

## NEPHROTIC SYNDROME IN PREGNANCY

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### Objectives

At the end of the session, the participant will be able to:

- Counsel their patient with nephrotic syndrome about the risks and complications of pregnancy
- Follow and manage the principal complications (oedema, hypertension, thromboembolic risk, etc.)

### Detection of nephrotic range proteinuria in pregnancy

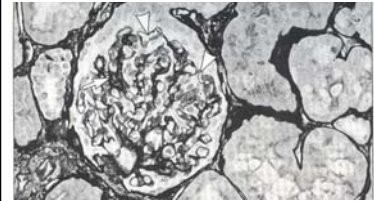
- Routine antenatal urine dipstick screening in an asymptomatic woman
- Focused work-up in specific high-risk population
  - known renal disease or risk factors for renal disease (e.g. diabetes)
  - hypertensive: to rule out preeclampsia or for baseline work-up of pre-existing hypertension
- New-onset oedema investigation  
**Prevalence: not well reported**

### Outline

- 1) GENERAL ISSUES
- 2) IMPACT OF NEPHROTIC SYNDROME IN PREGNANCY
- 3) MANAGEMENT CHALLENGES DURING PREGNANCY
- 4) POSTPARTUM MANAGEMENT

### GENERAL ISSUES FOR NEPHROTIC SYNDROME

Physiology/definitions  
Detection  
Causes  
Assessment



### Physiology and definitions

Significant proteinuria  
= 150 → 300mg/d in pregnancy  
glomerular and tubular proteinuria

Nephrotic syndrome  
>3g/d, albumin < 30g/L, oedema  
hypercholesterolemia, lipiduria

Nephrotic range proteinuria  
>3g/d, usually glomerular proteinuria

### Nephrotic syndrome in pregnancy

Most common cause = **preeclampsia**  
After 20wks GA :

**R/O preeclampsia until proven otherwise**

**proteinuria with hypertension:  
Hematuria, red cell casts, ↑ creatinine  
Symptoms and signs of systemic disease  
(“preeclampsia mimickers”)**



## Causes of Proteinuria

### Glomerular diseases

- **Preeclampsia\*\***
- **Diabetes (type 1 and 2)\***
- **IgA GN\***
- **Focal and segmental glomerulosclerosis (FSGS)\***
- **Lupus nephritis**

## IMPACT OF NEPHROTIC SYNDROME IN PREGNANCY

### Maternal/fetal considerations Preconception counselling

## Maternal/fetal considerations

### Maternal

- Conditions to consider:
- Preexisting renal insufficiency
  - Preexisting hypertension
  - Type of underlying renal disease
  - Concomitant maternal comorbidities

## Maternal/fetal considerations

### Maternal:

#### Risks

- vary according to associated conditions
- Acute kidney injury
- Chronic renal failure / ESRD
- Gestational hypertension
- Preeclampsia / severe preeclampsia
- Maternal renal and life expectancy
  - Modified by acute renal complications in pregnancy / postpartum

## Maternal/fetal considerations

### Fetal

- Fetal growth restriction
  - most likely related to reduced utero-placental perfusion / low colloid osmotic pressure and reduction in effective blood volume
- Prematurity
- Stillbirth
- Fetal anasarca
- Polyhydramnios

## Preconception counselling

### Maternal condition

- Renal disease controlled
  - Nephrotic syndrome
  - Renal function
  - Blood pressure
- Proteinuria likely to increase
  - Antiproteinuric drugs cessation
  - Physiology of pregnancy
- Genetic transmission: rare
  - e.g. minimal change, FSGS or membranous GN

## Preconception counselling

### Drugs

- Antiproteinuric
  - ACEI/ARB/anti-aldo
- Furosemide / HCTZ
  - Less data with amiloride
- Statins
- Immunosuppressives
  - AZA, cyclosporine, tacrolimus
  - MMF, CYC
- ASA for prevention of preeclampsia
  - Less data for renal diseases
- Biphosphonate / Others

## MANAGEMENT CHALLENGES DURING PREGNANCY

### Clinical issues

## Clinical issues in the management of nephrotic syndrome during pregnancy

- Oedema
- Blood pressure control
- Acute kidney injury
- Thrombotic risk
- Anemia
- Malnutrition
- Vitamin D deficiency
- Risk of infection
- Timing of delivery

## Management challenges

### Oedema: strategies

- Stockings / Leg elevation
- Salt restriction <100mmol/day (2.3g of sodium)
- Water restriction = 1.5L/day
- Diuretics: aim at a negative balance of no more than 0.5-1.0 L/d
  - Furosemide (oral or iv): start with lower dose 5-10 mg (to prevent acute intravascular dehydration and hypotension; see below for monitoring) and titrate according to clinical response (diureses, weight, BP); use shorter intervals (e.g. q 6-8hr)
  - Thiazide if resistance to loop diuretic
- Colloids
  - Controversial / use in exceptional circumstances

## Management challenges

### Oedema : Monitoring of diuretic treatment:

- Response to diuretics:
  - Daily weight and input/output, BP and heart rate when adjusting treatment
- Metabolic disturbances:
  - electrolytes (sodium, potassium, magnesium, calcium)
  - diuretic-induced alkalosis (normal bicarbonate levels in pregnancy around 18-20meq/L)
- Renal function
  - serum creatinine and urea;  $\pm$  24hr creatinine clearance
- 24hr urinary sodium excretion
  - may be useful to assess resistance to diuretics (aim for sodium excretion >100mmol/day (2.3g/day))

## Management challenges

### Blood pressure control

- BP goal 110-140/80-90  
→no data on best threshold  
→balance between maternal BP and uteroplacental blood flow
- Antihypertensives drugs
  - When hypervolemia present:
    - salt and water restriction / diuretics

## Antihypertensive drugs in nephrotic range proteinuria during pregnancy

Choices most frequently used for the HDP in Canada (including proteinuric preeclampsia):

- labetalol** easy to titrate; other betablockers OK (avoid atenolol)
- nifedipine** outside pregnancy, not first choice in proteinuric renal disease as dihydropyridine calcium channel blockers may increase proteinuria by preferential dilation of afferent arteriole; however remain an alternative when needed for BP control
- methyldopa** if already anemic, beware of hemolytic anemia and warm antibodies

SOGC HDP guidelines 2008

## Antihypertensive drugs in nephrotic range proteinuria during pregnancy

Other choices:

- diltiazem** use to decrease proteinuria outside pregnancy; very small study in pregnant women with renal disease (N=7); good choice in 2<sup>nd</sup>, 3<sup>rd</sup> trimester (caution in 1st trimester as security not yet established). Avoid to use concomitantly with betablockers
- hydralazine** and others

## Management challenges

### Acute kidney injury (AKI)

- Prerenal:
  - decreased oncotic pressure
  - aggressive use of diuretics
    - especially when strict water and salt restrictions are applied (be careful with in-hospital versus outpatient modification in lifestyle and intake)
  - diarrhea, nausea and vomiting
  - infection and sepsis

## Management challenges

### Acute kidney injury (AKI)

- Renal:
  - underlying renal disease progression
  - preeclampsia
  - acute tubular necrosis
  - acute interstitial nephritis
  - other
- Post renal:
  - ureteral compression from gravid uterus
    - especially in multiple pregnancy or polyhydramnios

## Management challenges

### Thrombotic risk

#### Contributing factors

- prothrombotic state of pregnancy
- ↑ urinary loss of anticoagulant proteins e.g. antithrombin III
- ↑ hepatic synthesis of clotting factors
- intravascular hypovolemia
  - interstitial fluid leak
  - Salt / water restriction / use of diuretics
- inflammation
- decreased mobilisation
  - when severe peripheral edema

## Management challenges

### Thrombotic risk

#### Other predisposing conditions and risk factors

- e.g. known thrombophilia, obesity, immobilisation due to obstetrical condition
- Threshold for prophylaxis  
→No consensus
- ? Proteinuria >3-3.5g/d
  - ? antithrombin III below normal
  - ? serum albumin <20-25g/L
- <28g/L Lionaki CJASN 2012

## Management challenges

### Thrombotic risk

#### Prophylaxis / anticoagulation

→ same as for other medical conditions

#### •choice of anticoagulant agent

– LMWH vs UFH

#### •dosing regimens / level of anticoagulation

– prophylactic vs. intermediate vs. therapeutic

n.b. LMWH not recommended when eGFR<30ml/min

## Anemia in nephrotic syndrome

### Contributing causes

•Physiologic anemia of pregnancy

•Inflammation of acute and/or chronic disease

•Decreased intestinal absorption of iron, B12 and folate

•Renal loss of transferrin

•Decreased erythropoietin production if GFR significantly decreased (usually<50ml/min)

•Gastro-intestinal spoliation and other sources of bleeding

## Anemia in nephrotic syndrome

### Baseline work up

•Blood smear, reticulocytes

•Iron stores (total iron, saturation, ferritin)

•Vitamin B12, folate

•Inflammation markers (C reactive protein, sedimentation rate)

•Erythropoietin level when GFR <50ml/min

•Hemolysis tests (haptoglobin, LDH, unconjugated bilirubin)

•Hemoglobinopathies screen (Hemoglobin electrophoresis)

## Management challenges

### Nutrition

#### Contributing factors

•Urinary loss of protein and other nutrients

•Decreased intestinal absorption secondary to intestinal wall edema

•Inflammation leading to increased catabolism

#### Role of dietician

•Evaluation of intake/nutritional needs

→Weight gain monitoring as surrogate of nutritional status may be misleading when excess of edema

→Parenteral nutrition not advocated (unproven benefits / associated risks)

## Management challenges

### Vitamin D deficiency

#### Various regimens

•for severe deficiency (level <30)

→e.g. 4000-5000 (up to 10 000) u/d for 2-4 wks, maintenance dose 1000 u/d

•adjust according to repeat calcium and vitamin D serum levels (at least monthly)

n.b. correction of total calcium for decreased albumin level or measure ionized calcium

Adequate calcium intake (1200-1500mg/d)

## Management challenges

### Risk of infection

Increased urinary loss of immunoglobulins

•No specific recommendation for nephrotic syndrome

•Prophylaxis treatment as needed

– e.g. UTI

•Vaccination

### Timing of delivery

## POSTPARTUM MANAGEMENT

### Clinical issues

## Postpartum management

### Avoidance of NSAIDs \*\*\*

#### Oedema

- spontaneous postpartum diuresis / daily assessment / diuretics if needed

#### Blood pressure control

- BP goal <130-140/80-90
- antiproteinuric drugs as first choice
  - Unless AKI ; caution if prematurity
- captopril, enalapril, spironolactone compatible with breastfeeding

## Postpartum management

### Acute kidney injury

### Thrombotic risk

–Thromboprophylaxis ≥ 6 weeks

–LMWH vs UFH vs coumadin

### Postpartum management

- Completion of renal investigation if needed
- Reassess appropriate medication for specific renal disease

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### Conclusion

#### Key points

- Nephrotic syndrome vs nephrotic range proteinuria
- Practical approach of the evaluation, management and monitoring
- Appropriate evaluation of the underlying renal disease and its specific prognosis and treatments
- Pluridisciplinary approach necessary to optimise both maternal and fetal care and outcomes

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### Questions



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### Causes of Proteinuria

#### Glomerular diseases

- Preeclampsia\*\***
- Diabetes (type 1 and 2)\***
- IgA GN\***
- Focal and segmental glomerulosclerosis (FSGS)\***
- Lupus nephritis**

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### Causes of Proteinuria

#### Glomerular diseases

- Infection-related GN**  
e.g. HIV, hepatitis B and C, post-streptococcal, visceral abscess, endocarditis
- Drugs-related GN**
- Other glomerular diseases in young women:**  
\*minimal change, membranous, membranoproliferative, other rare causes (e.g. amyloidosis, Fabry, Alport)

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### Causes of Proteinuria

#### Other causes of proteinuria<sup>1</sup>

**Renal diseases**  
Reflux nephropathy, congenital anomalies, polycystic kidney disease, interstitial nephritis

**Transient causes**  
exercise, fever/sepsis, congestive cardiac disease, subarachnoid/intracranial hemorrhage, seizures

<sup>1</sup>Rarely or not causing nephrotic range proteinuria

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### Assessment of Proteinuria

#### Questionnaire

**ask mom!**

**Birth**  
• Birth weight / Prematurity / Perinatal complications

**Infancy and childhood**  
•urinary tract infections / vesicoureteral reflux  
•previous urinary tract investigations  
•nycturia  
•childhood GN  
e.g. post-infectious GN, Henoch-Schonlein purpura, minimal change

**Familial history of renal diseases**

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### Assessment of Proteinuria

#### Questionnaire (cont)

**Current / recent symptoms:**  
•oedema (onset, progression)  
•urinary symptoms (hematuria, frothy urine)  
•systemic symptoms, in particular suggestive of SLE,  
•infectious symptoms and risk factors for HIV/viral hepatitis

**Drugs**  
•prescription, over the counter, recreational

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## Assessment of Proteinuria

### Physical examination

Vitals: Blood pressure, heart rate, O<sub>2</sub> sat, T°, weight, fluid balance

Look for signs of:

- Nephrotic syndrome
  - puffy eyelids, presence or absence of jugular vein distension, lungs (crackles, pleural effusion), ascites (more difficult with gravid uterus), presacral edema, lower limb (severe edema and signs of deep vein thrombosis)
- Systemic diseases

## Assessment of Proteinuria

### Baseline work up: Urine

- Urine analysis / culture, urine sediment
  - obtain also previous results
- Quantification of nephrotic range proteinuria
  - Urinary dipstick
  - Urinary spot protein/creatinine ratio
  - Urinary spot albumin/creatinine ratio
  - 24hr urine collection

n.b. methods differ according to local laboratories

## Assessment of Proteinuria

### Baseline work up: Blood work

- CBC
- creatinine,
- Na, K, Cl
- albumin
- glucose

## Assessment of Proteinuria

### Additional investigations (as indicated):

Renal ultrasound

'Renal' lab : Bicarbonate, Mg, Ca, PO<sub>4</sub>, PTH, urea, uric acid ± cholesterol

Systemic / renal disease markers:

- C-Reactive protein, sedimentation rate
- HbA1c / liver enzymes
- C3, C4, ANA, DsDNA
- viral serology (hepatitis B and C, HIV)
- ANCA, anti-GBM, ASLO

## Assessment of Proteinuria

### Additional investigations (as indicated)(cont):

- Renal biopsy → when diagnostic is needed for *de novo* nephrotic syndrome
  - especially for initiation of treatment with immunosuppressive drugs during pregnancy
- decision according to gestational age, clinic and balance of risks of procedure and maternal-fetal risks/benefits ratio of diagnosis