Glomerular diseases in pregnancy: pragmatic recommendations for clinical management

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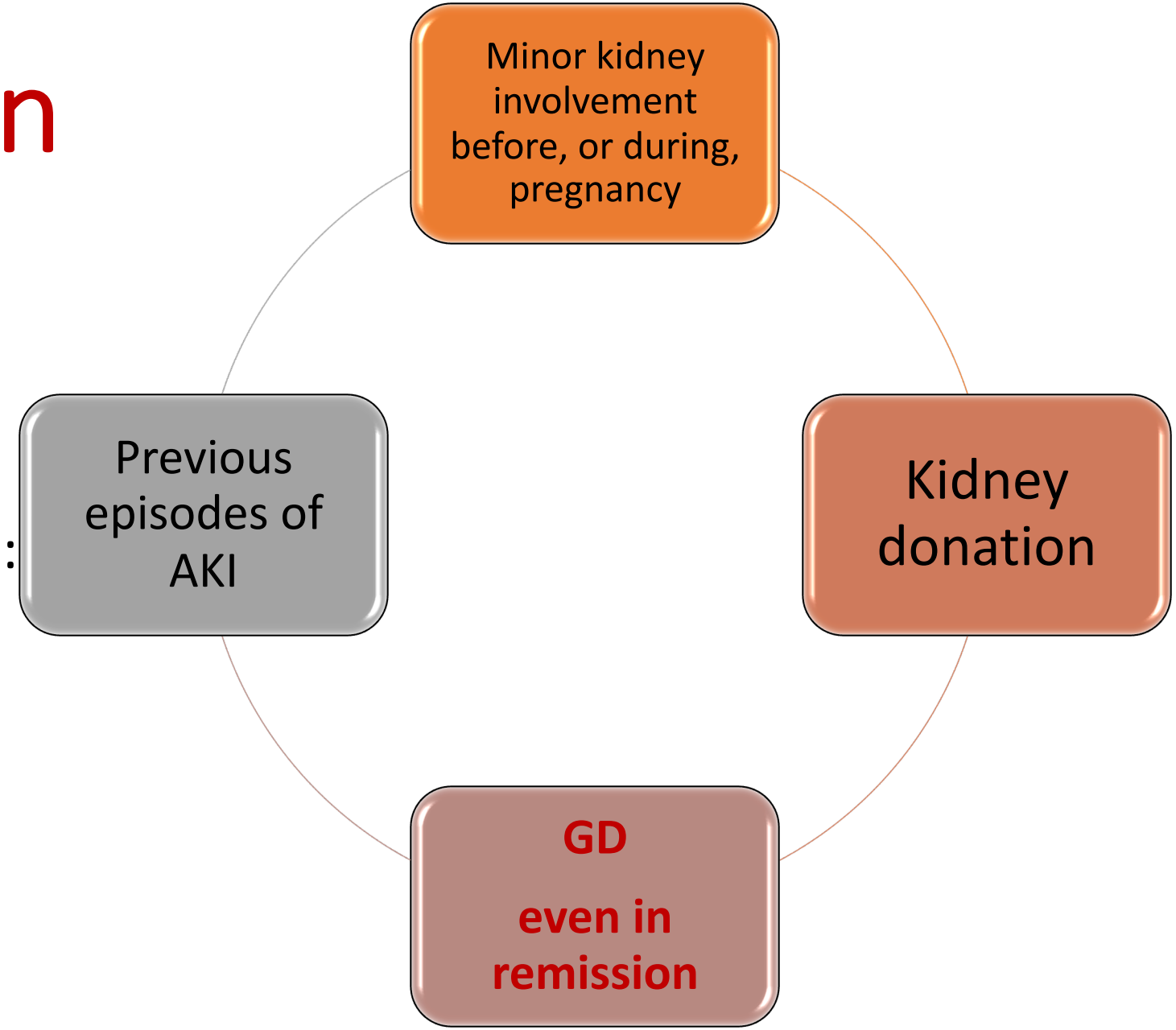
Agenda

- Introduction to pregnancy and glomerular disease(GD)
- Epidemiology
- Diagnosis and monitoring of GD
- Pregnancy conselling and approach to GD and pregnancy
- Specific GN in pregnancy: MCD/FSGS, MN, MPGN, LN, Vasculitis
- Diagramatic conclusion

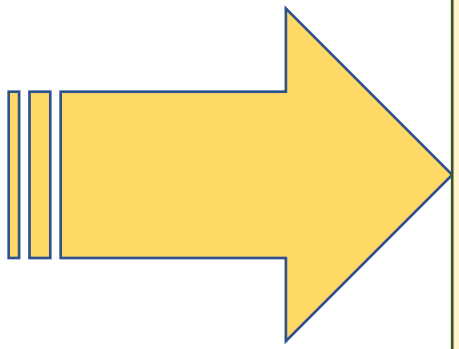
Introduction

- High risk pregnancies:



Introduction

- GDs:
  - Appear, be initially diagnosed
  - Flare during pregnancy



Subsequent therapy is often limited by the actual risk or concern for fetal toxicity.

EPIDEMIOLOGY: WHAT ARE WE TALKING ABOUT?

- 3%-6% of women of child-bearing age have CKD
- Up to 3% of women with CKD are of child-bearing age
- Up to 3.3% of pregnant women have laboratory evidence of CKD.

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doi: 10.1093/ndt/gfq169
Advance Access publication 26 March 2010

Previous preeclampsia and risk for progression of biopsy-verified kidney disease to end-stage renal disease

Bjørn Egil Vikse[1,2], Stein Hallan[3,4], Leif Bostad[5], Torbjørn Leivestad[6] and Bjarne M. Iversen[1,2]

582 female (women who, after their last pregnancy, had had a representative kidney biopsy in 1988– 2005)

Results

76 developed ESRD: 3.9 ± 3.4 years after diagnosis

Women with clinically diagnosed preeclampsia in their first pregnancy had a relative risk of ESRD of 1.2, and women with preterm birth had a relative risk of 2.1

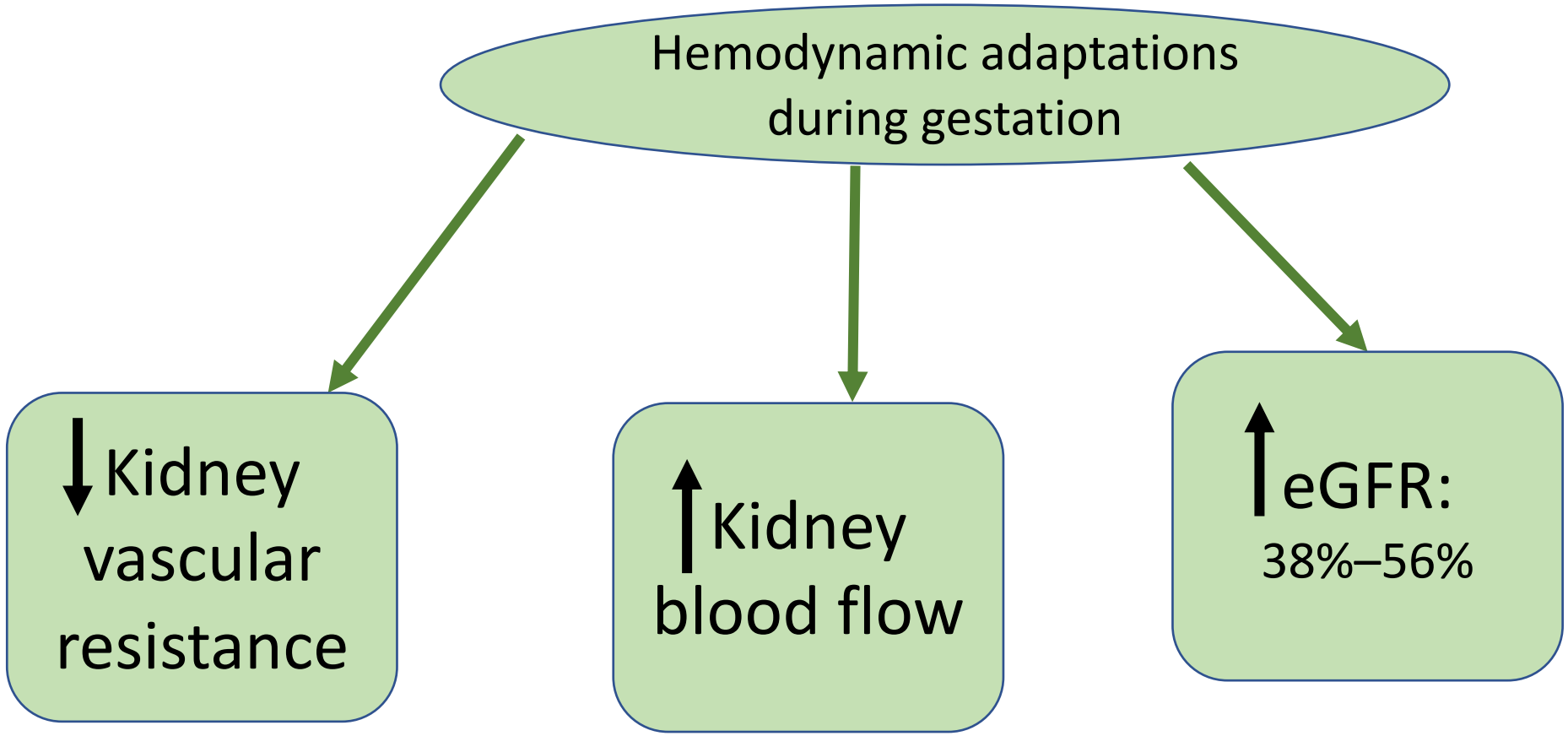
Conclusion

In women with kidney disease diagnosed at kidney biopsy, previous preeclampsia does not seem to be a risk marker for progression to ESRD.

In Conclusion

- Those who had a **history of preterm birth or preeclampsia had higher rates of FSGS, crescentic glomerulonephritis, or ANCA vasculitis**

TOOLS FOR THE DIAGNOSIS AND MONITORING OF GDs IN PREGNANCY



Kidney function estimation

- Urinary creatinine clearance as the gold standard.
- Abnormal serum creatinine concentration:
  - Serum Cr>85% (0.86mg/dL)
  - Serum Cr 80% (0.81mg/dL)
  - Serum Cr 86% (0.87 mg/dL)
    - of the nonpregnant upper limit of normal

First trimester

Second trimester

Third trimester

TOOLS FOR THE DIAGNOSIS AND MONITORING OF GDs IN PREGNANCY

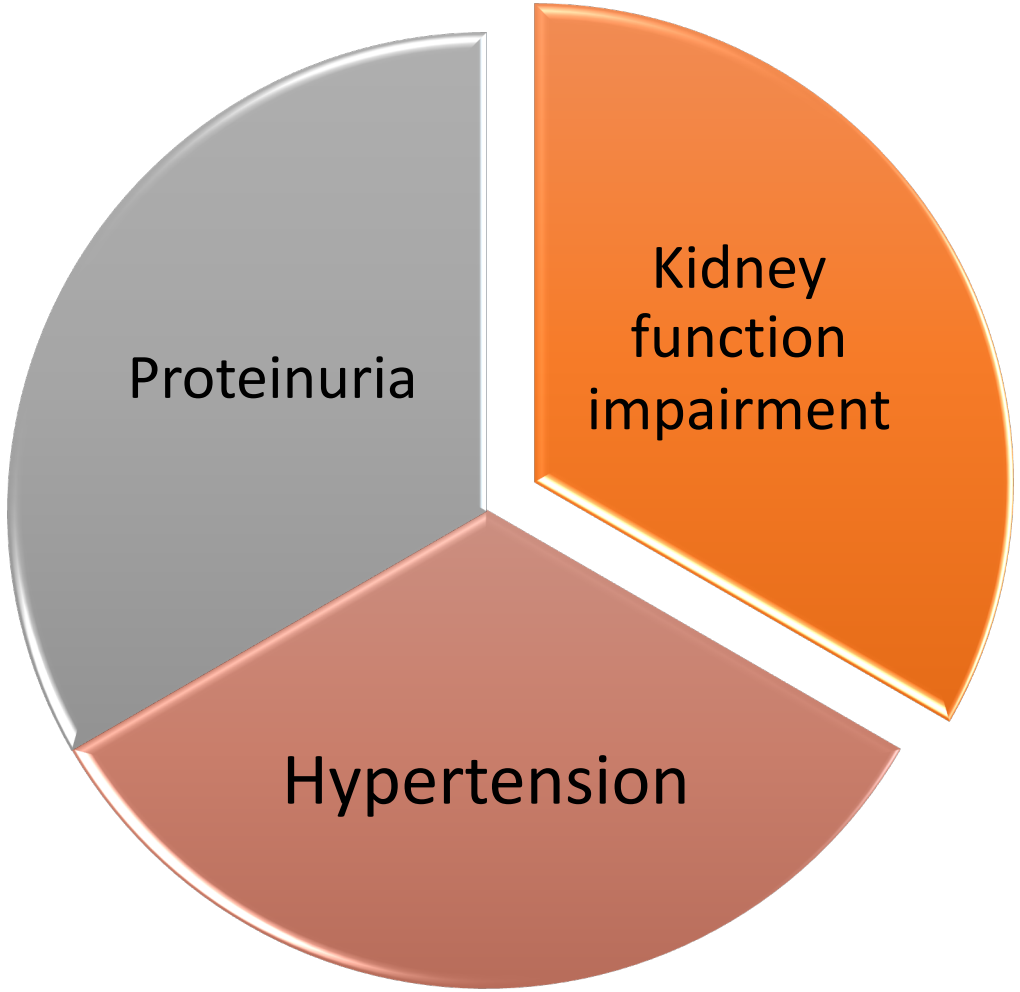
- Staging of CKD in pregnant patients with a GD: based on pre-pregnancy values
- The absence of an early decrease in Cr during pregnancy compared with pre-pregnancy concentrations: a poor prognostic marker of renal function outcome.
- Glomerular hyperfiltration: **not been associated** consistently with **better pregnancy-related outcomes**, at least during the **early** stages of CKD.

Assessing proteinuria in pregnancy

- No consensus regarding the best method
- Spot UPCR: is preferred to timed urine collections because of the possibility of **underestimation**, variability, and inconvenience with the latter.
- UPCR: **screening for hypertensive** disorders of pregnancy
- New onset of proteinuria (UPCR >30 mg/gr) is one discriminating parameter between preeclampsia and gestational hypertension.

RISK EVALUATION FOR PREGNANCY, THE WOMAN, AND THE FETUS IN PATIENTS WITH A KNOWN GD

Three major determinants of pregnancy-related outcomes



Their effects are most likely also modulated by the type of kidney disease.

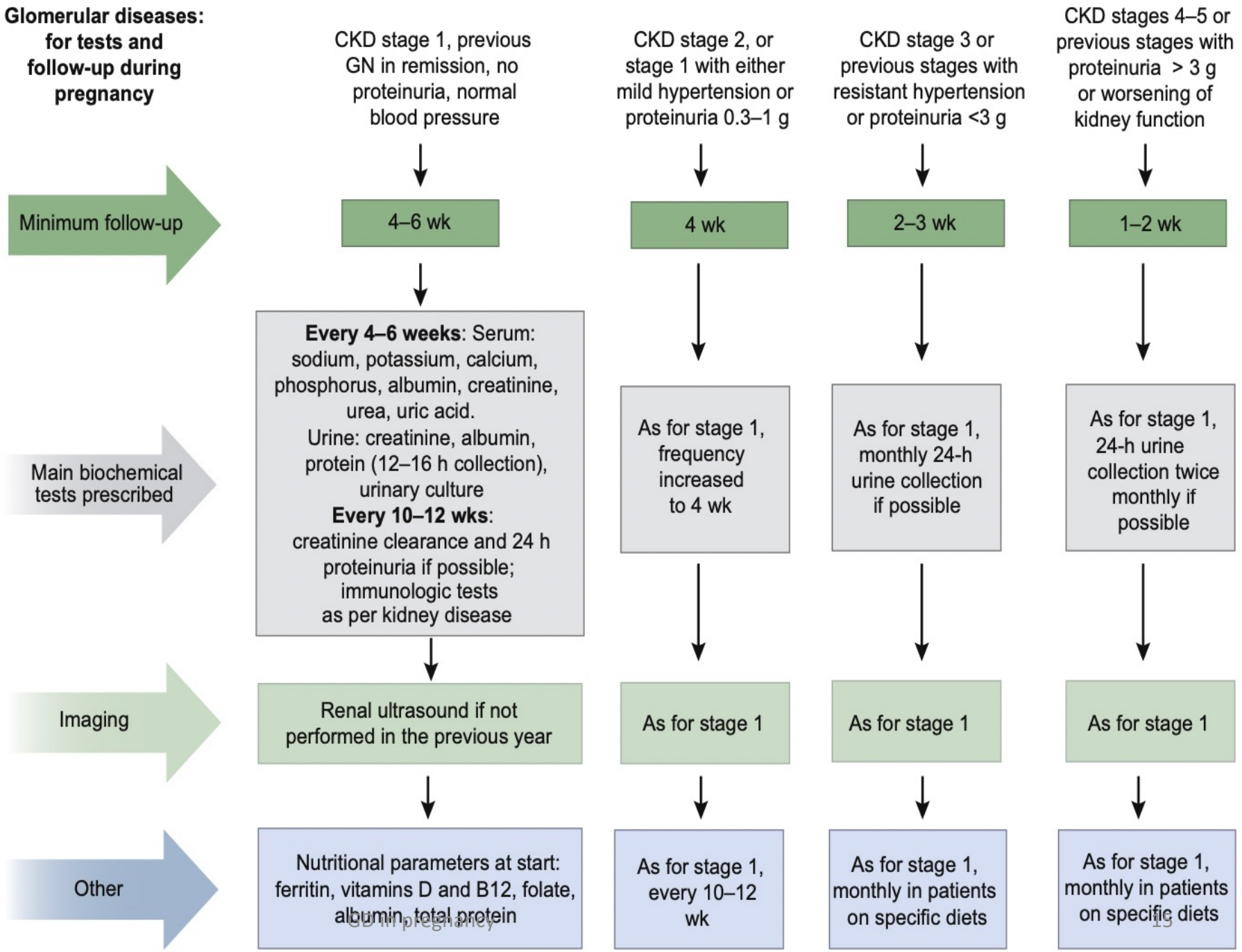
RISK EVALUATION FOR PREGNANCY, THE WOMAN, AND THE FETUS IN PATIENTS WITH A KNOWN GD

- As for maternofetal outcomes excluding kidney function, GDs generally seem to be associated with a higher risk of adverse pregnancy events compared with patients with other types of kidney diseases
- This increased risk **even applies** to women with a GD and **CKD stage 1**, **mild proteinuria (<1 g/ 24 h),** or **normal blood pressure** (i.e., a GD in complete clinical remission).
- Pregnancy outcomes in these patients are **similar to those of women with kidney transplantation.**

RISK EVALUATION FOR PREGNANCY, THE WOMAN, AND THE FETUS IN PATIENTS WITH A KNOWN GD

- With respect to kidney function, **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.
- This finding has been documented particularly in women with IgAN and LN.

How should women with GD and CKD starting a pregnancy be monitored?



How to distinguish GD worsening from preeclampsia?

- Linking preeclampsia to an angiogenic-antiangiogenic imbalance.
- The measurement of the soluble **fms-like tyrosine kinase 1/placental growth factor ratio** is increasingly being recommended
- Within the **normal range**: **pure worsening of preexistent CKD.**
- **Increased in the case of preeclampsia**
- Preeclampsia superimposed on CKD: intermediate, but nonspecific

How to distinguish GD worsening from preeclampsia?

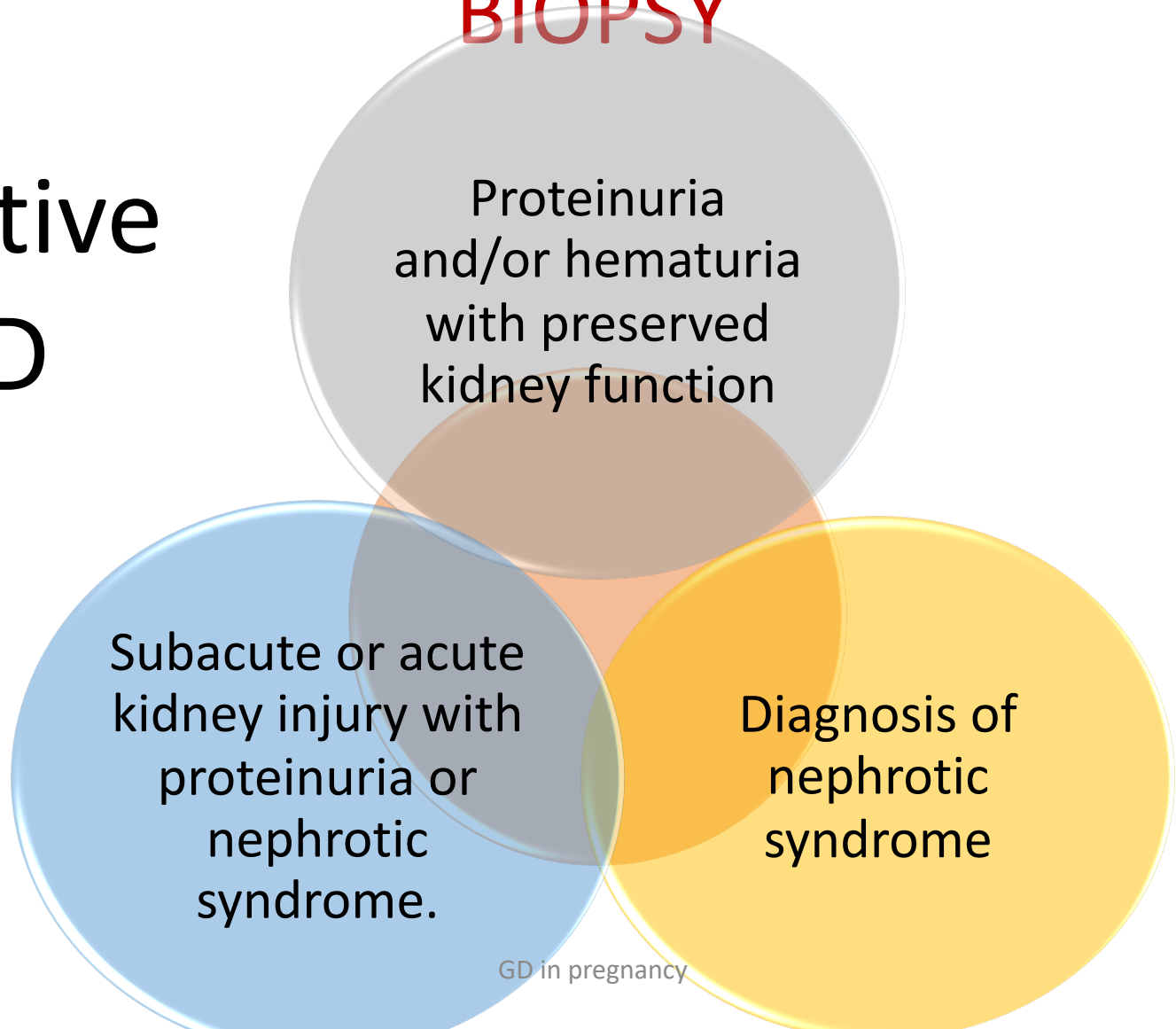
- Severely impaired uteroplacental Doppler flows: indicate placental involvement, commonly associated with intrauterine growth restriction

How to distinguish GD worsening from preeclampsia?

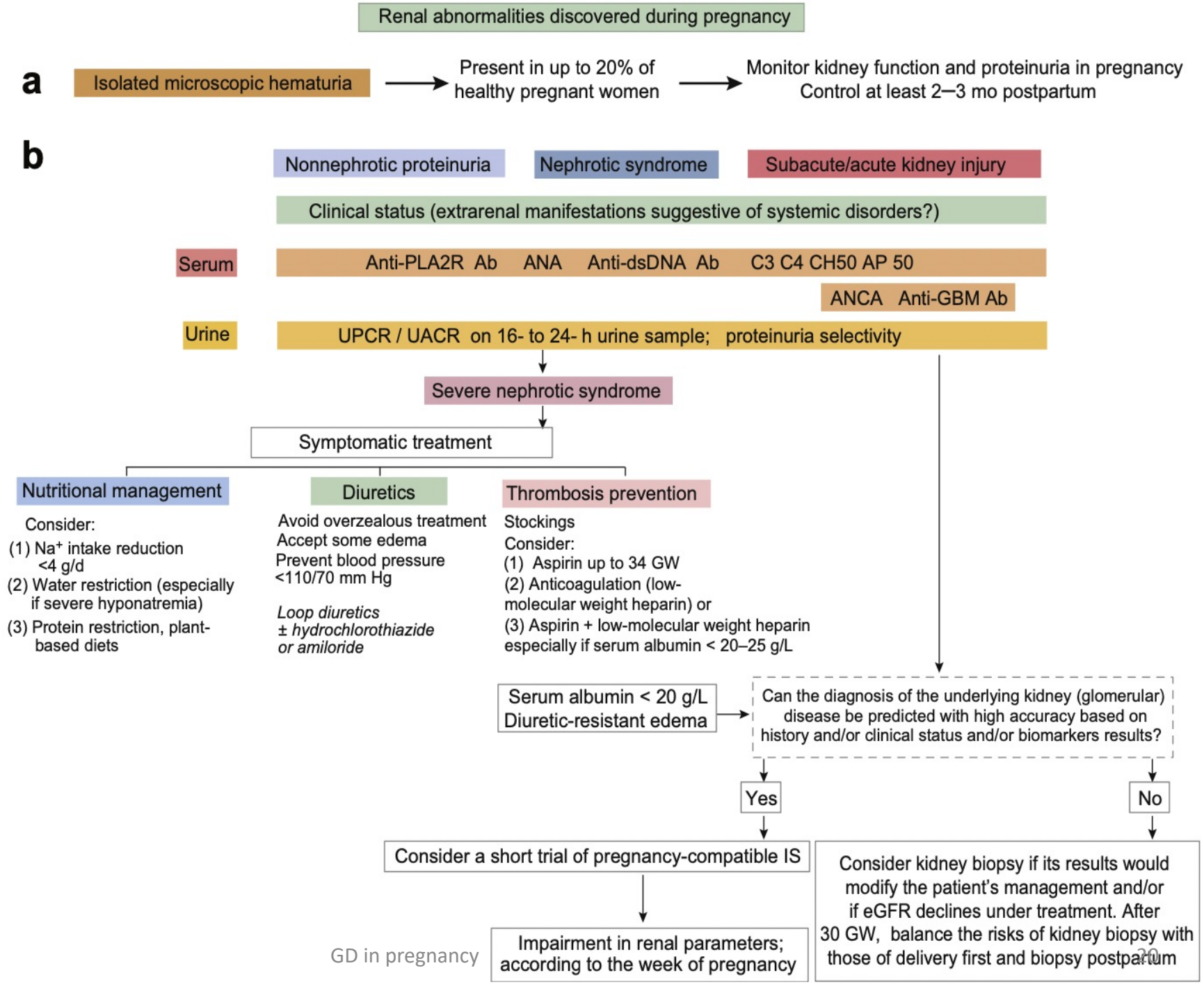
- The simplest and perhaps most simplistic way to make a differential diagnosis between preeclampsia and GD after delivery is based on the **persistence** of proteinuria and hypertension **beyond 3 months** postpartum.
- The absence of proteinuria, however, does not fully rule it out.

DIAGNOSTIC ISSUES IN PATIENTS WITH DE NOVO GD, WITH PARTICULAR EMPHASIS ON KIDNEY BIOPSY

Suggestive of GD



Management of patients with renal abnormalities suggestive of a glomerular disease discovered during pregnancy



Definition of nephrotic syndrome in pregnancy

- Not clear
- Hyperhydration ⇨ gradually ⇩ in Alb
  - Serum Alb < the lower limit of Nl for gestational age
  - Proteinuria >3 g/d

} Suggestive of nephrotic syndrome

- Severe nephrotic syndrome: serum Alb <50% of the lower limit of normal.

Limits of normal of serum albumin

Albumin (g/l)		
Week 7–17	32.2 (30.9–33.5)	43.2 (42.6–43.8)
Week 17–24	27.9 (27.4–28.4)	36.9 (36.4–37.3)
Week 24–28	27.0 (26.5–27.4)	34.6 (33.8–35.4)
Week 28–31	25.1 (24.3–25.9)	33.7 (33.3–34.0)
Week 31–34	24.4 (23.5–25.3)	33.7 (33.1–34.3)
Week 34–38	23.1 (21.9–24.4)	33.8 (32.5–35.2)
Predelivery	24.0 (23.0–24.9)	38.2 (34.4–42.0)
Postpartum	37.0 (36.4–37.6)	47.2 (46.6–47.8)

DOI: 10.1111/j.1471-0528.2008.01709.x
www.blackwellpublishing.com/bjog

Reference values for clinical chemistry tests during normal pregnancy

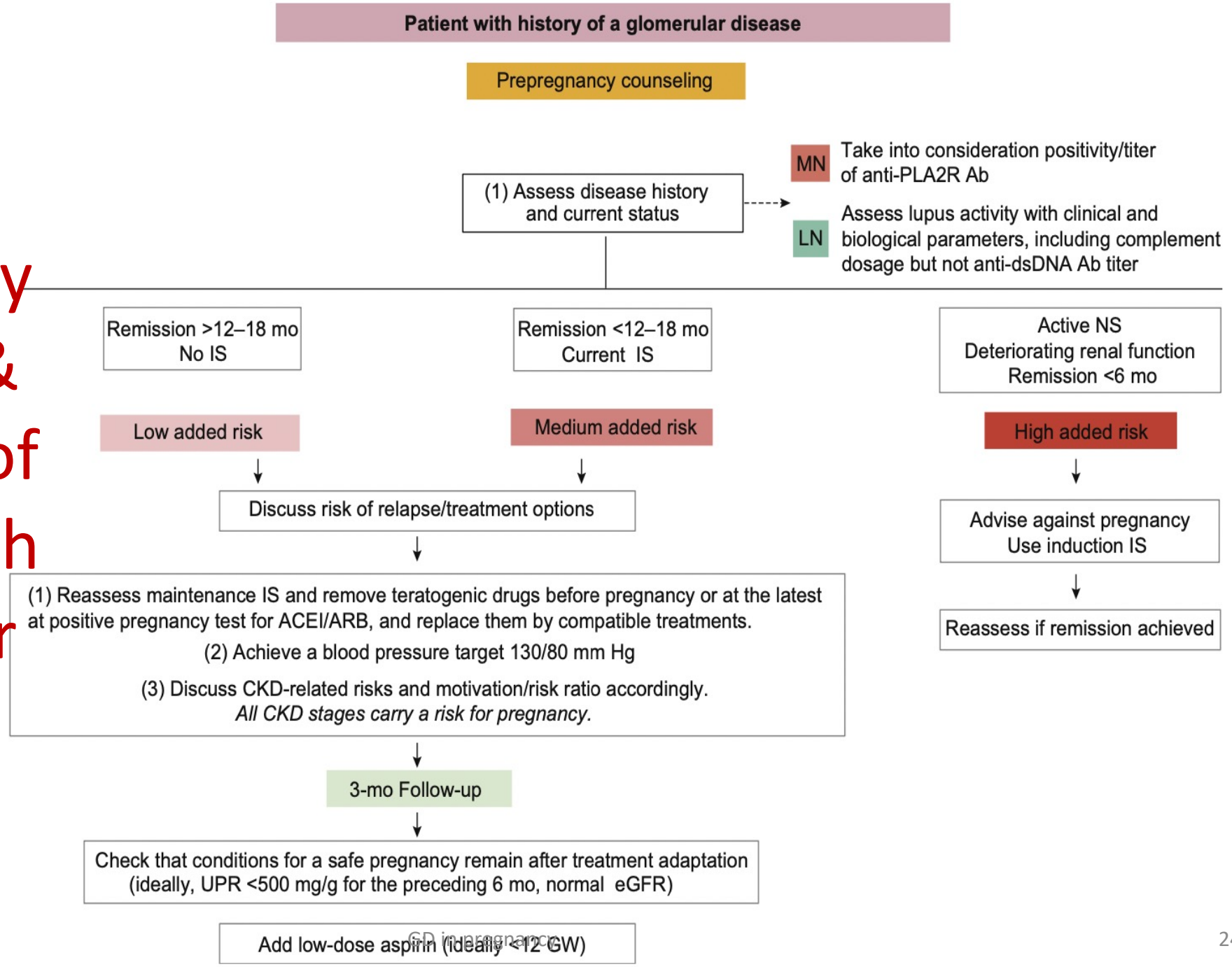
A Larsson,[a] M Palm,[b] L-O Hansson,[a] O Axelsson[b]

When should a kidney biopsy be performed in pregnancy?

Table 1 | Considerations regarding the use of kidney biopsy in pregnant women

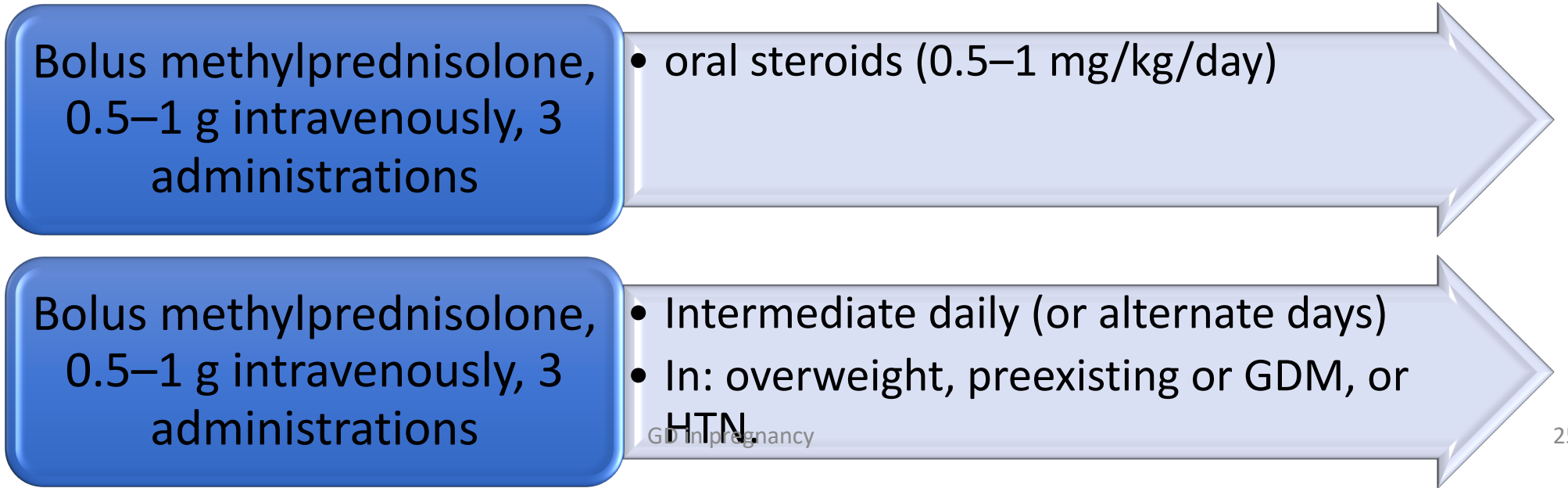
Kidney biopsy in pregnant women
(i) Clinicians are usually reluctant to perform a kidney biopsy during pregnancy. This is because of the increased risk of complications, estimated in a systematic review to be as high as 7%, compared with 1% after delivery (2% risk of major bleeding in the late second trimester[58]). The bleeding risk has been attributed to the increase in kidney blood flow and is thought to be reversible within ≈3 months after delivery.
(ii) More recent reports indicate that the risks of a kidney biopsy during pregnancy are minor when performed by an experienced physician and suggest that this procedure may be more frequently considered.[59,60]
(iii) The availability of laboratory tests, including the characterization of proteinuria, antibody workup for LN, ANCA, and anti-PLA2R antibodies, or the presence of highly selective proteinuria, may lead first to empiric treatment with postponement of biopsy to the postpartum period (Figure 1).
(iv) A normal ratio of soluble fms-like tyrosine kinase 1/placental growth factor may be useful in ruling out severe or superimposed preeclampsia.[50,61]
(v) Timing is crucial when considering kidney biopsy. In early pregnancy (<12 weeks), the risks of kidney biopsy are relatively low, and the advantages of precisely knowing the kidney disease are high. This profile of risks changes throughout pregnancy and may decrease after 30 to 34 weeks.
(vi) In some countries in which the health care system covers pregnancy but not later follow-up, the importance of establishing a clear diagnosis to guide subsequent therapy may outweigh the risks of kidney biopsy.
(vii) In kidney transplantation, the technically easier access to the grafted kidney may positively affect the risk-to-benefit ratio. In this context, the differential diagnosis includes graft rejection, recurrence, or a *de novo* glomerular disease and preeclampsia.[62,63]

Prepregnancy counseling & assessment of a woman with a glomerular disease



Pregnancy in a patient with a history of MCD or of FSGS

- Relapse of MCD during pregnancy: reported
- Higher risk of relapse: In corticosteroid-dependent MCD
- Control of relapses: corticosteroids, and pregnancy outcomes are generally favorable.
-



Other therapies for MCD

- Calcineurin inhibitors are an alternative: frequent blood monitoring, screening for GDM.
- In more recent reports of selected cases of MCD with high recurrence rates,pregnancy **outcome was favorable** with **maintenance rituximab therapy**.

Therapies for FSGS

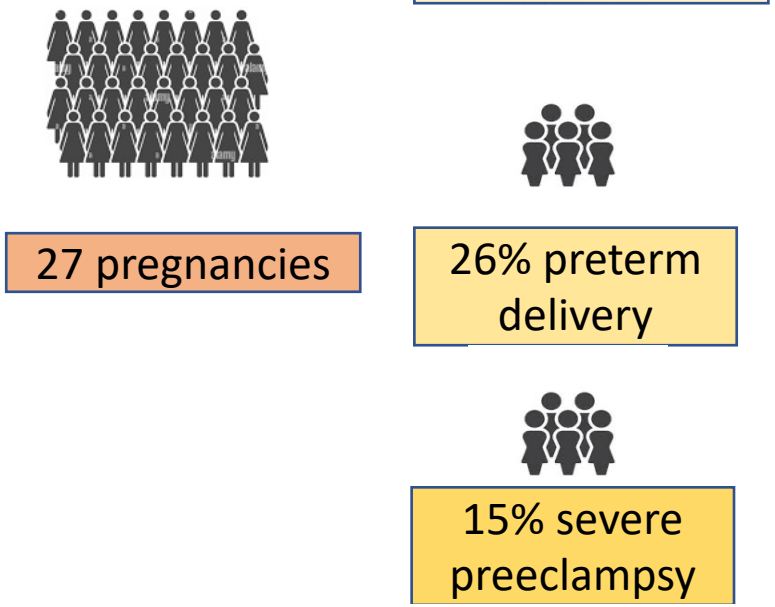
- Risks of adverse pregnancy outcomes: moderate in the presence of **mild proteinuria**
- In corticosteroid- resistant FSGS with persistent heavy proteinuria/nephrotic syndrome and/or CKD: higher risk for maternal and fetal complications

MCD or FSGS diagnosed in pregnancy

- It is rare event

- FSGS diagnosed in pregnancy may respond well to treatment, even in the presence of severe, collapsing lesions

Pregnancy in women with a history of MN



Risk factors for adverse maternal-fetal outcomes:

- Heavy proteinuria, especially before the 20th week of gestation
- Severe hypoalbuminemia
- Presence of anti- PLA2R antibodies
- Absence of remission during pregnancy

> Am J Nephrol. 2020;51(4):304-317. doi: 10.1159/000505175. Epub 2020 Feb 25.

Membranous Nephropathy in Pregnancy

Zi-Ning Liu [1], Zhao Cui [2], Ying-Dong He [3], Yi-Miao Zhang [1], Fang Wang [1], Xin Wang [1], Li-Qiang Meng [1], Xu-Yang Cheng [1], Gang Liu [1], Ming-Hui Zhao [1 4]

Immunosuppresive therapy in MN

- If the patient is proteinuric
- Immunologically active disease (presence of high-titer anti-PLA2R antibodies)

- If an anti-CD20 antibody is used, the manufacturer's recommendation is that conception should be **avoided for 6 to 12 months after the last infusion**, although the data reporting fetal toxicity are weak and sparse

Immunosuppresive therapy in MN

- Unplanned pregnancy in the setting of **nephrotic** syndrome: **extensive information**, the patient still **wishes to continue her pregnancy**, strict monitoring:

  = Repeated assessment of anti- PLA2R antibodies

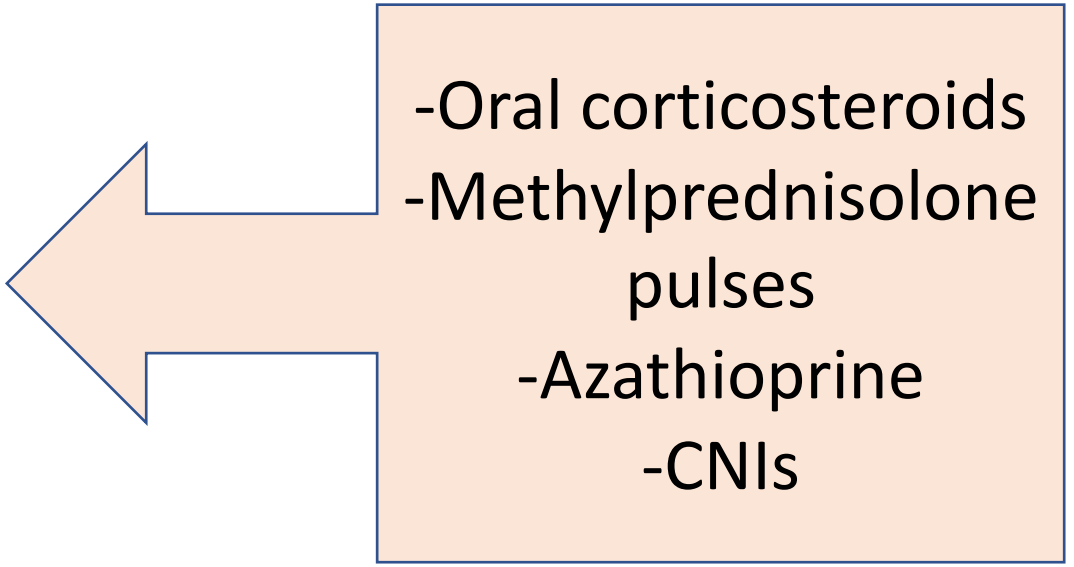
- CNIs: first-line therapy
- Cyclophosphamide and anti-CD20 antibodies:
  - Delayed clinical response observed outside pregnancy
  - Rescue treatment in patients who do not respond to CNIs.

MN diagnosed during pregnancy

- Few cases of de novo PLA2R-associated MN diagnosed during pregnancy have been published, and diagnosis **is usually based on the positivity of autoantibodies.**
- Transplacental transfer of PLA2R antibodies: has been reported & much lower in cord blood
- The newborns: free of proteinuria at birth and at later visits
- The transfer of PLA2R antibodies into breast milk has also been reported

Primary Ig-associated MPGN and C3 glomerulopathy in pregnancy

- Increased proteinuria
- Declining kidney function
- Nephrotic syndrome



- A kidney biopsy: to assess the respective: chronic/fibrotic lesions and acute/inflammatory.
- In patients with crescentic, rapidly progressing C3G and Ig-MPGN, **eculizumab** is an option.

IgA nephropathy

- Pregnancy did not accelerate kidney disease deterioration in women with IgAN in stages of chronic kidney disease 1–3.
- Patients with IgAN had a relatively low risk of adverse pregnancy events compared with those with lupus nephritis or diabetic nephropathy

American Journal of Nephrology

Am J Nephrol 2019;49:214–224
DOI: 10.1159/000496410

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Renal Outcomes of Pregnant Patients with Immunoglobulin A Nephropathy: A Systematic Review and Meta-Analysis

Fan Wang Jian-Da Lu Ying Zhu Ting-Ting Wang Jun Xue

IgA nephropathy

- IgAN may rarely be associated with **“flares” during pregnancy**, including episodes of visible hematuria, requiring a careful workup for other causes of hematuria.
  - **IgAN diagnosed during pregnancy**

- Presentation As:
  - Severe proteinuria during pregnancy
  - Rapidly progressive glomerulonephritis due to IgAN

Lupus nephritis

- **Presence and severity of CKD or of antiphospholipid syndrome** but also because pregnancy may trigger a lupus **flare**
- **LN diagnosed before pregnancy**
- The higher risk of flares: women with active lupus and the duration of remission before pregnancy.

CJASN

Clin J Am Soc Nephrol. 2010 Nov; 5(11): 2060–2068.
doi: 10.2215/CJN.00240110
PMCID: PMC3001786
PMID: 20688887
Original Articles

A Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus and Lupus Nephritis

Andrew Smyth,* Guilherme H.M. Oliveira,† Brian D. Lahr,‡ Kent R. Bailey,‡ Suzanne M. Norby,§‖ and Vesna D. Garovic§‖

26% Lupus flare

2751 pregnants with LN

16% HTN

16% nephritis

0.8% eclampsia

8% preeclampsia

13% IUGR

16% spontaneous abortion

3.6% stillbirth

2.5% neonatal death

Results

-Successful pregnancy rate: 77%
-The preterm birth rate: 39%

Not only disease activity but also chronic hypertension and overweight are determinants of pregnancy outcomes in patients with systemic lupus erythematosus

G Normand, F Sens, [...], and on behalf of the French Collaborative Group on Lupus Nephritis +9 View all authors and affiliations

Volume 28, Issue 4 | https://doi.org/10.1177/0961203319832097

- Main determinants for fetal and maternal complications:
  - Maternal age
  - Prepregnancy hypertension
  - BMI>25 kg/m^2
  - Lupus immunological activity

- Reduced risk of renal flare during pregnancy: remission time > 12 months

Immunosuppresive therapy in LN

- The benefit over risk ratio of hydroxychloroquine use: OK
- Steroids, azathioprine, and CNIs: may be used
- Rituximab may be considered in the absence of more appropriate alternatives in **severe and resistant cases**.
- Belimumab, voclosporin, and anifrolumab **are not recommended** during pregnancy because of lack of experience.

Other therapies in LN

- Low-dose aspirin: strongly recommended in **all patients+ LN**.
- Antiphospholipid syndrome, **aspirin** + **heparin**
- In the presence of anti-Ro/SSA antibodies, systematic fetal heart rhythm monitoring: advised for early detection of fetal atrioventricular block (detected in 1%–2% of anti-Ro/SSA pregnancies).
- Routine screening: has recently been challenged: may be reserved for patients + **a history of congenital heart block**.

LN diagnosed during pregnancy

- Proliferative LN in pregnancy with declining renal function requires **urgent therapy** and the discussion of therapeutic termination of pregnancy in case of organ-threatening disease.
- The aim of treatment is, at least, to attempt to contain LN so as to allow pregnancy continuation and fetal growth for as long as possible

Vasculitis in pregnancy

- **Vasculitis diagnosed before pregnancy.**
- Clinical spectrum: mild flares in most cases (crusting rhinitis, skin lesions, and arthritis) to severe complications mostly documented in case reports (alveolar haemorrhage, crescentic glomerulonephritis, or thrombotic microangiopathy)

Vasculitis in pregnancy

- In remission for >6 months at conception: favorable outcomes.
- In all planned pregnancies, women were switched to azathioprine in combination with prednisolone or additional cyclosporine.

Vasculitis diagnosed during pregnancy

- Most of which occurred in the second trimester
- Conclusion: De novo AAV in pregnancy can result in uncomplicated pregnancies; however, serious maternal risks exist.

Clinical Kidney Journal, 2018, vol. 11, no. 5, 659–666

doi: 10.1093/ckj/sfy011
Advance Access Publication Date: 15 March 2018
Original Article

ORIGINAL ARTICLE

De novo antineutrophil cytoplasmic antibody-associated vasculitis in pregnancy: a systematic review on maternal, pregnancy and fetal outcomes

Nicole L. Veltri[1], Michelle Hladunewich[2], Arrti Bhasin[2], Jocelyn Garland[3] and Benjamin Thomson[3]

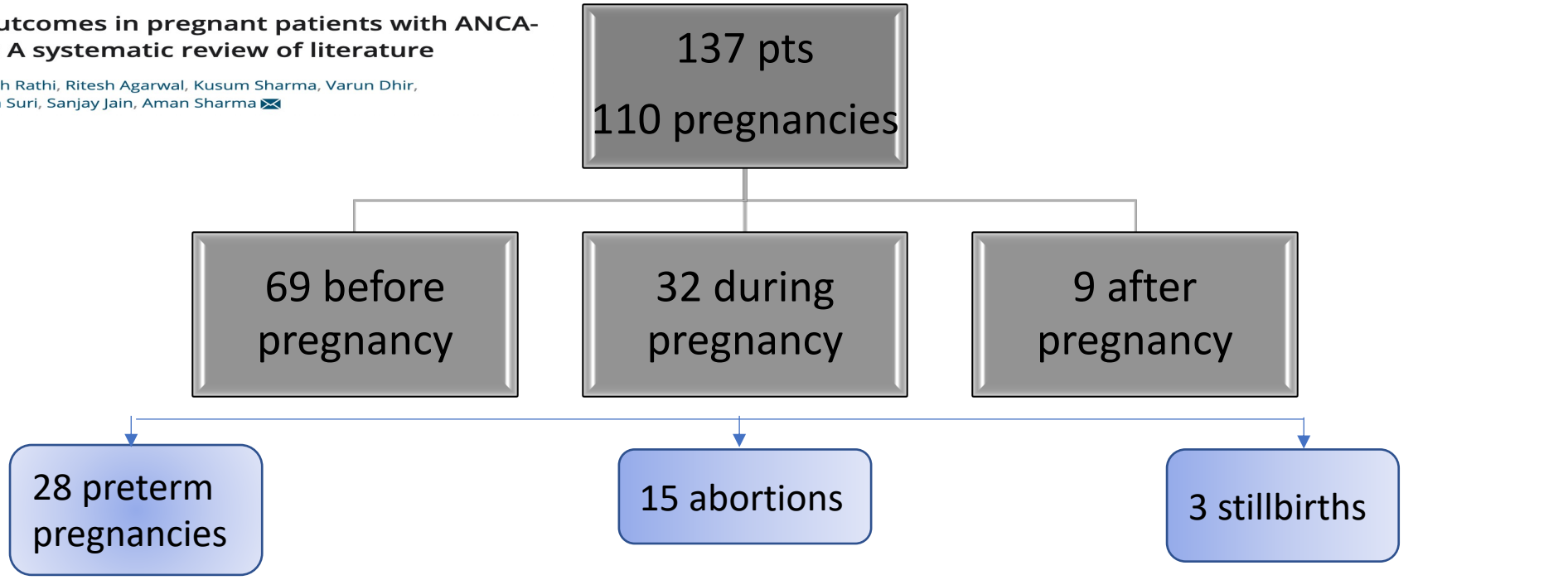
Vasculitis diagnosed during pregnancy

International Journal of Rheumatic Diseases

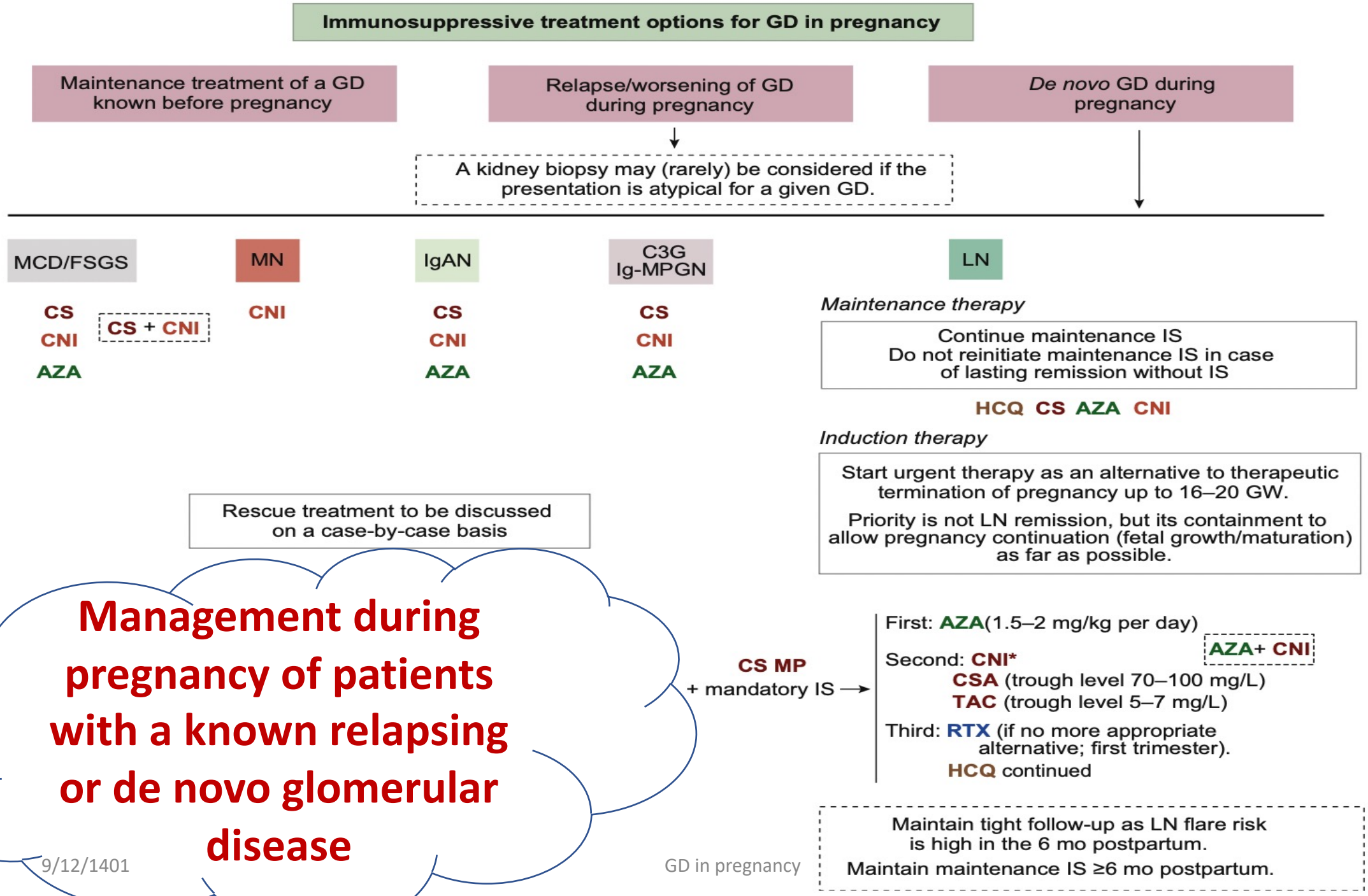
ORIGINAL ARTICLE

Successful treatment outcomes in pregnant patients with ANCA-associated vasculitides: A systematic review of literature

Pawan Singh, Aadhaar Dhooria, Manish Rathi, Ritesh Agarwal, Kusum Sharma, Varun Dhir, Ritambhra Nada, Ranjana Minz, Vanita Suri, Sanjay Jain, Aman Sharma



The authors do not report significant differences between those who were diagnosed before and during pregnancy



Management during pregnancy of patients with a known relapsing or de novo glomerular disease