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
• Focussed 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

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’)

Prevalence: not well reported
**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

**Fetal:**
- Fetal growth restriction
- 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

**Drugs**
- Antiproteinuric
  - ACEI/ARB/anti-ald
  - Furosemide / HCTZ
  - Less data with amiloride
- Statins
- Immunosuppressives
  - AZA, ciclosporine, tacrolimus
  - MMF, CYC
- ASA for prevention of preeclampsia

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

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

**Management challenges during pregnancy**

**Clinical issues**

- Oedema
- Blood pressure control
- Acute kidney injury
- Thrombotic risk
- Anaemia
- 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 (diuresis, weight, BP); use shorter intervals (e.g. q 6-8hr)
- Thiazide if resistance to loop diuretic
- Colloids
  - Controversial / use in exceptional circumstances

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 alcalosis (normal bicarbonate levels in pregnancy around 18-20meq/L)
- Renal function
  - serum creatinine and urea; ± 24hr creatinine clearance
  - Urinary sodium excretion
    - may be useful to assess resistance to diuretics (aim for sodium excretion >100mmol/day)

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 hypertension present:

Other choices:
- Diltiazem: use to decrease proteinuria outside pregnancy; very small study in pregnant women with renal disease (N=7); good choice in 2nd-3rd trimester (caution in 1st trimester as security not yet established). Avoid to use concomitantly with betablockers
- Hydralazine and others

Acute kidney injury (AKI)
- Prerenal:
  - Decreased oncotic pressure
  - Aggressive use of diuretics
- Renal:
  - Underlying renal disease progression
  - Preeclampsia
  - Acute interstitial nephritis
- Postrenal:
  - Ureteral compression from gravid uterus
    - Especially in multiple pregnancy or polyhydramnios

Acute kidney injury (AKI)
- Threshold for prophylaxis
  - No consensus
  - Proteinuria >3-3.5g/d
  - Antithrombin III below normal
  - Serum albumin <20-25g/L

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 hypertension present:
    - Salt and water restrictions / diuretics
  - Other choices:
    - 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

Management challenges

Other choices:
- Hydralazine and others

Management challenges

Antithrombotic drug in the HDP in Canada (including proteinuric preeclampsia):
- Labetalol: easy to titrate, other betablockers OK (avoid atenolol)
- Nifedipine: outside pregnancy, first choice in proteinuric nephrotic range proteinuria during pregnancy
- Methyldopa: already anemic, beware of hemolytic anemia and warm antibodies

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- Hydralazine and others
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

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)

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

Vitamin D deficiency

Various regimens
- For severe deficiency (level <50)
  - 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)

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

Acute kidney injury

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
  - Captopril, enalapril, spironolactone compatible with breastfeeding

Thrombotic risk
- LMWH vs UFH vs Coumadin

Postpartum management

Clinical issues
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
- Multidisciplinary approach necessary to optimise both maternal and fetal care and outcomes

Postpartum management

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

Questions

Causes of Proteinuria

Other causes of proteinuria

Renal diseases

- Reflux nephropathy, congenital anomalies, polycystic kidney disease, interstitial nephritis
- Transient causes
  - exercise, fever/sepsis, congestive cardiac disease, subarachnoid/intracranial hemorrhage, seizures

Causes of Proteinuria

Glomerular diseases

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

Causes of Proteinuria

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)

Assessment of Proteinuria

Questionnaire

Birth

- Birth weight / Prematurity / Perinatal complications
- Infancy and childhood
  - urinary tract infections / vesicoureteral reflux
  - previous urinary tract investigations
- Myopia
- Childhood GN
  - e.g. post-infectious GN, Henoch-Schönlein purpura, minimal change
- Familial history of renal diseases

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
**Assessment of Proteinuria**

**Physical examination**

Vitals: Blood pressure, heart rate, O₂ 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

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, P, 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

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, clinical and balance of risks of procedure and maternal-fetal risks/benefits ratio of diagnosis