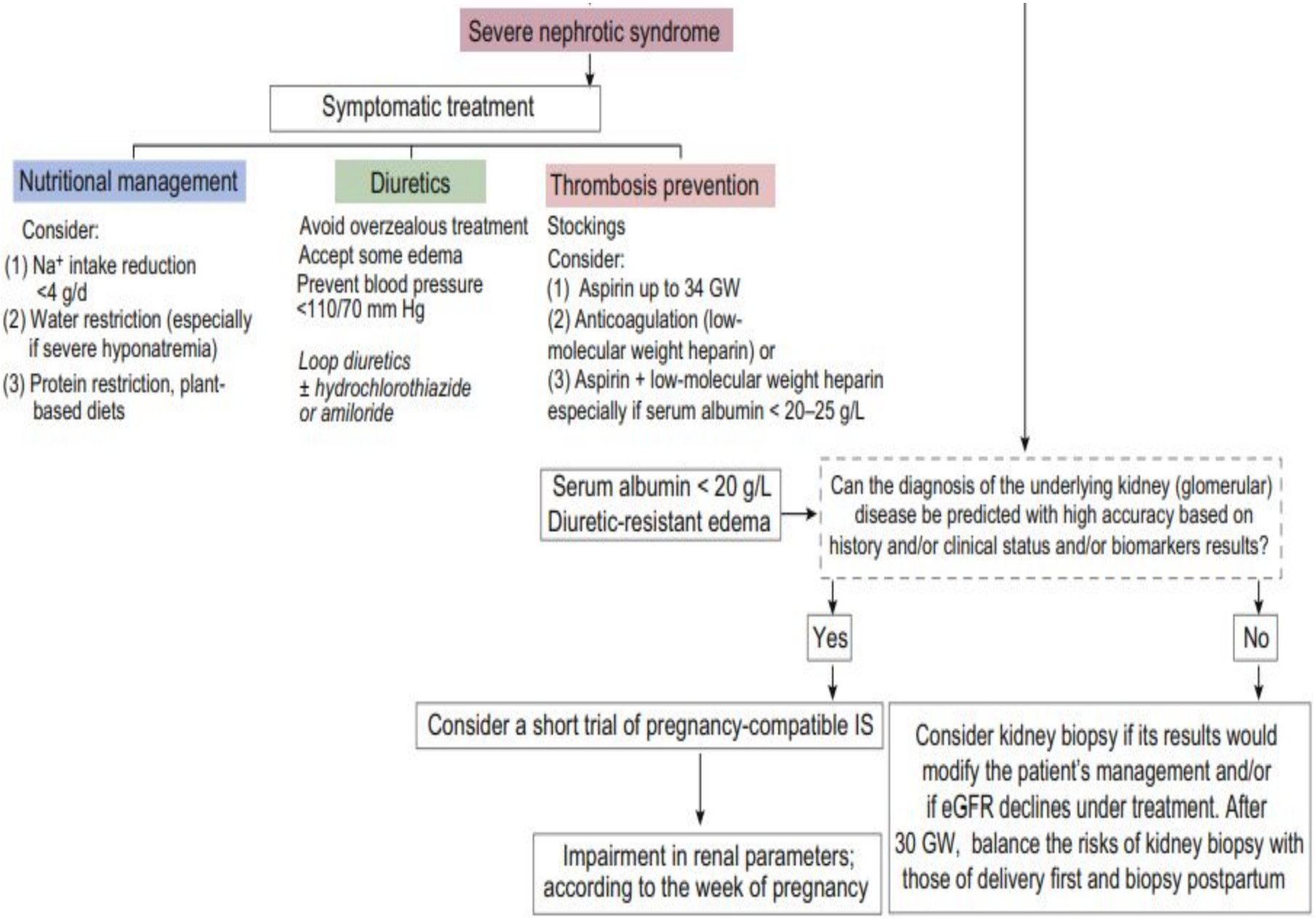
- Three distinct situations
  - proteinuria and/or hematuria with preserved kidney function
  - nephrotic syndrome
  - subacute or AKI with proteinuria or nephrotic syndrome.
- Definition of nephrotic syndrome in pregnant

  $\longrightarrow$ serum albumin < lower limit of normal for GA and proteinuria >3 g/d

Albumin (g/L)	Lower limit of normal
Week 7–17	32.2 (30.9–33.5)
Week 17–24	27.9 (27.4–28.4)
Week 24–28	27.0 (26.5–27.4)
Week 28–31	25.1 (24.3–25.9)
Week 31–34	24.4 (23.5–25.3)
Week 34–38	23.1 (21.9–24.4)
Predelivery	24.0 (23.0–24.9)
Post-partum	37.0 (36.4–37.6)

Serum creatinine (mmol/L)	Upper limit of normal
Week 7–17	62 (61–63)
Week 17–24	58 (57–59)
Week 24–28	62 (60–63)
Week 28–31	56 (55–58)
Week 31–34	58 (57–60)
Week 34–38	60 (56–64)
Predelivery	72 (67–78)
Postpartum	86 (79–93)


Renal abnormalities discovered during pregnancy
a
Isolated microscopic hematuria
Present in up to 20% of healthy pregnant women
Monitor kidney function and proteinuria in pregnancy
Control at least 2–3 mo postpartum
b
Nonnephrotic proteinuria
Nephrotic syndrome
Subacute/acute kidney injury
Clinical status (extrarenal manifestations suggestive of systemic disorders?)
Serum
Anti-PLA2R Ab ANA Anti-dsDNA Ab C3 C4 CH50 AP 50
ANCA Anti-GBM Ab
Urine
UPCR / UACR on 16- to 24- h urine sample; proteinuria selectivity
Severe nephrotic syndrome
Symptomatic treatment
Nutritional management
Consider:
(1) Na+ intake reduction <4 g/d
(2) Water restriction (especially if severe hyponatremia)
(3) Protein restriction, plant-based diets
Diuretics
Avoid overzealous treatment
Accept some edema
Prevent blood pressure <110/70 mm Hg
Loop diuretics ± hydrochlorothiazide or amiloride
Thrombosis prevention
Stockings
Consider:
(1) Aspirin up to 34 GW
(2) Anticoagulation (low-molecular weight heparin) or
(3) Aspirin + low-molecular weight heparin especially if serum albumin < 20–25 g/L
Serum albumin < 20 g/L
Diuretic-resistant edema
Can the diagnosis of the underlying kidney (glomerular) disease be predicted with high accuracy based on history and/or clinical status and/or biomarkers results?
Yes
No
Consider a short trial of pregnancy-compatible IS
Impairment in renal parameters; according to the week of pregnancy
Consider kidney biopsy if its results would modify the patient's management and/or if eGFR declines under treatment. After 30 GW, balance the risks of kidney biopsy with those of delivery first and biopsy postpartum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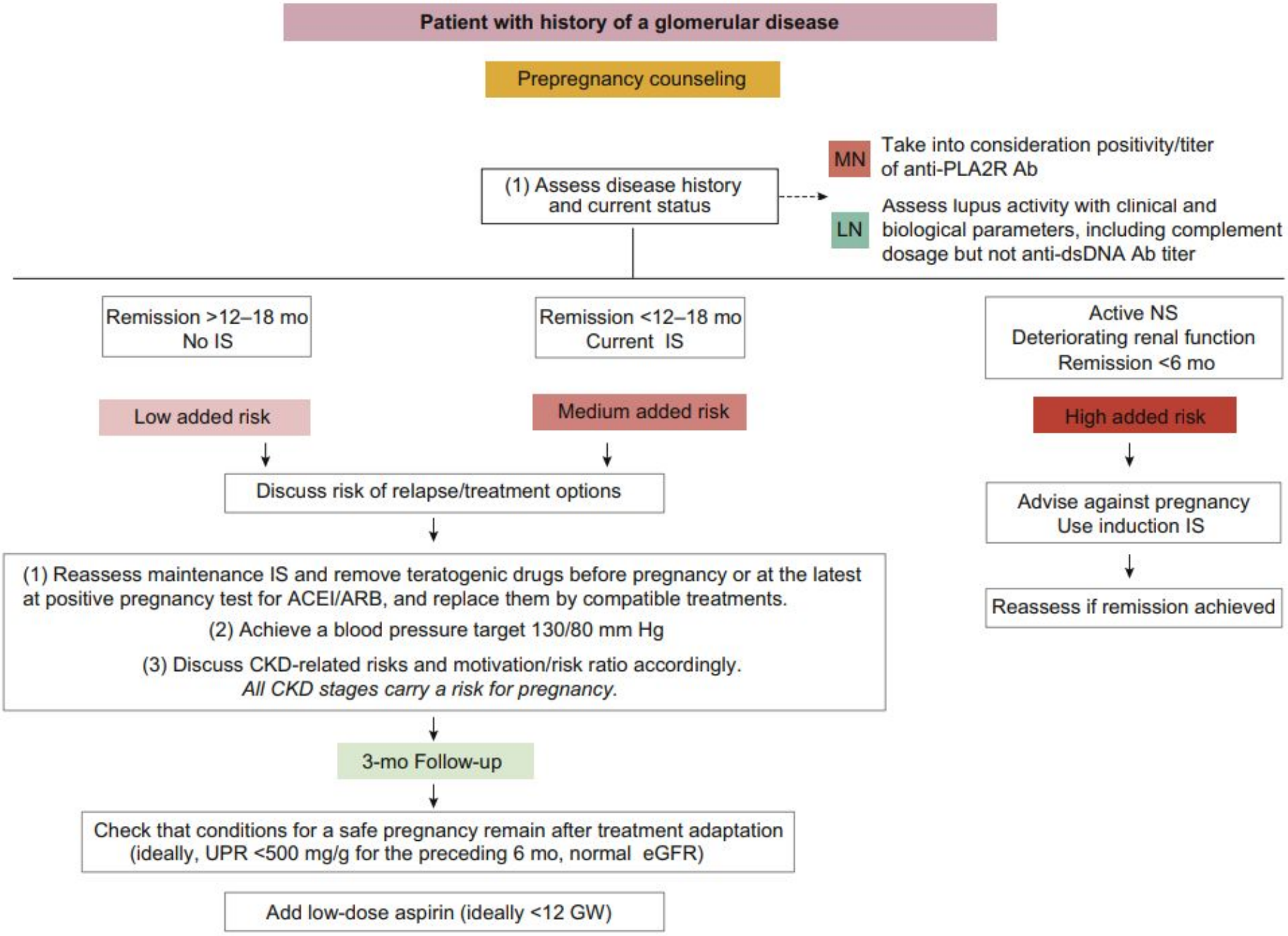
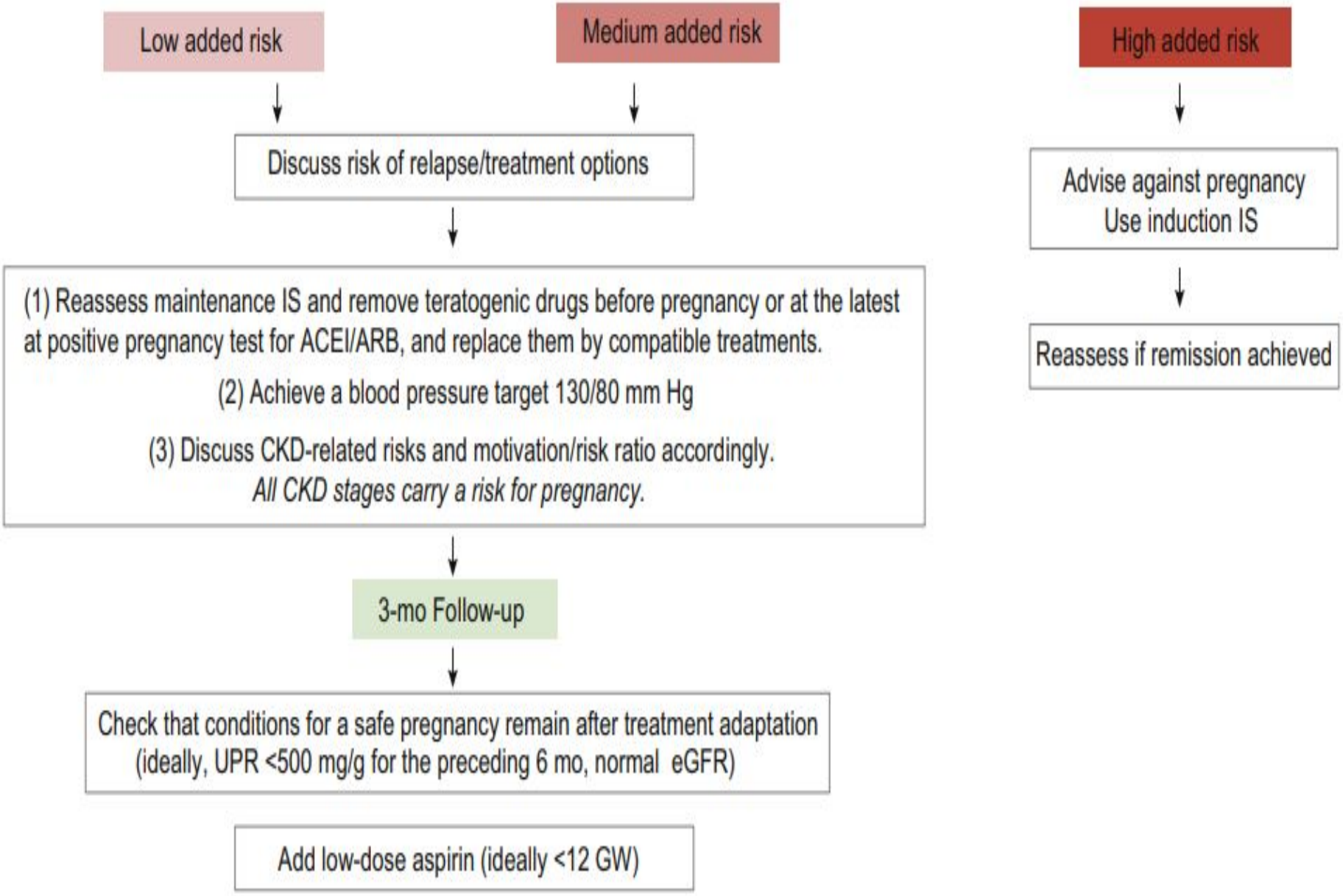
Kidney biopsy in pregnant women

- Complications rates: 7%, compared with 1% after delivery (**2% risk of major bleeding** in the late second trimester)
- Check laboratory tests, including the characterization of proteinuria, antibody workup for LN, ANCA, and anti-PLA2R Abs
- A normal ratio of soluble fms-like tyrosine kinase 1/placental growth factor
- Timing: **early pregnancy (<12 weeks)**
- **Grafted kidney** first if presence


Patient with history of a glomerular disease
Prepregnancy counseling
(1) Assess disease history and current status
MN
Take into consideration positivity/titer of anti-PLA2R Ab
LN
Assess lupus activity with clinical and biological parameters, including complement dosage but not anti-dsDNA Ab titer
Remission >12–18 mo
No IS
Remission <12–18 mo
Current IS
Active NS
Deteriorating renal function
Remission <6 mo
Low added risk
Medium added risk
High added risk
Discuss risk of relapse/treatment options
Advise against pregnancy
Use induction IS
Reassess if remission achieved
(1) Reassess maintenance IS and remove teratogenic drugs before pregnancy or at the latest at positive pregnancy test for ACEI/ARB, and replace them by compatible treatments.
(2) Achieve a blood pressure target 130/80 mm Hg
(3) Discuss CKD-related risks and motivation/risk ratio accordingly.
All CKD stages carry a risk for pregnancy.
3-mo Follow-up
Check that conditions for a safe pregnancy remain after treatment adaptation (ideally, UPR <500 mg/g for the preceding 6 mo, normal eGFR)
Add low-dose aspirin (ideally <12 GW)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Obstetric perspective of GD in pregnancy

- Preeclampsia superimposed on GD typically occurs late in pregnancy and is associated with relatively well-preserved fetal growth.
- **Low-dose aspirin prophylaxis** is a standard of care in all pregnancies at risk of preeclampsia, including those with GD. **Early start (<12 gestational weeks)** until GA 34-36 weeks, or in the risk conditions for imminent delivery.
- **Vitamin D deficiency** should be corrected.

Recommendations for plan a pregnancy

- Take into account the **woman's wish**
- Integrate **psychological** aspects
- Individualize the assessment of pregnancy risks
- Objective assessment of the risk of adverse pregnancy outcomes and progression of CKD

Recommendations for plan a pregnancy

- If **eGFR <30 ml/min at the start of pregnancy**, discuss the issue of potential **dialysis need**
- Explain the need to **adapt treatment** before/at the start of pregnancy and therapeutic options
- Discuss the **induced/premature delivery** and prematurity-related complications

BP monitoring and diagnosis of HTN

- **Goal: < 140/90 mm Hg**. (otherwise fetal survival is decreased)

- Standard: **Out-of-office BP** measurement

- Cutoffs for the diagnosis of hypertension in pregnancy: **office SBP > 140 or DBP > 90** mm Hg, on at least 2 occasions measured **4 hours apart**.

BP target

- No guidelines are specifically targeted at BP control in pregnant women with CKD or GD.

- Guidelines from the United Kingdom : target BP of ≤135/85 mm Hg during pregnancy.

- We **recommend a target BP of 130/80** mm Hg, unless systolic BP is consistently <110 mm Hg or diastolic BP is consistently <70 mm Hg, and/or symptomatic hypotension occurs.

ACEi/ARBs use or hold ?

- This question is still debated.
- No consensus.

Antihypertensive drugs choice

Setting	Drug	Route	Dose	Contraindications	Adverse effects
Emergency	Labetalol	I.v.	10–20 mg initially, then 20–80 mg every 10–30 min to a maximum cumulative dose of 300 mg; infusion: 1–2 mg/min	Second- or third-degree AVB Systolic heart failure Asthma bradycardia	Bronchoconstriction Fetal bradycardia
	Urapidil	I.v.	12.5–25 mg as bolus injection; 5–40 mg/h as continuous infusion		Hypotension Reflex tachycardia
	Hydralazine	I.v.	5 mg, then 5–10 mg every 20–40 min		Hypotension Reflex tachycardia Headaches
No emergency	Labetalol	Oral	100 mg bid to 800 mg tid	Second- or third-degree AVB Systolic heart failure Asthma Bradycardia	Bronchoconstriction Fetal bradycardia
	Nifedipine	Oral	20–30 mg bid		Reflex tachycardia Headaches
	α-Methyldopa	Oral	250 mg bid to 1000 mg tid; titrate every 48 h		Orthostatic hypotension Sedation

Avoidance of nutritional deficits

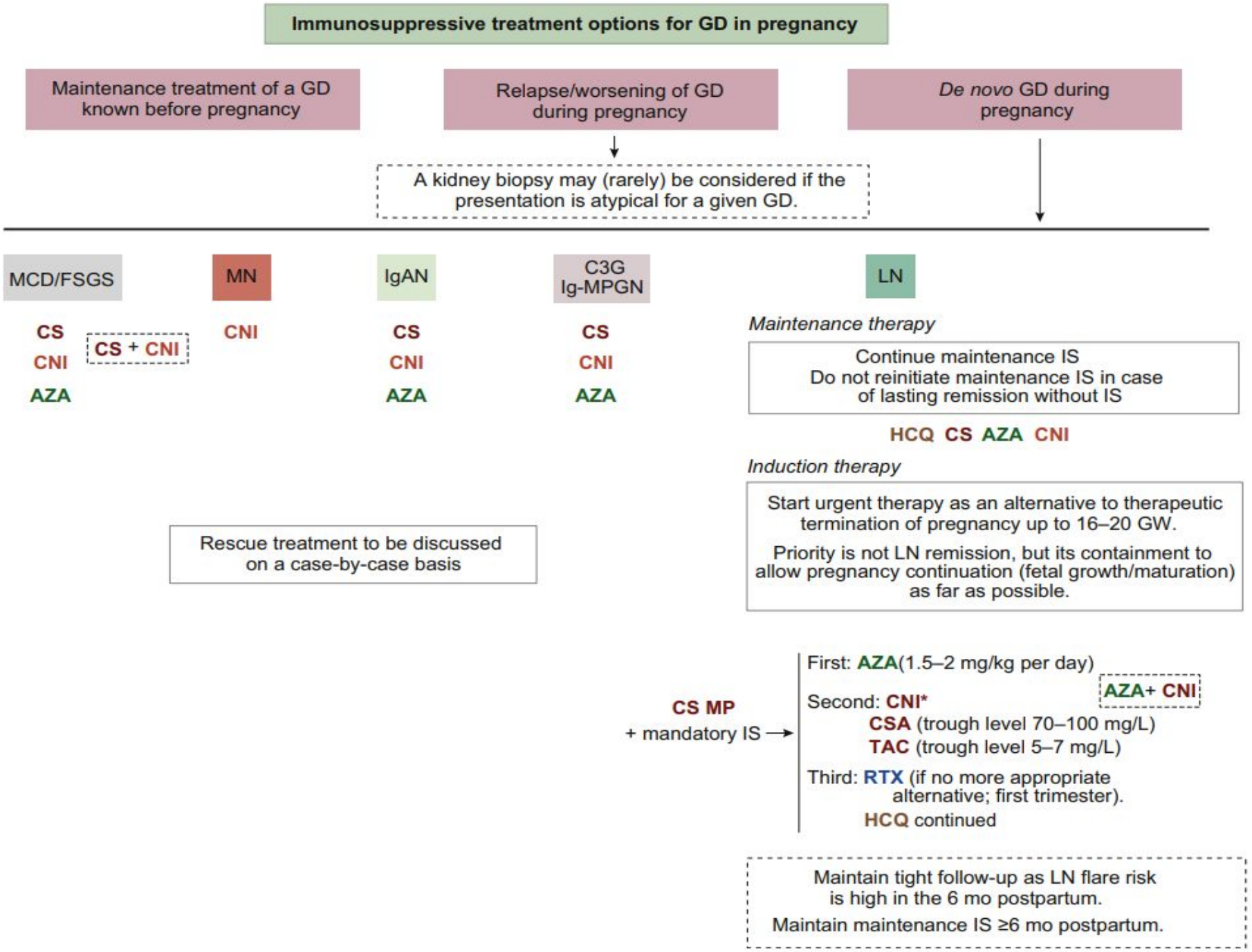
- **Folic acid**: water soluble, may be lost in the urine in nephrotic patients.
- **Vitamin D**: reduced in advanced CKD; low levels -> higher risk of preeclampsia.
- Vitamin B12: may be reduced in patients on plant-based and low-protein diets.
- **Iron**: may be reduced in patients on plant-based and low-protein diets or lost in nephrotic syndrome.

Dietary management in pregnancy

- Avoidance of excessive weight gain
  -> preeclampsia and hypertensive disorders
  >1 kg per month – prepregnancy BMI.

- Avoidance of high-protein diets
  → protein-restricted and plant-based diets

- Food quality
  → No additive and preservation products


Immunosuppressive treatment options for GD in pregnancy
Maintenance treatment of a GD known before pregnancy
Relapse/worsening of GD during pregnancy
De novo GD during pregnancy
A kidney biopsy may (rarely) be considered if the presentation is atypical for a given GD.
MCD/FSGS
MN
IgAN
C3G Ig-MPGN
LN
CS
CNI
AZA
CS + CNI
CNI
CS
CNI
AZA
CS
CNI
AZA
Maintenance therapy
Continue maintenance IS
Do not reinitiate maintenance IS in case of lasting remission without IS
HCQ CS AZA CNI
Induction therapy
Start urgent therapy as an alternative to therapeutic termination of pregnancy up to 16–20 GW.
Priority is not LN remission, but its containment to allow pregnancy continuation (fetal growth/maturation) as far as possible.
Rescue treatment to be discussed on a case-by-case basis
CS MP
+ mandatory IS
First: AZA(1.5–2 mg/kg per day)
AZA+ CNI
Second: CNI*
CSA (trough level 70–100 mg/L)
TAC (trough level 5–7 mg/L)
Third: RTX (if no more appropriate alternative; first trimester).
HCQ continued
Maintain tight follow-up as LN flare risk is high in the 6 mo postpartum.
Maintain maintenance IS ≥6 mo postpartum.

Maintenance therapy

Continue maintenance IS
Do not reinitiate maintenance IS in case of lasting remission without IS

HCQ CS AZA CNI

Induction therapy

Start urgent therapy as an alternative to therapeutic termination of pregnancy up to 16–20 GW.

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CS MP
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First: **AZA**(1.5–2 mg/kg per day)

Second: **CNI***
CSA (trough level 70–100 mg/L)
TAC (trough level 5–7 mg/L)

AZA+ CNI

Third: **RTX** (if no more appropriate alternative; first trimester).

HCQ continued

Maintain tight follow-up as LN flare risk is high in the 6 mo postpartum.

Maintain maintenance IS ≥6 mo postpartum.

Conclusions

- The **involvement of patients in shared choices** is the key to face, in the best possible way, the challenges of a high-risk pregnancy.

- Although preconception information and preparation is advisable, discovery of a kidney disease in pregnancy is not rare and may raise important **ethical and psychological issues**.

- Collaborative prospective studies are still needed.

Take home messages

- Preeclampsia and (further) GN
- Low-dose aspirin prophylaxis and BP target: 130/80
- Woman's wish, ethical and psychological issues

Thank you!