Renal Disease in Pregnancy

Darren Farley, MD
Clinical Assistant Professor
Division of Maternal-Fetal Medicine
Dept. of Obstetrics and Gynecology
University of Kansas School of Medicine – Wichita
Objectives

- Physiology
- Pregnancy outcomes
- Specific diseases
- Dialysis
- Transplant patients
- PKD
Physiologic changes - Renal
Normal pregnancy renal physiology

- **Effective renal plasma flow**
  - Rises 75% over nonpregnant levels by 16 weeks gestation; maintained until 34 weeks gestation, then declines by 25%

- **Glomerular filtration rate (GFR)**
  - Measured by inulin clearance
  - Increases by 5-7 weeks to 50% above nonpregnant levels by end of first trimester and this is maintained t/o pregnancy
  - 3 months PP goes to normal

- **ERPF/GFR** = filtration fraction falls from nonpregnant levels until late 3rd trimester (due to ERPF increasing more than GFR in early pregnancy)
  - Nonpregnant values of 20-21%
Normal pregnancy renal physiology

• GFR = endogenous creatinine clearance
  – Normal in pregnancy to be increased to 150-200 mL/min (nonpregnant 120 mL/min)
  – Reliable predictor of renal function provided complete urine collection is taken during a specific time period

• BUN
  – Decreases from 12 to 9 mg/dL (14 mg/dL is suggestive of underlying pathology)

• Creatinine
  – Decreases from 0.7 to 0.5 mg/dL (0.9 is suggestive of underlying renal impairment)

• BUN, Cr will likely not be elevated even with severe proteinuria
Normal pregnancy renal physiology

- Serum uric acid
  - Declines in early pregnancy
  - Nadir 2-3 mg/dL at 24 weeks after which rise until the end of pregnancy (close to nonpregnant values)
  - Rise is caused by increased renal tubular absorption of urate
  - ? Diagnostic value in preeclampsia

- Urine protein excretion
  - Increases from nonpreg values of 60-90 mg/24 hrs to 180-250 mg/24 hrs in 3rd trimester
  - Absorption of filtered protein in proximal tubule is reduced
  - Screening method – urine dipstick
    - 1+ ~ 30mg/dL ~ 300mg/24 hr
  - 24 hr urine does not change much trimester to trimester (Higby et al)
  - Abnormal when >300mg/24 hr period
  - 20 weeks as cutoff for determining if underlying renal impairment or pregnancy related

- Preexisting proteinuria tends to increase in 2nd and 3rd trimesters
  - Study of pts with diabetic nephropathy
    - Amount of proteinuria increased from mean of 1.74 g/24 hr to 4.82 g/24 hr irrespective of presence of pre-eclampsia
Creatinine clearance (CrCl)

- Estimation of glomerular filtration rate
- \( \text{GFR} = \text{CrCl} \) (assumptions in notes)
  - \( \text{GFR} \times \text{SCr} = \text{UCr} \times V \)
  - \( \text{GFR} = \frac{\text{UCr} \times V}{\text{SCr}} \)
  - \( \text{CrCl} = \frac{\text{UCr} (\text{mg/dL}) \times \text{vol}(\text{urine flow rate per unit time L/day})}{\text{SCr} (\text{mg/dL})} \)
  - Collection for 24hrs, multiply above by 1000 to convert to mL and divide by 1440 (minutes in a day) = mL/min
  - \( \text{CrCl} = \left\{ \frac{\text{UCr} (\text{mg/dL}) \times \text{vol}(\text{L/day})}{\text{SCr} (\text{mg/dL})} \right\} \times 1000 \div 1440 \)
  - Adjust to body surface area
    - As an example, a creatinine clearance of 70 mL/min in a small woman with a weight and height of 50 kg and 160 cm, who has a BSA of 1.5 kg/m², is corrected to a body surface area of 1.73 m² as follows:
      - \( \text{CCr} \times 1.73/\text{BSA} = \frac{[70 \text{ mL/min} \times 1.73]}{1.5} = 80 \text{ mL/min per 1.73 m²} \)
Urine protein/creatinine ratio

- <0.3 – Per ACOG – predicts low chance of proteinuria (>300mg) in 24 hr collection; TP level not in criteria for diagnosis of severe preeclampsia

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**TABLE E-1. Diagnostic Criteria for Preeclampsia**

| Blood pressure | Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
|                | Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
| and            |

| Proteinuria    | Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection)
|                | or
|                | Protein/creatinine ratio greater than or equal to 0.3*
|                | Dipstick reading of 1+ (used only if other quantitative methods not available)

Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

| Thrombocytopenia | Platelet count less than 100,000/microliter
| Renal insufficiency | Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
| Impaired liver function | Elevated blood concentrations of liver transaminases to twice normal concentration
| Pulmonary edema | Cerebral or visual symptoms

*Each measured as mg/dL.
Glomerular filtration rate changes with pregnancy in normal women, those stable after unilateral nephrectomy, and those with a successful renal transplant. (Data from Newcastle-upon-Tyne, 1974–2006, courtesy of Dr. John Davison.)
Comparison of blood volume expansion in 44 normally pregnant women at term with 29 who had eclampsia; 10 with moderate chronic renal insufficiency (CRI)—serum creatinine 1.5 to 2.9 mg/dL; and 4 with severe CRI—serum creatinine ≥3.0 mg/dL. (Data from Zeeman and colleagues, 2009, and Cunningham and associates, 1990.)
Chronic Renal Insufficiency and Pregnancy Outcomes (vs serum creatinine mg/dL)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
<th>Cr 1.5-3</th>
<th>Cr &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>13%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5%</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>IUGR</td>
<td>10%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Abortion</td>
<td>11%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Surviving infants</td>
<td>84%</td>
<td>62%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Queenan 2007, Williams Obstetrics
Birthweight percentiles of infants born to 29 women at Parkland Hospital with mild to moderate renal insufficiency—serum creatinine 1.4–2.4 mg/dL (black points) and severe renal insufficiency—serum creatinine ≥2.5 mg/dL (red points). (Data are from Cunningham and colleagues, 1990; and Stettler and Cunningham, 1992. Growth curves are those reported by Alexander and co-workers, 1996.)
Renal Disease

- Diabetic Nephropathy
- Nephrotic syndrome
- Lupus Nephritis
- Glomerulonephritis
Periarteritis Nodosa

- In contrast to lupus nephritis, the outcome of pregnancy in women with renal involvement as a result of periarteritis nodosa is very poor, largely because of the associated hypertension, which frequently is malignant. Many cases in the literature have involved maternal demise. However, this dismal prognosis is based primarily on selected anecdotal studies, and a few successful pregnancies have been reported. Still, until more data are available (perhaps through a registry), consideration of early therapeutic termination must be made in the best interests of maternal health.
Periarteritis Nodosa

Multiple aneurysms of renal vessels in Polyarteritis

Diabetic Nephropathy
Diabetic nephropathy

• Diagnosis
  – White classification - >500mg /24hr – Class F
  – Macroalbuminuria (>300mg/24 hours) – Cleveland Clinic
  – Abnormal renal function as represented by an abnormality in serum creatinine, CrCl, GFR
  – Increase in proteinuria and decline in GFR, hypertension, and a high risk of CV morbidity and mortality

• ADA 2009 - Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD).
  – Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes.
  – Microalbuminuria is also a well-established marker of increased CVD risk.
  – Patients with microalbuminuria who progress to macroalbuminuria (300 mg/24 h) are likely to progress to ESRD
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis. Courtesy of Helmut Rennke, MD.

Advanced nephropathy

Normal glomerulus

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows). Courtesy of Helmut G Rennke.
Diabetic nephropathy

- **Management**
  - Optimizing glucose control
  - Renoprotective medications – diltiazem, nifedipine, amlodipine
    - CI – Right heart failure
  - If also chronic hypertensive –
    - BP goals – <140/90
    - 110-129/65-79 (ADA, 2009)
  - Monitoring for preeclampsia
  - Fetal surveillance
  - Ophthalmic surveillance
Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial lupus&lt;br&gt;Normal glomeruli by LM but mesangial immune deposits by IF</td>
</tr>
<tr>
<td>Class II</td>
<td>Mesangial proliferative lupus nephritis&lt;br&gt;Purely mesangial hypercellularity of any degree or mesangial matrix expansion on LM with mesangial immune deposits. A few subendothelial or subepithelial deposits may be visible by IF or EM but not by LM.</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal lupus nephritis&lt;br&gt;III (A) - Active or inactive, segmental or global, endo or extracapillary&lt;br&gt;III (A/C) - Glomerulonephritis involving &lt;50% of all glomeruli typically with focal&lt;br&gt;III (C) - Subendothelial deposits with or without mesangial alterations. Active lesions: focal proliferative lupus nephritis Active and chronic lesions: focal proliferative and sclerosing lupus nephritis Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse lupus nephritis&lt;br&gt;IV-S (A) - Active lesions: diffuse segmental proliferative lupus nephritis&lt;br&gt;IV-G (A) - Active lesions: diffuse global proliferative lupus nephritis&lt;br&gt;IV-S (A/C) - Active and chronic lesions: diffuse segmental proliferative &amp; sclerosing lupus nephritis&lt;br&gt;IV-G (A/C) - Active and chronic lesions: diffuse global proliferative &amp; sclerosing lupus nephritis&lt;br&gt;IV-S (C) - Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis&lt;br&gt;IV-G (C) - Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous lupus nephritis&lt;br&gt;Global or segmental subepithelial immune deposits or crescent formation</td>
</tr>
</tbody>
</table>

Fig 5. Renal biopsy showing enlarged glomerulus displaying thickening of glomerular basement membrane and epimembranous spikes consistent with SLE WHO class V (PAS by LM, IF and EM with or without mesangial alterations. Class V lupus nephritis may occur with class III or IV in which case both will be diagnosed. Class V lupus nephritis may show advanced sclerosis. Advanced sclerotic lupus nephritis ≥ 90% glomeruli globally sclerosed without residual activity.  

GUPTA 2005 – Rheum association lupus nephritis classes

This section, in addition, complexity of specification of selective designation of segment or segment of previous or crescent is important.
Lupus nephritis

- Indications for a renal biopsy in nonpregnant SLE patients include:
  - Hematuria and proteinuria;
  - Renal dysfunction;
  - Hypertension;
  - Low levels of the complement factor C3;
  - The presence of chronic renal lesions;
  - Modifications in therapy: initiation, changes, or discontinuation.
Lupus nephritis (Foley ICU book)-Dr. Silver

- Preexisting renal disease
  - 50% of patients with SLE will develop renal disease
  - Results from immune complex deposition, complement activation, and inflammation of the kidney
  - Potential for permanent decrease in renal function after pregnancy with renal disease
    - Burkett 1985 – 242 pregns, 59% no change, 30% transient renal impairment, 7% permanent renal insufficiency
    - Serum creatinine of 1.5mg/dL; if greater – ‘correlation of deterioration of renal function during and after pregnancy’; if <1.5, pt can reassured that pregnancy will not increase the rate of deterioration of renal function; specific type of renal disease documented histologically does not appear to influence pregnancy outcome or renal function
Lupus nephritis (Silver – ICU book)

- Pt with severe nephritis may present with acute renal insufficiency
  - DDX – preeclampsia, lupus flare, acute rejection (if transplanted kidney) – may require renal biopsy
  - Frequently respond to glucocorticoids (prednisone 1mg/kg/d)
  - If proliferative nephritis – may require cyclophosphamide
  - If not responsive to medical therapy, serum cr >3.5mg/dL, dialysis should be started to optimize pregnancy outcome
Glomerular and interstitial nephritis (e.g. lupus nephritis)

• Management
  – Baseline labs – 24 hr urine analysis; metabolic profile/serum creatinine, CBC,
  – If also chronic hypertensive –
    • BP goals – <140/90
  – Monitoring for preeclampsia
  – Fetal surveillance
  – Renoprotective medications – diltiazem, nifedipine, amlodipine; No ACE inhibitors, ARBS
## Lupus Flare vs. Preeclampsia

<table>
<thead>
<tr>
<th>Finding/test</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased anti-ds DNA Ab</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III decreased</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia (Ab screen -)</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia (Ab screen +)</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Renal Biopsies in Pregnancy

• Complications -
  – Hematoma formation
  – Bleeding
  – Death

• Usually does not help change management

• If steroids are the change in management, then steroid administration is of lower risk than a renal biopsy
Renal Biopsy

• **Risks in pregnancy**
  – Hematoma formation
  – Renal dysfunction

• **Lupus Nephritis**
  – Increased mesangial matrix and mesangial hypercellularity (increased leukocytes)

• **Preeclampsia - Endotheliosis**
Renal biopsy in pregnancy – N=18, Kuller 2001

- Objective: Our aim was to review our experience with renal biopsy in pregnancy. Study Design: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case. Results: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosi confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy. Conclusion: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term. (Am J Obstet Gynecol 2001;184:1093-6.)
Renal Biopsy

- **Preeclampsia**
  - A – endothelial swelling
  - B – Glomerular necrosis
  - C – sloughing of tubular epithelial cells
A – Normal kidney
B – Endotheliosis, C – electron micrograph of B
http://www.nature.com/ki/journal/v67/n6/fig_tab/4495287f2.html
Lupus Nephritis

Figure 1. Glomerular tuft with proliferation of mesangial cells, segments with endocapillary proliferation, and a small circumscribed crescent (arrow). In lupus nephritis active proliferation and glomerular changes are frequently segmental; nevertheless, to determine if it is class III (focal) or IV (diffuse) it is necessary to quantify the percentage of glomeruli with lesions

http://www.kidneypathology.com/English_version/Lupus_nephritis.html
Uterine Artery Notching – Present in Preeclampsia
Dialysis
Indications for dialysis (in pregnancy)

- AEIOU (acidosis, electrolytes, Intox, overload/volume, uremia)
- Clinical evidence of uremia (pericarditis, encephalopathy, metabolic, neurologic, GI, cardiac – arrhythmias)
  - BUN > 50-70mg/dL (lower than for nonpreg)
  - Serum creatinine >6-7mg/dL (lower than for nonpreg)
- Volume overload - Intractable intravascular volume overload (despite diuresis)
- Hyperkalemia (>5.0) or severe acidosis (<7.2) resistant to conservative measures
- Above Conditions not responsive to conservative measures
• Modes
  – Hemodialysis
  – Peritoneal dialysis
    • Continuous ambulatory PD
    • Continuous cycling PD
    • Nocturnal intermittent PD
Dialysis — p191 CC OB 4th ed (Gail Seiken)

• Advantage in pregnancy of
  – Hemodialysis – less work intensive for patient
    • No risk if peritoneal catheter-related complications
      (laceration of uterine vessels, infection, peritonitis, PTL, but
      PTL is also observed in HD pts)
    • No interruption in therapy needed after Csection
  – Peritoneal Dialysis – stable biochemical environment
    • Continuous fluid removal avoids hypotension
    • Allows liberal fluid intake
    • Permits continuous insulin administration in DM
    • No anticoagulation needed
    • Permits administration of intraperitoneal MgSO4 in pree
      (ideally better steady state, but still IV bolusing and rates in
      patients with renal failure is typically needed)
    • HTN easier to control; Less severe anemia
Dialysis – p191 CC OB 4th ed (Gail Seiken)

• Mode of dialysis and fetal outcome
  – Initially improved with peritoneal
  – National Registry for pregnancy in Dialysis pts
    • N=184; ~40% HD and 40% PD – identical fetal survival rates (Okundaye 1998)
  – Chou – 2008 – Preg outcome –
    • Avg GA of delivery – 31 wks
    • HD – 70% success ; PD 64.2% success
    • BW not different
• Intensive dialysis
  – Daily dialysis in pregnancy to minimize fetal exposure to uremic toxins and improve outcome
  – NPDR – infant survival 73% in women needed to start dialysis in pregnancy vs being dialyzed at the beginning (40%)
  – Initiate dialysis at BUN 60-70mg/dL and creatinine of 6-7mg/dL with goal of BUN <50, cr <5
    • Fetal urea production 540mg/d in 3rd trim
    • HD – daily – 5+ hours /day
    • Best outcomes if >20+ hours of dialysis weekly
    • Low level of azotemia prevents hydramnios, PTL – based on urea diuresis that normally occurs in utero due to high fetal BUN
  – Avoids large dialytic weight gains and fluid shifts and labile BPs, less hypotension, also better HTN control
Dialysis in pregnancy  (CCOB 4th ed)

- Maternal – Fetal complications
  - Accelerated decline in renal function – 1/3 (Imbasciata 1991, n=80pt)
  - Accelerated HTN – 50%
  - Superimposed preeclampsia – 60% (Cunningham 1990, n=37)
  - PTL
  - Worsening anemia
  - HD access thrombosis
  - Placental abruption
  - Pregnancy loss – 50%
  - PTB - >90%
  - IUGR – 20%
  - Polyhydramnios
• Fetal monitoring? - Before and after?
  – Uptodate – ‘Careful uterine and fetal monitoring during hemodialysis, such as assessment of the fetal heart rate (particularly during the last portion of a session), combined with measures aimed at preventing dialysis-induced hypotension should be performed. Maternal hemodynamic instability may compromise the uteroplacental circulation and may be associated with the induction of uterine contractions’
  – Continuous if initiating dialysis after 24 weeks
  – NSTs after dialysis once on schedule
  – Serial growth scans q 4 weeks
• **Mode of delivery – CD for obstetric indications**
  – If CD performed and peritoneal dialysis is mode – will need to interrupt dialysis regimen to allow healing or switch to HD temporarily
Anemia –
- Deficient EPO production, short red cell survival, bone marrow suppression by uremia toxins
- Iron supplementation oral, IV if persistent deficiency
- EPO – if refractory anemia and HCT <18-21%
- Caution re: HTN
- Transfusion for fetal behalf at HCT <18% (ACOG)
  - increased perinatal mortality and maternal morbidity secondary to high output cardiac failure
Dialysis

• Diet –
  – Protein – 1g/kg/d HD; 1.5 for PD; add 20g/d for pregnancy
  – Prenatal vitamin with minimal or no vitamin A - Rx, consult with Pharmacist
  – Folic acid 2mg/d
Table 48-4. Pregnancy Outcomes in 118 Women Undergoing Dialysis during Pregnancy – Willams - Textbook

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Delivery (wks)</th>
<th>Birthweight (g)</th>
<th>HTN</th>
<th>Hydramnios</th>
<th>Perinatal Mortality</th>
<th>Surviving Infants</th>
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</thead>
<tbody>
<tr>
<td>Toma et al (1999)</td>
<td>54</td>
<td>31.9</td>
<td>1545</td>
<td>35</td>
<td>44</td>
<td>33</td>
<td>67</td>
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<tr>
<td>Chao et al (2002)</td>
<td>13</td>
<td>32</td>
<td>1540</td>
<td>72</td>
<td>46</td>
<td>31</td>
<td>69</td>
</tr>
<tr>
<td>Chou et al (2008)</td>
<td>13</td>
<td>30.8</td>
<td>1510</td>
<td>57</td>
<td>71</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Approximate averages</td>
<td>118</td>
<td>31–32</td>
<td>1500</td>
<td>40–50</td>
<td>40</td>
<td>25–30</td>
<td>70–80</td>
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</tbody>
</table>
Pregnancy after Kidney Transplant
Renal transplantation — CC OB 4th ed J Scott

- 1 in 20 women of childbearing age with a functioning renal allograft becomes pregnant, >10,000 pregnancies have occurred
- Ideal if serum creatinine is <1.5mg/dL
- Risks of deterioration of renal function, rejection, maternal death; no direct evidence that pregnancy has a deleterious effect on the transplanted kidney
- Risk of graft rejection and permanent renal dysfunction is 10-20% (same for nonpregnant pt)
- Signs of rejection – fever, oliguria, deteriorating renal function, enlargement of kidney, tenderness to palpation - need to rule out infection, preeclampsia, glomerulonephritis, nephrotoxicity from immunosuppressant meds
- Risks of PTB, IUGR, fetal death – from CHTN, pree
- BP goal <140/90, ACE inhib good, but not in pregnancy, CCB (nifedipine) help counter vasoconstrictive effect of cyclosporine
Optimal pregnancy outcome – prognostic factors  


- 1-2 years since transplant
- Good general health and prognosis
- Satisfactory graft function with no evidence of rejection
- Stable immunosuppressive regimen
- No/minimal HTN or proteinuria
- Serum cr <1.5-2mg/dL
- Family support
Immunosuppressants in transplant pt (Scott CC OB)

• All drugs cross placenta, diffuse to fetus
• No convincing evidence that prednisone, azathioprine, cyclosporine, tacrolimus produce congenital abnormalities;
• Drugs of choice in preg transplant pts
• A/e IUGR, PTB, o/w neonates do well
  – Short term ‘prematurity issues of infection, hypoglycemia, bone marrow hypoplasia, leukopenia, reduced IGM, IGG, elevated serum cr’ hard to know if it’s the drug or prematurity
• Long term – poss infertility, autoimmune disease, neoplasia – need for long term f/u
Immunosuppressants
Azathioprine
per Dr. Scott in CC in OB book 4th ed

• Azathioprine – MOA – inhibits T-lymphocytes; D
  – More toxic metabolite 6-mercaptopurine- purine analog that decreases delayed hypersensitivity and cellular cytotoxicity
  – A/e – infection, neoplasia, liver tox, bone marrow suppression
  – 64-90% of azathioprine crosses the placenta, majority if inactive thiouric acid
  – D b/c increased anomaly rate of 9 and 6.4%, not found in recent series, no specific pattern, possible bone marrow suppression in fetus, with anemia, leukopenia, thrombocytopenia
  – One approach – titrate to normal WBC counts in preg
Immunosuppressants

per Dr. Scott in CC in OB book 4th ed

- **Tacrolimus** – MOA – inhibits T-lymphocytes; C
  - FK506 – macrolide abx from streptomyces;
  - Incidence of post transplant DM with tacrolimus is 11-20%; median time to onset is 68d; 50% reversible
  - Nephrotoxicity, hyperkalemia in 1/3; HA, tremor, motor fxn, sensory fxn are neuro a/e
  - Cord blood concentrations 50% of maternal levels, no proven association with anomalies to date
Immunosuppressants - Cyclosporine per Dr. Scott in CC in OB book 4th ed

- Cyclosporine – MOA – inhibits T-lymphocytes; C
  - Fungal metabolite, inhibits Tcell response by inhibiting IL2
  - Improved survival in transplant pt, in most regimen
  - a/e – nephrotoxicity, HTN; others hirsutism, tremor, gingival hyperplasia, hepatotoxicity, risk of lymphomas
  - Cyclosporine levels drop in pregnancy, but graft function remains stable in most pts (Bumgardner Matas 1992)
  - Readily crosses placenta, no evidence of teratogenicity
Immunosuppressants - prednisone

- Prednisone- IV used to tx acute rejection reactions
  - MOA – inhibit humoral and cell mediated immune response
  - a/e – glucose intolerance, PPROM, hirsutism, acne, wt gain, cushinoid appearance, striae, osteonecrosis, osteoporosis, fluid retention, HTN, infection, impaired wound healing, mood changes
  - Metabolized by placental 11-hydroxygenase to inactive 11-keto form – fetus is exposed to 10% of maternal dose
  - Dose – 10-30mg/d
  - A/e preg – poss PPROM, PTB, pree, IUGR
  - Prolonged courses of fluorinated steroids (dexa, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob
  - Stress dosing at delivery
Immunosuppressants-
Cyclophosphamide per Dr. Scott in CC in OB book 4th ed

- Cyclophosphamide – MOA – alkylating agent; D
  - cancer chemotherapy and as an immunosuppressant
  - In human pregnancies, cyclophosphamide exposures that occurred during the first trimester have been associated with skeletal and palate defects, as well as malformations of the limbs and eyes
  - Cyclophosphamide is excreted into human milk (34). Two reports indicates that the platelet and leukocyte counts of a nursing infants were reversibly depressed during maternal cyclophosphamide therapy (35, 48). Cyclophosphamide was classified among the cytotoxic drugs that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics (36).
Renal Biopsies in Pregnancy

• Complications -
  – Hematoma formation
  – Bleeding
  – Death

• Usually does not help change management

• If steroids are the change in management, then steroid administration is of lower risk than a renal biopsy
PKD
Polycystic Kidney Disease

• AD disease of kidneys
• 1 in 800 live births
• Cause of 10 % of end-stage renal disease in the United States
• 85% due to *PKD1* gene mutations (C16)
• 15% due to *PKD2* (C4), Salant 2008
• Variable penetrance and expressivity
• PNDX possible if mutation is known (family member or linkage studies)
PKD

• Renal complications M>F, 20s and 30s
• HTN in 75%
• Flank pain, hematuria, nocturia, proteinuria, calculi, infection, progression to renal failure, superimposed acute renal failure may also develop from infection or obstruction from ureteral angulation by cyst displacement
• Other organs –
  – Hepatic (F>M), 1/3 of patients
  – Cardiac – Valve lesions, mitral, aortic, and tricuspid incompetence
  – CNS – 10% of patients with PKD die from rupture of associated intracranial berry aneurysm
PKD

• Pregnancy
• Pregnancy outcome depends on the degree of associated hypertension and renal insufficiency.
• UTIs are common
• Chapman -1994
  – 235 affected women, 605 pregnancies vs 108 unaffected family members, 244 pregnancies
  – Composite perinatal complication rates were similar—33 versus 26 percent—but hypertension, including preeclampsia, was more common in women with polycystic kidneys.
• Pregnancy does not seem to accelerate the natural disease course (Lindheimer and colleagues, 2007).
PKD
Take home points

• CCBs for HTN in renal patients (DM, Lupus)
• PKD – check head MRI, echo; GHR
• Dialysis – Outcomes similar re: mode, extra folic acid, increase dialysis time
• Transplant – Outcomes better >2yr of Cr <1.5, on immunosuppressants, no HTN, no rejection
• Polyarteritis nodosa – CI to pregnancy
End

- References available on request
- See specific slides
Indications for PA Catheter in Hypertensive Disease

- Severe preeclampsia with refractory oliguria or pulmonary edema
- Ineffective IV antihypertensive therapy
- Intraoperative or intrapartum cardiac failure
- Significant cardiac disease
Pulmonary Edema in Preeclampsia – 3 subsets

- Management
  - Intravascular volume depletion (oliguria), low PCWP, high CO, high SVR, low CVP –
    • Fluids
  - Renal Vasoconstriction (High PCWP, Normal CO and SVR, uroconcentration):
    • Dopamine – 1-5µg/kg/min; furosemide
  - LV Dysfunction/Failure with Vasospasm (high PCWP, high SVR, low CO <5 L/min, NL-high CVP):
    • Needs Afterload Reduction (Sodium nitroprusside 0.25-0.5µg/kg/min IV infusion)
    • Digoxin, Volume Restriction
    • Diuretics (max acute dose of furosemide is 120mg, start with 20-40mg)
  - Mechanical Ventilation for Respiratory Failure (If still Pregnant, Intubate Early rather than Late)
Renal transplantation — CC OB 4th ed J Scott

• 1 in 20 women of childbearing age with a functioning renal allograft becomes pregnant, >10,000 pregnancies have occurred
• Ideal if serum creatinine is <1.5mg/dL
• Risks of deterioration of renal function, rejection, maternal death; no direct evidence that pregnancy has a deleterious effect on the transplanted kidney
• Risk of graft rejection and permanent renal dysfunction is 10-20% (same for nonpregnant pt)
• Signs of rejection – fever, oliguria, deteriorating renal function, enlargement of kidney, tenderness to palpation - need to rule out infection, preeclampsia, glomerulonephritis, nephrotoxicity from immunosuppressant meds
• Risks of PTB, IUGR, fetal death – from CHTN, pree
• BP goal <140/90, ACE inhib good, but not in pregnancy, CCB (nifedipine) help counter vasoconstrictive effect of cyclosporine
Prenatal care in allograft recipients

• PRENATAL care – close surveillance for allograft rejection, infection, HTN, anemia, preeclampsia, fetal growth, monitoring for UTIs (esp in kidney transplant); Asx bacteruria tx for 2 weeks with f/u cultures, poss suppression doses
  – Other infections of note – bacterial/fungal endometritis, wound infection, skin abscesses, pneumonia (aspergillus, Pneumocystis, Mycobacterium TB, listeria)
  – Poss for Rh sens from graft;
  – CMV infection (usually ppx 3 mo after transplant, poss primary or recurrent CMV can cause congenital infection)
  – HBV, HCB – HBIG, HBV vaccine to newborn are 90% effective at preventing chronic HBV hepatitis
  – ACV for HSV
Dialysis – p191 CC OB 4th ed (Gail Seiken)

• Dialysis changes
  – Less Na taken off due to hyponatremia of preg; less HCO3 to avoid untoward alkalosis that exists in pregnancy
  – No acetate dialysis b/c of hypotension?
  – Monitor K and Ca to avoid hypokalemia and hypercalcemia (b/c of placental calcitriol increasing the absorption of calcium for fetal stores)
Below are long version slide sets
MFM Rounds
Question sessions, ABOG/oral board vignettes, PBL

Darren Farley, MD
Clinical Assistant Professor
Division of Maternal-Fetal Medicine
Dept. of Obstetrics and Gynecology
University of Kansas School of Medicine – Wichita
Objectives for Resident Sessions

- Review of Medical complication of pregnancy, notes Precis, ACOG bulletins, when applicable
- 1-2 residents present cases/oral exam format, if no cases, provide cases from resources
- Quiz (Williams test bank) last 10min, then residents grade, results tabulate
- Follow up
Renal Disease in Pregnancy

- October 22, 2014
Physiologic changes - Renal
Normal pregnancy renal physiology

- **Effective renal plasma flow**
  - Rises 75% over nonpregnant levels by 16 weeks gestation; maintained until 34 weeks gestation, then declines by 25%

- **Glomerular filtration rate (GFR)**
  - Measured by inulin clearance
  - Increases by 5-7 weeks to 50% above nonpregnant levels by end of first trimester and this is maintained t/o pregnancy
  - 3 months PP goes to normal

- **ERPF/GFR = filtration fraction falls from nonpregnant levels until late 3rd trimester (due to ERPF increasing more than GFR in early pregnancy)**
  - Nonpregnant values of 20-21%
Normal pregnancy renal physiology

• GFR = endogenous creatinine clearance
  – Normal in pregnancy to be increased to 150-200 mL/min (nonpregnant 120 mL/min)
  – Reliable predictor of renal function provided complete urine collection is taken during a specific time period

• BUN
  – Decreases from 12 to 9 mg/dL (14 mg/dL is suggestive of underlying pathology)

• Creatinine
  – Decreases from 0.7 to 0.5 mg/dL (0.9 is suggestive of underlying renal impairment)

• BUN, Cr will likely not be elevated even with severe proteinuria
Normal pregnancy renal physiology

- **Serum uric acid**
  - Declines in early pregnancy
  - Nadir 2-3 mg/dL at 24 weeks after which rise until the end of pregnancy (close to nonpregnant values)
  - Rise is caused by increased renal tubular absorption of urate
  - ? Diagnostic value in preeclampsia

- **Urine protein excretion**
  - Increases from nonpreg values of 60-90 mg/24 hrs to 180-250 mg/24 hrs in 3rd trimester
  - Absorption of filtered protein in proximal tubule is reduced
  - Screening method – urine dipstick
    - 1+ ~ 30mg/dL ~ 300mg/24 hr
  - 24 hr urine does not change much trimester to trimester (Higby et al)
  - Abnormal when >300mg/24 hr period
  - 20 weeks as cutoff for determining if underlying renal impairment or pregnancy related

- **Preexisting proteinuria tends to increase in 2nd and 3rd trimesters**
  - Study of pts with diabetic nephropathy
    - Amount of proteinuria increased from mean of 1.74 g/24 hr to 4.82 g/24 hr irrespective of presence of pre-eclampsia
Creatinine clearance (CrCl)

- Estimation of glomerular filtration rate
- \( \text{GFR} = \text{CrCl} \) (assumptions in notes)
  - \( \text{GFR} \times \text{SCr} = \text{UCr} \times V \)
  - \( \text{GFR} = \frac{\text{UCr} \times V}{\text{SCr}} \)
  - \( \text{CrCl} = \frac{\text{UCr}(\text{mg/dL}) \times \text{vol}(\text{urine flow rate per unit time L/day})}{\text{SCr}(\text{mg/dL})} \)
  - Collection for 24hrs, multiply above by 1000 to convert to mL and divide by 1440 (minutes in a day) = mL/min
  - \( \text{CrCl} = \frac{\{\text{UCr}(\text{mg/dL}) \times \text{vol}(L/day) / \text{SCr}(\text{mg/dL})\} \times 1000}{1440} \)
  - Adjust to body surface area
    - As an example, a creatinine clearance of 70 mL/min in a small woman with a weight and height of 50 kg and 160 cm, who has a BSA of 1.5 kg/m2, is corrected to a body surface area of 1.73 m2 as follows:
      - \( \text{CCr} \times 1.73/\text{BSA} = \frac{[70 \text{ mL/min} \times 1.73]}{1.5} = 80 \text{ mL/min per 1.73 m2} \)
Legend:
Glomerular filtration rate changes with pregnancy in normal women, those stable after unilateral nephrectomy, and those with a successful renal transplant. (Data from Newcastle-upon-Tyne, 1974–2006, courtesy of Dr. John Davison.)
Comparison of blood volume expansion in 44 normally pregnant women at term with 29 who had eclampsia; 10 with moderate chronic renal insufficiency (CRI)—serum creatinine 1.5 to 2.9 mg/dL; and 4 with severe CRI—serum creatinine ≥3.0 mg/dL. (Data from Zeeman and colleagues, 2009, and Cunningham and associates, 1990.)
Chronic Renal Insufficiency and Pregnancy Outcomes (vs serum creatinine mg/dL)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
<th>Cr 1.5-3</th>
<th>Cr &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>13%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5%</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>IUGR</td>
<td>10%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Abortion</td>
<td>11%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Surviving infants</td>
<td>84%</td>
<td>62%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Queenan 2007
Diabetic nephropathy

- Diagnosis
  - White classification - >500mg /24hr
  - Macroalbuminuria (300mg/24 hours) – cleveland clinic def
    - http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/diabetic-nephropathy/#cesec1
  - Abnormal renal function as represented by an abnormality in serum creatinine, CrCl, GFR
  - ‘clinically – diabetic nephropathy is characterized by a progressive increase in proteinuria and decline in GFR, hypertension, and a high risk of CV morbidity and mortality

- ADA 2009 - Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD).
  - Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes.
  - Microalbuminuria is also a well-established marker of increased CVD risk.
  - Patients with microalbuminuria who progress to macroalbuminuria (300 mg/24 h) are likely to progress to ESRD

- Landon 2007 – 30-299mg/ 24hr (incipient nephropathy ‘pre’); overt = 500mg/24 hr ;–
Glucose + NH₂-R $\rightarrow_{K_1}$ Schiff base $\rightarrow_{K_2}$ Amadori product $\rightarrow_{K_n}$ Intermediate glycosylation products $\rightarrow_{K_2}$ Advanced glycosylation endproducts
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis. Courtesy of Helmut Rennke, MD.

Advanced nephropathy

Normal glomerulus

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows). Courtesy of Helmut G Rennke
Diabetic nephropathy

• Management
  – Optimizing glucose control
  – Renoprotective medications – diltiazem, nifedipine, amlodipine
  – If also chronic hypertensive –
    • BP goals – 110-129/65-79 (ADA, 2009)
  – Monitoring for preeclampsia
  – Fetal surveillance
  – Ophthalmic surveillance
Glomerular and interstitial nephritis (e.g. lupus nephritis)

- Diagnosis (Gupta 2005)
  - WHO classifications 1974, 1982, ; 2005 Gupta review
  - Morphological diagnosis – 6 levels of classification; latest study from 2005
  - Level of proteinuria and serum creatinine - used more to follow progression

- LN is thus divided into 6 classes according to severity of the lesions observed\(^{16}\): (Mariani 2004 from renal pathology society working group conf in 2002)
  - Class I, minimal mesangial LN;
  - Class II, mesangial proliferative LN;
  - Class III, focal LN;
  - Class IV, diffuse segmental LN;
  - Class V, membranous LN; and
  - Class VI, advanced sclerosing LN.
Lupus Nephritis

Table 1. WHO 1974 Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Normal glomeruli by LM, IF, EM</td>
</tr>
<tr>
<td>Class II</td>
<td>Purely mesangial disease</td>
</tr>
<tr>
<td>IIa</td>
<td>Normocellular mesangium by LM but mesangial deposits on IF and EM</td>
</tr>
<tr>
<td>IIb</td>
<td>Mesangial hypercellularity with mesangial deposits by IF or EM</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal proliferative glomerulonephritis (&lt;50%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse proliferative glomerulonephritis (≥50%)</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous glomerulonephritis</td>
</tr>
</tbody>
</table>

and vascular lesions were also not included in this classification.

This classification was first modified in 1982 by International Study of Kidney Diseases in Children group\(^4,15\) (Table 2). In this classification, class I was subdivided into:

\[\text{Class Ia: Normal glomeruli by LM, IF, EM} \]
\[\text{Class Ib: Normal glomeruli by IF and EM, mesangial deposits by EM} \]
GUPTA 2005 – Rheum association lupus nephritis classes


<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial lupus</td>
</tr>
<tr>
<td></td>
<td>Normal glomeruli by LM but mesangial immune deposits by IF</td>
</tr>
<tr>
<td>Class II</td>
<td>Mesangial proliferative lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Purely mesangial hypercellularity of any degree or mesangial matrix expansion on LM with mesangial immune deposits. A few subendothelial or subepithelial deposits may be visible by IF or EM but not by LM.</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal lupus nephritis</td>
</tr>
<tr>
<td>III (A)</td>
<td>- Active or inactive, segmental or global, endo or extracapillary</td>
</tr>
<tr>
<td>III (A/C)</td>
<td>- Glomerulonephritis involving &lt;50% of all glomeruli typically with focal</td>
</tr>
<tr>
<td>III (C)</td>
<td>- Subendothelial deposits with or without mesangial alterations. Active lesions: focal proliferative lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Active and chronic lesions: focal proliferative and sclerosing lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse lupus nephritis</td>
</tr>
<tr>
<td>IV-S (A)</td>
<td>- Active lesions: diffuse segmental proliferative lupus nephritis</td>
</tr>
<tr>
<td>IV-G (A)</td>
<td>- Active lesions: diffuse global proliferative lupus nephritis</td>
</tr>
<tr>
<td>IV-S (A/C)</td>
<td>- Active and chronic lesions: diffuse segmental proliferative &amp; sclerosing lupus nephritis</td>
</tr>
<tr>
<td>IV-G (A/C)</td>
<td>- Active and chronic lesions: diffuse global proliferative &amp; sclerosing lupus nephritis</td>
</tr>
<tr>
<td>IV-S (C)</td>
<td>- Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis</td>
</tr>
<tr>
<td>IV-G (C)</td>
<td>- Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Global or segmental subepithelial immune deposits or crescents</td>
</tr>
</tbody>
</table>

Fig 5. Renal biopsy showing enlarged glomerulus displaying thickening of glomerular basement membrane and epimembranous spikes consistent with SLE WHO class V (PAS)
Lupus nephritis

- Indications for a renal biopsy in nonpregnant SLE patients include:
  - Hematuria and proteinuria;
  - Renal dysfunction;
  - Hypertension;
  - Low levels of the complement factor C3;
  - The presence of chronic renal lesions;
  - Modifications in therapy: initiation, changes, or discontinuation.
Lupus nephritis (Foley ICU book)-Dr. Silver

• Preexisting renal disease
  – 50% of patients with SLE will develop renal disease
  – Results from immune complex deposition, complement activation, and inflammation of the kidney
  – Potential for permanent decrease in renal function after pregnancy with renal disease
    • Burkett 1985 – 242 pregns, 59% no change, 30% transient renal impairment, 7% permanent renal insufficiency
    • Serum creatinine of 1.5mg/dL; if greater – ‘correlation of deterioration of renal function during and after pregnancy; if <1.5, pt can reassured that pregnancy will not increase the rate of deterioration of renal function; specific type of renal disease documented histologically does not appear to influence pregnancy outcome or renal function
Lupus nephritis (Silver – ICU book)

- Pt with severe nephritis may present with acute renal insufficiency
  - DDX – preeclampsia, lupus flare, acute rejection (if transplanted kidney) – may require renal biopsy
  - Frequently respond to glucocorticoids (prednisone 1mg/kg/d)
  - If proliferative nephritis – may require cyclophosphamide
  - If not responsive to medical therapy, serum cr >3.5mg/dL, dialysis should be started to optimize pregnancy outcome
Glomerular and interstitial nephritis (e.g. lupus nephritis)

• Management
  – Baseline labs – 24 hr urine analysis; metabolic profile/serum creatinine, CBC,
  – If also chronic hypertensive –
    • BP goals – 110-129/65-79 (ADA, 2009)
  – Monitoring for preeclampsia
  – Fetal surveillance
  – Renoprotective medications – diltiazem, nifedipine?
**Lab tests that may be used to distinguish preeclampsia from lupus flare** (Silver, ICU book)

<table>
<thead>
<tr>
<th>Lab test to differentiate lupus vs preeclampsia</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement levels</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased dsDNA</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Increased serum cr</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Objective: Our aim was to review our experience with renal biopsy in pregnancy. Study Design: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case. Results: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosi confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy. Conclusion: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term. (Am J Obstet Gynecol 2001;184:1093-6.)
# Lupus Flare vs. Preeclampsia

<table>
<thead>
<tr>
<th>Finding/test</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased anti-ds DNA Ab</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III decreased</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia (Ab screen -)</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia (Ab screen +)</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Uterine Artery Notching – Present in Preeclampsia
Indications for PA Catheter in Hypertensive Disease

- Severe preeclampsia with refractory oliguria or pulmonary edema
- Ineffective IV antihypertensive therapy
- Intraoperative or intrapartum cardiac failure
- Significant cardiac disease
Pulmonary Edema in Preeclampsia – 3 subsets

- Management
  - Intravascular volume depletion (oliguria), low PCWP, high CO, high SVR, low CVP –
    - fluids
  - Renal Vasoconstriction (High PCWP, Normal CO and SVR, uroconcentration):
    - Dopamine – 1-5µg/kg/min; furosemide
  - LV Dysfunction/Failure with Vasospasm (high PCWP, high SVR, low CO <5 L/min, NL-high CVP):
    - Needs Afterload Reduction (Sodium nitroprusside 0.25-0.5µg/kg/min IV infusion)
    - Volume Restriction
    - Diuretics (max acute dose of furosemide is 120mg, start with 20-40mg)
  - Mechanical Ventilation for Respiratory Failure (If still Pregnant, Intubate Early rather than Late)
Renal Biopsies in Pregnancy

• Complications -
  – Hematoma formation
  – Bleeding
  – Death

• Usually do not help change management

• If steroids are the change in management, then steroid administration is of lower risk than a renal biopsy
Renal Biopsy

- **Risks in pregnancy**
  - Hematoma formation
  - Renal dysfunction

- **Lupus Nephritis**
  - Increased mesangial matrix and mesangial hypercellularity (increased leukocytes)

- **Preeclampsia - Endotheliosis**
Renal Biopsy

- Preeclampsia
  - A – endothelial swelling
  - B – Glomerular necrosis
  - C – sloughing of tubular epithelial cells
<table>
<thead>
<tr>
<th>Diagnostic index</th>
<th>Prerenal azotemia</th>
<th>Ischemic intrinsic renal azotemia/ acute tubular necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENA (%)</td>
<td>&lt;1</td>
<td>&gt;1 -2 (1 = obstructive)</td>
</tr>
<tr>
<td>Urine Na conc (meq/L)</td>
<td>&lt;10 (&lt;20 CCOB 4th ed)</td>
<td>&gt;10 (&gt;40 CCOB)</td>
</tr>
<tr>
<td>Urine cr / plasma cr ratio</td>
<td>&gt;40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Urinary urea nitrogen / plasma urea nitrogen ratio</td>
<td>&gt;8`</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Urine spec gravity</td>
<td>&gt;1.018</td>
<td>&lt;1.012</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/Kg H20)</td>
<td>&gt;500</td>
<td>&lt;250-350</td>
</tr>
<tr>
<td>Plasma BUN/ cr ratio</td>
<td>&gt;20</td>
<td>&lt;10-15</td>
</tr>
<tr>
<td>Renal failure index (Una/Ucr/Pcr)</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Hyaline casts</td>
<td>Muddy brown granular casts</td>
</tr>
</tbody>
</table>

Urine indices used in the DDX of prerenal and Ischemic intrinsic renal disease/azotemia

Foley ICU book – Naegotte/Asrot – Urine indices used in the DDX
Acute and chronic renal failure

- Management
  - Establish etiology
  - Attempts to reverse or treat underlying process
  - Nephrology consultation
  - Supportive therapy
  - Correction of metabolic acidosis with bicarbonate or dialysis (p153 Foley ICU book)
  - Prevent hyperphosphatemia (diet restriction, calcium binders with meals)
  - Prevent hyperkalemia (avoid in diet, kayexalate – cation/exchange resin)
    - If associated ECG changes (peaked T waves) IV calcium gluconate (1gm); infusion of glucose/insulin; inhaled beta agonist; dialysis
  - Fluid balance !!
  - Dialysis (cr >3.5)
  - Control of HTN
  - Evaluation for preeclampsia, and continue basic principles to establish M-F wellbeing
Chronic Renal Insufficiency and Pregnancy Outcomes (expressed by serum creatinine mg/dL)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
<th>Cr 1.5-3</th>
<th>Cr &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>13%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5%</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>IUGR</td>
<td>10%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Abortion</td>
<td>11%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Surviving infants</td>
<td>84%</td>
<td>62%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Birthweight percentiles of infants born to 29 women at Parkland Hospital with mild to moderate renal insufficiency—serum creatinine 1.4–2.4 mg/dL (black points) and severe renal insufficiency—serum creatinine ≥2.5 mg/dL (red points). (Data are from Cunningham and colleagues, 1990; and Stettler and Cunningham, 1992. Growth curves are those reported by Alexander and co-workers, 1996.)
Indications for dialysis (in pregnancy)

- AEIOU (acidosis, electrolytes, Intox, overload/volume, uremia)
- Clinical evidence of uremia (pericarditis, encephalopathy, metabolic, neurologic, GI, cardiac – arrhythmias)
  - BUN > 50-70mg/dL (lower than for nonpreg)
  - Serum creatinine >6-7mg/dL (lower than for nonpreg)
- Volume overload - Intractable intravascular volume overload (despite diuresis)
- Hyperkalemia (>5.0) or severe acidosis (<7.2) resistant to conservative measures
- Above Conditions not responsive to conservative measures
Dialysis — p191 CC OB 4th ed (Gail Seiken)

• Needed for acute renal failure, ESRD, deterioration of chronic renal function, possible prophylactic dialysis
  – Pregnant women that have progressive loss of renal function represent ~20% of women undergoing dialysis (Hou 1999)

• In CRF – cutoff of GFR (24 hr urine CrCl gets <5-10ml/min hyperkalemia, metabolic acidosis, fluid overload, uremia is likely to develop (15ml/min in diabetics with end organ disease)
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- **Modes**
  - Hemodialysis
  - Peritoneal dialysis
    - Continuous ambulatory PD
    - Continuous cycling PD
    - Nocturnal intermittent PD
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- Advantage in pregnancy of
  - hemodialysis – less work intensive for patient
    - No risk if peritoneal catheter-related complications (laceration of uterine vessels, infection, peritonitis, PTL, but PTL is also observed in HD pts)
    - No interruption in therapy needed after Csection
  - Peritoneal D – stable biochemical environment
    - Continuous fluid removal avoids hypotension
    - Allows liberal fluid intake
    - Permits continuous insulin administration in DM
    - No anticoagulation needed
    - Permits administration of intraperitoneal MgSO4 in pree (ideally better steady state, but still IV bolusing and rates in patients with renal failure is typically needed)
    - HTN easier to control; Less severe anemia
Dialysis – p191 CC OB 4th ed (Gail Seiken)

- Mode of dialysis and fetal outcome
  - Initially improved with peritoneal
  - National Registry for pregnancy in Dialysis pts
    - N=184; ~40% HD and 40% PD – identical fetal survival rates (Okundaye 1998)
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- **Intensive dialysis**
  - Daily dialysis in pregnancy to minimize fetal exposure to uremic toxins and improve outcome
  - NPDR – infant survival 73% in women needed to start dialysis in pregnancy vs being dialyzed at the beginning (40%)
  - Initiate dialysis at BUN 60-70mg/dL and creatinine of 6-7mg/dL with goal of BUN <50, cr <5
    - Fetal urea production 540mg/d in 3rd trim
    - HD – daily – 5+ hours /day
    - Best outcomes if >20+ hours of dialysis weekly
    - Low level of azotemia prevents hydramnios, PTL – based on urea diuresis that normally occurs in utero due to high fetal BUN
  - Avoids large dialytic weight gains and fluid shifts and labile BPs, less hypotension, also better HTN control
Dialysis in pregnancy (CCOB 4th ed)

- Maternal – Fetal complications
  - Accelerated decline in renal function – 1/3 (Imbasciata 1991, n=80pt)
  - Accelerated HTN – 50%
  - Superimposed preeclampsia – 60% (Cunningham 1990, n=37)
  - PTL
  - Worsening anemia
  - HD access thrombosis
  - Placental abruption
  - Pregnancy loss – 50%
  - PTB - >90%
  - IUGR – 20%
  - Hydramnios
Dialysis – p191 CC OB 4th ed (Gail Seiken)

- Dialysis changes
  - Less Na taken off due to hyponatremia of preg; less HCO3 to avoid untoward alkalosis that exists in pregnancy
  - No acetate dialysis b/c of hypotension?
  - Monitor K and Ca to avoid hypokalemia and hypercalcemia (b/c of placental calcitriol increasing the absorption of calcium for fetal stores)
Fetal monitoring? - Before and after?

- Uptodate – ‘Careful uterine and fetal monitoring during hemodialysis, such as assessment of the fetal heart rate (particularly during the last portion of a session), combined with measures aimed at preventing dialysis-induced hypotension should be performed. Maternal hemodynamic instability may compromise the uteroplacental circulation and may be associated with the induction of uterine contractions

- N=5 Bamburg Germany – ‘intensive fetal surveillance not well defined’

- NSTs twice weekly; serial growth scans q 4weeks
Dialysis — p191 CC OB 4th ed (Gail Seiken)

• Mode of delivery – CD for obstetric indications
  – If CD performed and peritoneal dialysis is mode – will need to interrupt dialysis regimen to allow healing or switch to HD temporarily
Dialysis — Anemia —

- Increase in plasma volume without a corresponding increase in red cell mass
- Deficient EPO production, short red cell survival, bone marrow suppression by uremia toxins
- Need for erythropoietin to get hct to 30%, transfusion to > 21%, higher if delivery imminent
- EPO - low chance of birth defects, minimal gets to fetus; doses needed during pregnancy increase
- Chao (2002 – retrospective – 18 pregnancies) used hgb 6 as cutoff for transfusion,
- CCOB – 4th ed - ‘It is accepted by most obstetricians that hgb < 6g/dL is associated with increased perinatal mortality and maternal morbidity secondary to high output cardiac failure)
- Iron supplementation oral, IV if persistent deficiency
Dialysis

- **Diet** –
  - Protein – 1g/kg/d HD; 1.5 for PD; add 20g/d for pregnancy
  - Supplement water soluble vitamins, folate, zinc, iron
  - Avoid standard prenatal vitamins b/c of too much vit A
Table 48-4. Pregnancy Outcomes in 118 Women Undergoing Dialysis during Pregnancy – Williams Textbook

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Delivery (wks)</th>
<th>Birthweight (g)</th>
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<th>Hydramnios</th>
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</tr>
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<tr>
<td>Toma et al (1999)</td>
<td>54</td>
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</tbody>
</table>
Pregnancy after Kidney Transplant
Renal transplantation

• 1 in 20 women of childbearing age with a functioning renal allograft becomes pregnant, >10,000 pregnancies have occurred.
• Ideal if serum creatinine is <1.5mg/dL.
• Risks of deterioration of renal function, rejection, maternal death; no direct evidence that pregnancy has a deleterious effect on the transplanted kidney.
• Risk of graft rejection and permanent renal dysfunction is 10-20% (same for nonpregnant pt).
• Signs of rejection – fever, oliguria, deteriorating renal function, enlargement of kidney, tenderness to palpation - need to rule out infection, preeclampsia, glomerulonephritis, nephrotoxicity from immunosuppressant meds.
• Risks of PTB, IUGR, fetal death – from CHTN, pree.
• BP goal <140/90, ACE inhib good, but not in pregnancy, CCB (nifedipine) help counter vasoconstrictive effect of cyclosporine.
Optimal pregnancy outcome – prognostic factors
(p639 – CC OB 4th ed)

- 1-2 years since transplant
- Good general health and prognosis
- Satisfactory graft function with no evidence of rejection
- Stable immunosuppressive regimen
- No/minimal HTN or proteinuria
- Serum cr <1.5-2mg/dL
- Family support
Prenatal care in allograft recipients

- PRENATAL care – close surveillance for allograft rejection, infection, HTN, anemia, preeclampsia, fetal growth, monitoring for UTIs (esp in kidney transplant); Asx bacteruria tx for 2 weeks with f/u cultures, poss suppression doses
  - Other infections of note – bacterial/fungal endometritis, wound infection, skin abscesses, pneumonia (aspergillus, Pneumocystis, Mycobacterium TB, listeria)
  - Poss for Rh sens from graft;
  - CMV infection (usually ppx 3 mo after transplant, poss primary or recurrent CMV can cause congenital infection)
  - HBV, HCB – HBIG, HBV vaccine to newborn are 90% effective at preventing chronic HBV hepatitis
  - ACV for HSV
Immunosuppressants in transplant pt (Scott CC OB)

- All drugs cross placenta, diffuse to fetus
- No convincing evidence that prednisone, azathioprine, cyclosporine, tacrolimus produce congenital abnormalities;
- Drugs of choice in preg transplant pts
- a/e IUGR, PTB, o/w neonates do well
  - Short term ‘prematurity issues of infection, hypoglycemia, bone marrow hypoplasia, leukopenia, reduced IGM, IGG, elevated serum cr’ hard to know if it’s the drug or prematurity
- Long term – poss infertility, autoimmune disease, neoplasia – need for long term f/u
**Immunosuppressants**

**Azathioprine**

per Dr. Scott in CC in OB book 4th ed

- Azathioprine – MOA – inhibits T-lymphocytes; D
  - More toxic metabolite 6-mercaptopurine- purine analog that decreases delayed hypersensitivity and cellular cytotoxicity
  - a/e – infection, neoplasia, liver tox, bone marrow suppression
  - 64-90% of azathioprine crosses the placenta, majority if inactive thiouric acid
  - D b/c increased anomaly rate of 9 and 6.4%, not found in recent series, no specific pattern, possible bone marrow suppression in fetus, with anemia, leukopenia, thrombocytopenia
  - One approach – titrate to normal WBC counts in preg
Immunosuppressants

per Dr. Scott in CC in OB book 4th ed

• Tacrolimus – MOA – inhibits T-lymphocytes; C
  – FK506 – macrolide abx from streptomyces;
  – Incidence of post transplant DM with tacrolimus is 11-20%; median time to onset is 68d; 50% reversible
  – Nephrotoxicity, hyperkalemia in 1/3; HA, tremor, motor fxn, sensory fxn are neuro a/e
  – Cord blood concentrations 50% of maternal levels, no proven association with anomalies to date
Immunosuppressants -

Cyclosporine  per Dr. Scott in CC in OB book 4th ed

- Cyclosporine – MOA – inhibits T-lymphocytes; C
  - Fungal metabolite, inhibits Tcell response by inhibiting IL2
  - Improved survival in transplant pt, in most regimen
  - a/e – nephrotoxicity, HTN; others hirsutism, tremor, gingival hyperplasia, hepatotoxicity, risk of lymphomas
- Cyclosporine levels drop in pregnancy, but graft function remains stable in most pts (Bumgardner Matas 1992)
  - Readily crosses placenta, no evidence of teratogenicity
Immunosuppressants - prednisone

- Prednisone- IV used to tx acute rejection reactions
  - MOA – inhibit humoral and cell mediated immune response
  - a/e – glucose intolerance, PPROM, hirsutism, acne, wt gain, cushinoid appearance, striae, osteonecrosis, osteoporosis, fluid retention, HTN, infection, impaired wound healing, mood changes
  - Metabolized by placental 11-hydroxygenase to inactive 11-keto form – fetus is exposed to 10% of maternal dose
  - Dose – 10-30mg/d
  - a/e preg – poss PPROM, PTB, pree, IUGR
  - Prolonged courses of fluorinated steroids (dexas, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob
Cyclophosphamide

- MOA – alkylating agent; D
  - cancer chemotherapy and as an immunosuppressant
  - In human pregnancies, cyclophosphamide exposures that occurred during the first trimester have been associated with skeletal and palate defects, as well as malformations of the limbs and eyes
  - Cyclophosphamide is excreted into human milk (34). Two reports indicate that the platelet and leukocyte counts of a nursing infant were reversibly depressed during maternal cyclophosphamide therapy (35,48). Cyclophosphamide was classified among the cytotoxic drugs that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics (36).
Polycystic Kidney Disease

- AD disease of kidneys
- 1 in 800 live births
- Cause of 10% of end-stage renal disease in the United States
- 85% due to *PKD1* gene mutations (C16)
- 15% due to *PKD2* (C4), Salant 2008
- Variable penetrance and expressivity
- PNDX possible if mutation is known (family member or linkage studies)
PKD

- Renal complications M>F, 20s and 30s
- HTN in 75%
- Flank pain, hematuria, nocturia, proteinuria, calculi, infection, progression to renal failure, superimposed acute renal failure may also develop from infection or obstruction from ureteral angulation by cyst displacement
- Other organs –
  - Hepatic (F>M), 1/3 of patients
  - Cardiac – Valve lesions, mitral, aortic, and tricuspid incompetence
  - CNS – 10% of patients with PKD die from rupture of associated intracranial berry aneurysm
• Pregnancy
• Pregnancy outcome depends on the degree of associated hypertension and renal insufficiency.
• UTIs are common
• Chapman -1994
  – 235 affected women, 605 pregnancies vs 108 unaffected family members, 244 pregnancies
  – Composite perinatal complication rates were similar—33 versus 26 percent—but hypertension, including preeclampsia, was more common in women with polycystic kidneys.
• Pregnancy does not seem to accelerate the natural disease course (Lindheimer and colleagues, 2007).
Take home points

• CCBs for HTN
• PKD – check head MRI, echo; GHR
• Dialysis – Outcomes similar re: mode
• Transplant – Outcomes better >2yr of Cr
Notes
Cases
End
Williams
Legend:

Glomerular filtration rate changes with pregnancy in normal women, those stable after unilateral nephrectomy, and those with a successful renal transplant. (Data from Newcastle-upon-Tyne, 1974–2006, courtesy of Dr. John Davison.)
Williams - UTI
A series of anterior-posterior projection chest radiographs of improving acute respiratory distress syndrome (ARDS) in a second-trimester pregnant woman with severe pyelonephritis. A. An extensive infiltrative process and complete obliteration of the diaphragm (white arrows) is seen. B. Improved aeration of lung fields bilaterally is noted as pleural disease resolves (arrows). C. Markedly improved visualization of the lungs fields with residual platelike atelectasis and normal appearance of the diaphragm.
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Nephrolithiasis -
Chronic Renal Disease and Dialysis
Comparison of blood volume expansion in 44 normally pregnant women at term with 29 who had eclampsia; 10 with moderate chronic renal insufficiency (CRI)—serum creatinine 1.5 to 2.9 mg/dL; and 4 with severe CRI—serum creatinine ≥3.0 mg/dL. (Data from Zeeman and colleagues, 2009, and Cunningham and associates, 1990.)
Birthweight percentiles of infants born to 29 women at Parkland Hospital with mild to moderate renal insufficiency—serum creatinine 1.4–2.4 mg/dL (black points) and severe renal insufficiency—serum creatinine ≥2.5 mg/dL (red points). (Data are from Cunningham and colleagues, 1990; and Stettler and Cunningham, 1992. Growth curves are those reported by Alexander and co-workers, 1996.)
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- Pregnancy does not seem to accelerate the natural disease course (Lindheimer and colleagues, 2007).
Glomerular nephropathies
### Table 48-5. Causes of Acute Nephritic Syndrome

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Poststreptococcal infection</strong></td>
</tr>
<tr>
<td>Subacute bacterial endocarditis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Antiglomerular basement membrane disease</td>
</tr>
<tr>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>ANCA small vessel vasculitis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Mesangioproliferative glomerulonephritis</td>
</tr>
</tbody>
</table>
## Causes of the Nephrotic Syndrome in Adults

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease (MCD) (10–15%)</td>
<td>primary idiopathic (most cases), drug-induced (NSAIDs), allergies, viral infections</td>
<td></td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis (FSGS)</td>
<td>(33%)</td>
<td>viruses, hypertension, reflux nephropathy, sickle-cell disease</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>(30%)</td>
<td>idiopathic (majority), malignancy, infection, connective-tissue diseases</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td></td>
<td>most common cause of ESRD</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acute Renal Failure
Williams
From MFM fellow didactic series

• Each disease – criteria for diagnosis; overall management
• Prediction of disease on pregnancy and vice versa slide
• Indications for dialysis slide
• Interpretation of FeNa, osmality slide
Diabetic nephropathy

• Diagnosis
  – White classification - >500mg /24hr
  – Macroalbuminuria (300mg/24 hours) – cleveland clinic def
    • http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/diabetic-nephropathy/#cesec1
  – Abnormal renal function as represented by an abnormality in serum creatinine, CrCl, GFR
  – ‘clinically – diabetic nephropathy is characterized by a progressive increase in proteinuria and decline in GFR, hypertension, and a high risk of CV morbidity and mortality

• ADA 2009 - Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD).
  – Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes.
  – Microalbuminuria is also a well-established marker of increased CVD risk.
  – Patients with microalbuminuria who progress to macroalbuminuria (300 mg/24 h) are likely to progress to ESRD
Glucose + NH$_2$-R $\xrightarrow{K_1} \text{Schiff base} \quad \xrightarrow{K_2} \text{Amadori product} \quad \xrightarrow{K_n} \text{Intermediate glycosylation products} \quad \xrightarrow{K_2} \text{Advanced glycosylation endproducts}$

\[ \text{H} = \text{C} \quad \text{(CHOH)$_4$} + \text{NH}_2$-R $\xrightarrow{\text{CH$_2$OH}} \text{(CHOH)$_4$} \quad \xrightarrow{\text{CH$_2$OH}} \text{(CHOH)$_3$} \quad \xrightarrow{\text{HO-}} \text{Advanced glycosylation endproducts} \]
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis. Courtesy of Helmut Rennke, MD.

Normal glomerulus

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows). Courtesy of Helmut G Rennke
Diabetic nephropathy

- **Management**
  - Optimizing glucose control
  - Renoprotective medications – diltiazem, nifedipine, amlodipine
  - If also chronic hypertensive –
    - BP goals – 110-129/65-79 (ADA, 2009)
  - Monitoring for preeclampsia
  - Fetal surveillance
  - Ophthalmic surveillance
Glomerular and interstitial nephritis (e.g. lupus nephritis)

- Diagnosis (Gupta 2005)
  - Morphological diagnosis – 6 levels of classification; latest study from 2005
  - Level of proteinuria and serum creatinine - used more to follow progression
- LN is thus divided into 6 classes according to severity of the lesions observed\(^{[16]}\): (Mariani 2004 from renal pathology society working group conf in 2002)
  - Class I, minimal mesangial LN;
  - Class II, mesangial proliferative LN;
  - Class III, focal LN;
  - Class IV, diffuse segmental LN;
  - Class V, membranous LN; and
  - Class VI, advanced sclerosing LN.
Lupus Nephritis

Table 1. WHO 1974 Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Normal glomeruli by LM, IF, EM</td>
</tr>
<tr>
<td>Class II</td>
<td>Purely mesangial disease</td>
</tr>
<tr>
<td>IIa</td>
<td>- Normocellular mesangium by LM but mesangial deposits on IF and EM</td>
</tr>
<tr>
<td>IIb</td>
<td>- Mesangial hypercellularity with mesangial deposits by IF or EM</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal proliferative glomerulonephritis (&lt;50%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse proliferative glomerulonephritis (≥50%)</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous glomerulonephritis</td>
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</table>

and vascular lesions were also not included in this classification.

This classification was first modified in 1982 by International Study of Kidney Diseases in Children group\(^4,15\) (Table 2). In this classification, class I was subdivided into two types: class Ia and class Ib.
GUPTA 2005 – Rheum association lupus nephritis classes

**Table 3. International Society of Nephrology/Renal Pathology Society (ISN/RPS-2003) Classification of Lupus Nephritis.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
</table>
| Class I | Minimal mesangial lupus  
Normal glomeruli by LM but mesangial immune deposits by IF |
| Class II | Mesangial proliferative lupus nephritis  
Purely mesangial hypercellularity of any degree or mesangial matrix expansion on LM with mesangial immune deposits. A few subendothelial or subepithelial deposits may be visible by IF or EM but not by LM. |
| Class III | Focal lupus nephritis  
III (A) - Active or inactive, segmental or global, endo or extracapillary  
III (A/C) - Glomerulonephritis involving <50% of all glomeruli typically with focal  
III (C) - Subendothelial deposits with or without mesangial alterations.  
Active lesions: focal proliferative lupus nephritis  
Active and chronic lesions: focal proliferative and sclerosing lupus nephritis  
Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis |
| Class IV | Diffuse lupus nephritis  
IV-S (A) -Active lesions: diffuse segmental proliferative lupus nephritis  
IV-G (A) -Active lesions: diffuse global proliferative lupus nephritis  
IV-S (A/C) -Active and chronic lesions: diffuse segmental proliferative & sclerosing lupus nephritis  
IV-G (A/C) -Active and chronic lesions: diffuse global proliferative & sclerosing lupus nephritis  
IV-S (C) -Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis  
IV-G (C) -Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis |
| Class V | Membranous lupus nephritis  
Global or segmental subepithelial immune deposits or electron dense deposits in the mesangium |

**Fig 5.** Renal biopsy showing enlarged glomerulus displaying thickening of glomerular basement membrane and epimembranous spikes consistent with SLE WHO class V (PAS)

Class V lupus nephritis may occur with class III or IV in which case both will be diagnosed.

Class V lupus nephritis may show advanced sclerosis.

Advanced sclerotic lupus nephritis.

≥ 90% glomeruli globally sclerosed without residual activity.
Lupus nephritis

- Indications for a renal biopsy in nonpregnant SLE patients include:
  - Hematuria and proteinuria;
  - Renal dysfunction;
  - Hypertension;
  - Low levels of the complement factor C3;
  - The presence of chronic renal lesions;
  and
  - Modifications in therapy: initiation, changes, or discontinuation.
Lupus nephritis  (Foley ICU book)-Dr. Silver

- Preexisting renal disease
  - 50% of patients with SLE will develop renal disease
  - Results from immune complex deposition, complement activation, and inflammation of the kidney
  - Potential for permanent decrease in renal function after pregnancy with renal disease
    - Burkett 1985 – 242 preg, 59% no change, 30% transient renal impairment, 7% permanent renal insufficiency
    - Serum creatinine of 1.5mg/dL; if greater – ‘correlation of deterioration of renal function during and after pregnancy; if <1.5, pt can reassured that pregnancy will not increase the rate of deterioration of renal function; specific type of renal disease documented histologically does not appear to influence pregnancy outcome or renal function
**Lupus nephritis** (Silver – ICU book)

- Pt with severe nephritis may present with acute renal insufficiency
  - DDX – preeclampsia, lupus flare, acute rejection (if transplanted kidney) – may require renal biopsy
  - Frequently respond to glucocorticoids (prednisone 1mg/kg/d)
  - If proliferative nephritis – may require cyclophosphamide
  - If not responsive to medical therapy, serum cr >3.5mg/dL, dialysis should be started to optimize pregnancy outcome
Glomerular and interstitial nephritis (e.g. lupus nephritis)

- Management
  - Baseline labs – 24 hr urine analysis; metabolic profile/serum creatinine, CBC,
  - If also chronic hypertensive –
    • BP goals – 110-129/65-79 (ADA, 2009)
  - Monitoring for preeclampsia
  - Fetal surveillance
  - Renoprotective medications – diltiazem, nifedipine?
Lab tests that may be used to distinguish preeclampsia from lupus flare (Silver, ICU book)

<table>
<thead>
<tr>
<th>Lab test to differentiate lupus vs preeclampsia</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement levels</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased dsDNA</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Increased serum cr</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Renal biopsy in pregnancy – N=18, Kuller 2001

- Objective: Our aim was to review our experience with renal biopsy in pregnancy. Study Design: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case. Results: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosis confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy. Conclusion: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term. (Am J Obstet Gynecol 2001;184:1093-6.)
Acute and chronic pyelonephritis

- **Diagnosis**
  - Acute (2%) of all pregnancies – fever, flank pain, urine analysis, culture; recurrence rate 20%
  - Association with MR? (McDermott 2000 – 41000 medicaid pregnancy chart review)) – in patients not treated or noncompliant – association of fetal death and postnatal mental retardation
  - Chronic - tubulointerstitial disease – infectious or noninfectious (p908- Creasy), outcome is good if normotensive and
Acute and chronic pyelonephritis

Management

- **Acute** – IV hydration, IV antibiotics; imaging if no improvement after 48-72hr
  - 10-20% rate of bacteremia
  - Monitor for preterm labor
  - Course of abx to treat infection
  - Oral suppression
  - Serial urine cultures (esp if no suppression)

- **Chronic** – surveillance of infections, acute infection
  - ? Suppression
  - Postnatal surveillance if acute infection develops during pregnancy, ck for persistent renal pelvis/calyceal dilation (Creasy p908, Twickler 1994)
Renal biopsy in pregnancy – N=18, Kuller 2001

Objective: Our aim was to review our experience with renal biopsy in pregnancy. Study Design: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case. Results: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosis confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy.

Conclusion: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term. (Am J Obstet Gynecol 2001;184:1093-6)
Periarteritis nodosa

Def - Polyarteritis nodosa is a rare multi-system disorder characterized by widespread inflammation, weakening, and damage to small and medium-sized arteries. Blood vessels in any organ or organ system may be affected, including those supplying the kidneys, heart, intestine, nervous system, and/or skeletal muscles. Damage to affected arteries may result in abnormally increased blood pressure (hypertension), "ballooning" (aneurysm) of an arterial wall, the formation of blood clots (thrombosis), obstruction of blood supply to certain tissues, and/or tissue damage and loss (necrosis) in certain affected areas.

- Guarded prognosis because of associated malignant hypertension
- Preconception, antenatal counseling – avoidance of pregnancy, recommendation for termination if pregnant
- Literature – case reports – mainly comprised of maternal deaths
  - Burkett G, Richards R. Pregnancy in patients with periarteritis resulted in maternal death in 7 of the 8 cases that have been reported. In the present case, periarteritis was in remission throughout the pregnancy; the patient was thus the second known maternal survivor. The infant also did well. It is suggested that pregnancy probably does not have as direct an effect on the course of the disorder as appears from the outcome of the previous cases. Extreme caution must prevail, especially as diagnosis is often difficult and experience so limited.
Systemic sclerosis

- **Def** – autoimmune systemic condition (Raynauds, hardening of skin, + anti centromere and anti topoisomerase ab, +ANA) – p 910

- Renal involvement in 60% of pt within 3-4 yrs of dx

- Treatment involves preventing pulmonary complications; treating hypertension

- Maternal deaths due to onset during pregnancy or pulmonary complication; pregnancy not common due to onset in 4-5th decades
Nephrotic syndrome

- **Diagnosis** – proteinuria (>3.5gm/day); hypoalbuminemia; hypercholesterolemia; hypertriglyceridemia; edema
- **Most common cause** – preeclampsia late in pregnancy
  - Next is diabetic nephropathy
  - Membranoproliferative glomerularnephritis; Glomerular disease, lupus nephritis, minimal change disease
Nephrotic syndrome

- Management

  - Rule out preeclampsia, define etiology
  - Biopsy
  - Sudden appearance of nephrotic syndrome with any of the glomerular diseases should prompt evaluation of preeclampsia, renal vein thrombosis
  - If renal function is adequate, no hypertension, pregnancy should be tolerated
  - Hypoalbuminemia of pregnancy increases fluid retention, edema
  - Diuretics for massive fluid retention causing hypertension
  - Anticoagulation
Chronic undifferentiated renal disease (arteriolar nephrosclerosis)

- Diagnosis – ‘malignant hypertension’
  - Hallmark - Hypertension first
  - See on u/s, MRI – small kidneys
  - Renal failure (elevated creatinine and BUN, hyperphosphatemia) in a hypertensive pt; biopsy is rarely indicated per uptodate
  - Hypertensive end organ damage (eg, retinal changes, left ventricular hypertrophy)
  - No other cause of chronic kidney disease
  - The diagnosis may be suspected when routine blood tests indicate deteriorating renal function in a hypertensive patient.
  - Hypertension should be present before onset of proteinuria and renal failure, and there should be no other clinically suspected cause of renal failure. (vs nephrotic syndrome where hypertension is after massive proteinuria)
  - At risk groups – blacks, marked elevations of BP, diabetics with nephropathy
Chronic undifferentiated renal disease (arteriolar nephrosclerosis)

- Management
  - Baseline lab assessment, renal function assessment
  - BP control (DBP <90) and prevention of labile hypertension
  - Maternal surveillance for hypertension, close surveillance for superimposed preeclampsia esp if renal dysfunction is significant;
  - What drug is best for renal protection and what level of BP control best prevents progression of renal dysfunction; no definite answer per up to date (ACE-, ARB, CCB)
Renal transplantation – CC OB 4th ed J

Scott

- 1 in 20 women of childbearing age with a functioning renal allograft becomes pregnant, >10,000 pregnancies have occurred
- Ideal if serum creatinine is <1.5mg/dL
- Risks of deterioration of renal function, rejection, maternal death; no direct evidence that pregnancy has a deleterious effect on the transplanted kidney
- Risk of graft rejection and permanent renal dysfunction is 10-20% (same for nonpregnant pt)
- Signs of rejection – fever, oliguria, deteriorating renal function, enlargement of kidney, tenderness to palpation - need to rule out infection, preeclampsia, glomerulonephritis, nephrotoxicity from immunosuppressant meds
- Risks of PTB, IUGR, fetal death – from CHTN, pree
- BP goal <140/90, ACE inhib good, but not in pregnancy, CCB (nifedipine) help counter vasoconstrictive effect of cyclosporine
Optimal pregnancy outcome – prognostic factors

- 1-2 years since transplant
- Good general health and prognosis
- Satisfactory graft function with no evidence of rejection
- Stable immunosuppressive regimen
- No/minimal HTN or proteinuria
- Serum cr <1.5-2mg/dL
- Family support
Prenatal care in allograft recipients

• PRENATAL care – close surveillance for allograft rejection, infection, HTN, anemia, preeclampsia, fetal growth, monitoring for UTIs (esp in kidney transplant); Asx bacteruria tx for 2 weeks with f/u cultures, poss suppression doses
  – Other infections of note – bacterial/fungal endometritis, wound infection, skin abscesses, pneumonia (aspergillus, Pneumocystis, Mycobacterium TB, listeria)
  – Poss for Rh sens from graft;
  – CMV infection (usually ppx 3 mo after transplant, poss primary or recurrent CMV can cause congenital infection)
Immunosuppressants in transplant pt  (Scott CC OB)

- All drugs cross placenta, diffuse to fetus
- No convincing evidence that prednisone, azathioprine, cyclosporine, tacrolimus produce congenital abnormalities;
- Drugs of choice in preg transplant pts
- a/e IUGR, PTB, o/w neonates do well
  - Short term ‘prematurity issues of infection, hypoglycemia, bone marrow hypoplasia, leukopenia, reduced IGM, IGG, elevated serum cr’ hard to know if it’s the drug or prematurity
- Long term – poss infertility, autoimmune disease, neoplasia – need for long term f/u
Immunosuppressants
Azathioprine
per Dr. Scott in CC in OB book 4th ed

• Azathioprine – MOA – inhibits T-lymphocytes; D
  – More toxic metabolite 6-mercaptopurine- purine analog that decreases delayed hypersensitivity and cellular cytotoxicity
  – a/e – infection, neoplasia, liver tox, bone marrow suppression
  – 64-90% of azathioprine crosses the placenta, majority if inactive thiouric acid
  – D b/c increased anomaly rate of 9 and 6.4%, not found in recent series, no specific pattern, possible bone marrow suppression in fetus, with anemia, leukopenia, thrombocytopenia
  – One approach – titrate to normal WBC counts in preg
Tacrolimus – MOA – inhibits T-lymphocytes; C

- FK506 – macrolide abx from streptomyces;
- Incidence of post transplant DM with tacrolimus is 11-20%; median time to onset is 68d; 50% reversible
- Nephrotoxicity, hyperkalemia in 1/3; HA, tremor, motor fxn, sensory fxn are neuro a/e
- Cord blood concentrations 50% of maternal levels, no proven association with anomalies to date
Immunosuppressants - Cyclosporine per Dr. Scott in CC in OB book 4th ed

- Cyclosporine – MOA – inhibits T-lymphocytes; C
  - Fungal metabolite, inhibits Tcell response by inhibiting IL2
  - Improved survival in transplant pt, in most regimen
  - a/e – nephrotoxicity, HTN; others hirsutism, tremor, gingival hyperplasia, hepatotoxicity, risk of lymphomas
  - Cyclosporine levels drop in pregnancy, but graft function remains stable in most pts (Bumgardner Matas 1992)
  - Readily crosses placenta, no evidence of teratogenicity
**Immunosuppressants - prednisone**

- **Prednisone- IV used to tx acute rejection reactions**
  - MOA – inhibit humoral and cell mediated immune response
  - a/e – glucose intolerance, PPROM, hirsutism, acne, wt gain, cushinoid appearance, striae, osteonecrosis, osteoporosis, fluid retention, HTN, infection, impaired wound healing, mood changes
  - Metabolized by placental 11-hydroxygenase to inactive 11-keto form – fetus is exposed to 10% of maternal dose
  - Dose – 10-30mg/d
  - a/e preg – poss PPROM, PTB, pree, IUGR
  - Prolonged courses of fluorinated steroids (dexta, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob
Immunosuppressants—

Cyclophosphamide per Dr. Scott in CC in OB book 4th ed

- Cyclophosphamide – MOA – alkylating agent; D
  - cancer chemotherapy and as an immunosuppressant
  - In human pregnancies, cyclophosphamide exposures that occurred during the first trimester have been associated with skeletal and palate defects, as well as malformations of the limbs and eyes
  - Cyclophosphamide is excreted into human milk (34). Two reports indicates that the platelet and leukocyte counts of a nursing infants were reversibly depressed during maternal cyclophosphamide therapy (35,48). Cyclophosphamide was classified among the cytotoxic drugs that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics (36).
Acute and chronic renal failure

- Diagnosis – decreased urine production, <400-500 cc/day
  - Elevated serum creatinine, BUN
  - Urine studies

- Acute kidney injury - rapidly progressive loss of renal function; oliguria; electrolyte imbalance; results from prerenal, intrinsic or post renal disease; goal is do identify the cause so as to halt the process or reverse it; dialysis may be needed in the meantime;

- Chronic kidney disease – long term result from an acute nonreversible insult or occurs from a chronic disease progression

- Acute-on-chronic renal failure – acute renal injury in a patient that has known or unknown chronic renal disease or insufficiency; goal is to identify the cause for the acute decompensation so as to reverse the process as measured by return of serum creatinine to baseline (difficulty arises when there is no baseline)
Acute renal failure in pregnancy DDX

- Preeclampsia (proteinuria, HTN, edema)
- HELLP syndrome (RUQ pain, proteinuria, hemolysis, elevated LFTs, thrombocytopenia, normal coags)
- TTP (microangiopathic hemolytic anemia - MAHA; thrombocytopenia; neurologic (confusion, HA, paresis, visual hallucinations, seizures); fever; renal dysfunction; All 5 in 40%; Anemia, thrombocytopenia, neuro in 75%)
- Prerenal azotemia (decreased renal perfusion
Acute renal failure - DDX

- Acute tubular necrosis - brown granular casts, renal tubular cells, proteinuria <2g/d; FENA >2%; HTN uncommon rather hypotension, sepsis, hemorrhage

- Acute interstitial nephritis – hematuria, pyuria, eosinophils, WBC casts; proteinuria <2g/d; FENA >2%; HTN uncommon rather fever, skin rash, new medication

- Acute glomerulonephritis – hematuria RBC casts, oval fat bodies; >2g, but <3.5 gm proteinuria/day, poss nephrotic range, FENA <1%; HTN common, collagen vascular disease, infection

- Obstruction – mass, stone; exam, CT
Acute renal failure DDX

• Acute fatty liver of pregnancy (elevated LFTs, hyperbilirubinemia, coagulopathy, oliguria, nausea, abd pain, leukocytosis, hypoglycemia)

• Postpartum renal failure /HUS – PP, MAHA, severe HTN, prodromal illness, thrombocytopenia, CNS sx

• Pyelonephritis _ urine culture, fever, flank pain

• Bilateral renal cortical necrosis – hemorrhage, hypotension/shock, oliguria/anuria (<50ml/d), flank pain, gross hematuria; dx by renal arteriogram demonstrating virtual absence of cortical blood flow despite renal artery patency; high mortality
Acute tubular necrosis and renal cortical necrosis – see renal failure slides

• Diagnosis
Acute tubular necrosis and renal cortical necrosis – see renal failure slides

- Management
<table>
<thead>
<tr>
<th>Diagnostic index</th>
<th>Prerenal azotemia</th>
<th>Ischemic intrinsic renal azotemia/ acute tubular necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENA (%)</td>
<td>&lt;1</td>
<td>&gt;1 -2(1 = obstructive)</td>
</tr>
<tr>
<td>Urine Na conc (meq/L)</td>
<td>&lt;10 (&lt;20 CCOB 4th ed)</td>
<td>&gt;10 (&gt;40 CCOB)</td>
</tr>
<tr>
<td>Urine cr / plasma cr ratio</td>
<td>&gt;40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Urinary urea nitrogen / plasma urea nitrogen ratio</td>
<td>&gt;8`</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Urine spec gravity</td>
<td>&gt;1.018</td>
<td>&lt;1.012</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/Kg H20)</td>
<td>&gt;500</td>
<td>&lt;250-350</td>
</tr>
<tr>
<td>Plasma BUN/ cr ratio</td>
<td>&gt;20</td>
<td>&lt;10-15</td>
</tr>
<tr>
<td>Renal failure index (Una/Ucr/Pcr)</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Hyaline casts</td>
<td>Muddy brown granular casts</td>
</tr>
</tbody>
</table>
Acute and chronic renal failure

- Management
  - Establish etiology
  - Attempts to reverse or treat underlying process
  - Nephrology consultation
  - Supportive therapy
  - Correction of metabolic acidosis with bicarbonate or dialysis (p153 Foley ICU book)
  - Prevent hyperphosphatemia (diet restriction, calcium binders with meals)
  - Prevent hyperkalemia (avoid in diet, kayexalate – cation/exchange resin)
    - If associated ECG changes (peaked T waves) IV calcium gluconate (1gm); infusion of glucose/insulin; inhaled beta agonist; dialysis
  - Fluid balance !!
  - Dialysis (cr >3.5)
  - Control of HTN
  - Evaluation for preeclampsia, and continue basic principles to establish M-F wellbeing
Indications for dialysis (in pregnancy)  

Foley ICU book; CCOB 4th ed

- AEIOU (acidosis, electrolytes, Intox, overload/volume, uremia)
- Clinical evidence of uremia (pericarditis, encephalopathy, metabolic, neurologic, GI, cardiac – arrythmias)
  - BUN > 50-70mg/dL (lower than for nonpreg)
  - Serum creatinine >6-7mg/dL (lower than for nonpreg)
- Volume overload - Intractable intravascular volume overload (despite diuresis)
- Hyperkalemia (>5.0) or severe acidosis (<7.2) resistant to conservative measures
- Above Conditions not responsive to conservative measures
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- **Needed for acute renal failure, ESRD, deterioration of chronic renal function, possible prophylactic dialysis**
  - Pregnant women that have progressive loss of renal function represent ~20% of women undergoing dialysis (Hou 1999)

- **In CRF – cutoff of GFR (24 hr urine CrCl gets <5-10ml/min hyperkalemia, metabolic acidosis, fluid overload, uremia is likely to develop (15ml/min in diabetics with end organ disease)**
Dialysis – p191 CC OB 4th ed (Gail Seiken)

• Modes
  – Hemodialysis
  – Peritoneal dialysis
    • Continuous ambulatory PD
    • Continuous cycling PD
    • Nocturnal intermittent PD
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- Advantage in pregnancy of
  - hemodialysis – less work intensive for patient
    - No risk if peritoneal catheter-related complications (laceration of uterine vessels, infection, peritonitis, PTL, but PTL is also observed in HD pts)
    - No interruption in therapy needed after Csection
  - Peritoneal D – stable biochemical environment
    - Continuous fluid removal avoids hypotension
    - Allows liberal fluid intake
    - Permits continuous insulin administration in DM
    - No anticoagulation needed
    - Permits administration of intraperitoneal MgSO4 in pree (ideally better steady state, but still IV bolusing and rates in patients with renal failure is typically needed)
    - HTN easier to control; Less severe anemia
Dialysis – p191 CC OB 4th ed (Gail Seiken)

• Mode of dialysis and fetal outcome
  – Initially improved with peritoneal
  – National Registry for pregnancy in Dialysis pts
    • N=184; ~40% HD and 40% PD – identical fetal survival rates (Okundaye 1998)
• Intensive dialysis
  – Daily dialysis in pregnancy to minimize fetal exposure to uremic toxins and improve outcome
  – NPDR – infant survival 73% in women needed to start dialysis in pregnancy vs being dialyzed at the beginning (40%)
  – Initiate dialysis at BUN 60-70mg/dL and creatinine of 6-7mg/dL with goal of BUN <50, cr <5
    • Fetal urea production 540mg/d in 3rd trim
    • HD – daily – 5+ hours /day
    • Best outcomes if >20+ hours of dialysis weekly
    • Low level of azotemia prevents hydramnios, PTL – based on urea diuresis that normally occurs in utero due to high fetal BUN
  – Avoids large dialytic weight gains and fluid shifts and labile BPs, less hypotension, also better HTN control
Dialysis in pregnancy (CCOB 4th ed)

- Maternal – Fetal complications
  - Accelerated decline in renal function – 1/3 (Imbasciata 1991, n=80 pt)
  - Accelerated HTN – 50%
  - Superimposed preeclampsia – 60% (Cunningham 1990, n=37)
  - PTL
  - Worsening anemia
  - HD access thrombosis
  - Placental abruption
  - Pregnancy loss – 50%
  - PTB - >90%
  - IUGR – 20%
  - Hydramnios
Dialysis changes

- Less Na taken off due to hyponatremia of preg; less HCO3 to avoid untoward alkalosis that exists in pregnancy
- No acetate dialysis b/c of hypotension?
- Monitor K and Ca to avoid hypokalemia and hypercalcemia (b/c of placental calcitriol increasing the absorption of calcium for fetal stores)
• Fetal monitoring? - Before and after?
  – Uptodate – ‘Careful uterine and fetal monitoring during hemodialysis, such as assessment of the fetal heart rate (particularly during the last portion of a session), combined with measures aimed at preventing dialysis-induced hypotension should be performed. Maternal hemodynamic instability may compromise the uteroplacental circulation and may be associated with the induction of uterine contractions
  – N=5 Bamburg Germany – ‘intensive fetal surveillance not well defined’
  – NSTs twice weekly; serial growth scans q 4weeks
• Mode of delivery – CD for obstetric indications
  – If CD performed and peritoneal dialysis is mode – will need to interrupt dialysis regimen to allow healing or switch to HD temporarily
• Anemia –
  – Increase in plasma volume without a corresponding increase in Red cell mass
  – Deficient EPO production, short red cell survival, bone marrow suppression by uremia toxins
  – Need for erythropoietin to get hct to 30%, transfusion to > 21%, higher if delivery imminent
  – EPO- low chance of birth defects, minimal gets to fetus; doses needed during pregnancy increase
  – Chao (2002 – retrospective – 18 pregnancies) used hgb 6 as cutoff for transfusion,
  – CCOB – 4th ed- ‘It is accepted by most obstetricians that hgb <6g/dL is associated with increased perinatal mortality and maternal morbidity secondary to high output cardiac failure)
  – Iron supplementation oral, IV if persistent deficiency
Dialysis

• Diet –
  – Protein – 1g/kg/d HD; 1.5 for PD; add 20g/d for pregnancy
  – Supplement water soluble vitamins, folate, zinc, iron
  – Avoid standard prenatal vitamins b/c of too much vit A
# Chronic Renal Insufficiency and Pregnancy Outcomes (expressed by serum creatinine mg/dL)

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**Williams Obstetrics**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
<th>Cr 1.5-3</th>
<th>Cr &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>13%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5%</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>IUGR</td>
<td>10%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Abortion</td>
<td>11%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Surviving infants</td>
<td>84%</td>
<td>62%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Antihypertensives

• Procardia (nifedipine) – CCB - C
• Diltiazem – CCB - C
• See ppt slides in folder of renal disease in preg

• Physiology
• DM nephropathy
• Lupus nephritis
• Renal transplant
• Indications for Dialysis
• Oliguria in severe preeclampsia
Renal Disease in Pregnancy

- END

- END END END END END END END END
Lupus pt

- 35 yo G2 P0101
- Lupus x5y, with nephritis and +Anticardiolipin abs
- Prepregnancy counseling/eval
- Pregnancy counseling /eval / management
- Anticoagulation?
DM

- Type 1 DM, counseling
- Type 2 DM, counseling
- Evaluation
- White classes
- Counseling
- Management
- ACE - ; CCBs
Kidney disease

• 24 yo  P0000
• PKD, Cr 3.5
• Prepregnancy evaluation
  – Counseling
  – Management
• Pregnancy counseling
  – Management
• Inheritance of PKD, AD, variable expressivity/penetrance
# Chronic Renal Insufficiency and Pregnancy Outcomes (vs serum creatinine mg/dL)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
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<tr>
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</tr>
</tbody>
</table>
TABLE 1 NEW RECOMMENDATIONS FOR TOTAL AND RATE OF WEIGHT GAIN DURING PREGNANCY, BY PREPREGNANCY BMI

<table>
<thead>
<tr>
<th>Prepregnancy BMI</th>
<th>BMI* (kg/m²) (WHO)</th>
<th>Total Weight Gain Range (lbs)</th>
<th>Rates of Weight Gain* 2nd and 3rd Trimester (Mean Range in lbs/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>28–40</td>
<td>1 (1–1.3)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5–24.9</td>
<td>25–35</td>
<td>1 (0.8–1)</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
<td>15–25</td>
<td>0.6 (0.5–0.7)</td>
</tr>
<tr>
<td>Obese (includes all classes)</td>
<td>≥30.0</td>
<td>11–20</td>
<td>0.5 (0.4–0.6)</td>
</tr>
</tbody>
</table>

* To calculate BMI go to www.nhlbissupport.com/bmi/

* Calculations assume a 0.5–2 kg (1.1–4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997)

The recommended weight gain ranges for short women and for racial or ethnic groups are the same as those for the whole population. In addition, teenagers who are pregnant should use the adult BMI categories to determine their weight gain range until more research is done to determine whether special categories are needed for them. Women who are pregnant with twins are given provisional guidelines. Those in the normal BMI category should aim to gain 37–54 pounds; overweight women, 31–50 pounds; and obese women, 25–42 pounds.
Calorie calculations

• Normal
• DM pregnancy
Pulmonary edema
Cardiac Manifestations of Preeclampsia

• Wedge and CVP Do Not Correlate
• SVR is Low Initially, and then Becomes Very High (along with BP)
• Pulmonary Artery Catheter Findings
  – Elevated SBP, SVR
  – Hyperdynamic LV Function
  – Normal to Increased PCWP
  – Low CVP
  – High Wedge with Low CVP May be Due to Increased Afterload with Volume Depletion
Pulmonary Edema in Preeclampsia

- Occurs in 3% of Women with Preeclampsia
- 70% Occurs Postpartum (Fluid Overload)
- Antepartum Pulmonary Edema Associated with Chronic HTN in 90% Cases
- Risk Factors: Older Women, Multigravidas, Chronic Hypertension
- Associated with Fluid Overload, either Colloid or Crystalloid
Pulmonary Edema in Preeclampsia

- Pathophysiology of Pulmonary Edema
  - Reduced COP
  - Alteration of Capillary Membrane Permeability and Integrity
  - Elevated Pulmonary Vascular Hydrostatic Pressures

- Extravasation of Fluids in Pulmonary Interstitium
Pulmonary Edema in Preeclampsia

- Etiology of Pulmonary Edema
  - Abnormal COP-Wedge Gradient
  - Capillary Leak
  - LV Failure

- Non-hydrostatic Forces can Cause Pulmonary Edema

- Fluid Overload is Common, Presenting with Preeclampsia in Pulmonary Edema is Not (If you see it, think LV failure and know that you are in trouble)
Pulmonary Edema in Preeclampsia

- Risk factors – fluid overload, preeclampsia, tocolysis, uncontrolled hypertension
- Diagnosis of Pulmonary Edema
  - Clinical Diagnosis: Progressive Dyspnea and Chest Discomfort
  - Tachypnea, Tachycardia, Bilateral crackles
  - Confirm with CXR and ABG
  - Don’t Forget about Pulmonary Embolism
Case

- 34 yo P0, admitted for preeclampsia
  - IVF pregnancy
- HD #3, developed progressive dyspnea, crackles on physical exam, oxygen requirements
  - CXR revealed bilateral pleural effusions
- Fluid restriction, diuretics (Lasix 20mgIV), delivery, seizure prophylaxis
CXR of pulmonary edema
Pulmonary Edema in Preeclampsia

• Management
  – Oxygen, Fluid Restriction, Semi-Fowler
  – Accurate intake/output
  – If Fluid Overload, then Lasix, Increasing Doses as Needed
  – Consider PA Catheter: Fluid Overload vs. LV Dysfunction vs. Nonhydrostatic Pulmonary Edema
Indications for PA Catheter in Hypertensive Disease

- Severe preeclampsia with refractory oliguria or pulmonary edema
- Ineffective IV antihypertensive therapy
- Intraoperative or intrapartum cardiac failure
Pulmonary Edema in Preeclampsia – 3 subsets

- Management
  - Intravascular volume depletion (oliguria), low PCWP, high CO, high SVR, low CVP –
    - fluids
  - Renal Vasoconstriction (High PCWP, Normal CO and SVR, uroconcentration):
    - Dopamine – 1-5µg/kg/min; furosemide
  - LV Dysfunction/Failure with Vasospasm (high PCWP, high SVR, low CO <5 L/min) :
    - Needs Afterload Reduction (Sodium nitroprusside 0.25-0.5µg/kg/min IV infusion)
    - Volume Restriction
    - Diuretics (max acute dose of furosemide is 120mg, start with 20-40mg)
  - Mechanical Ventilation for Respiratory Failure (If still pregnant, intubate early rather than late)
Renal Disease in Pregnancy

- October 22, 2014
Physiologic changes - Renal
Normal pregnancy renal physiology

• **Effective renal plasma flow**
  – Rises 75% over nonpregnant levels by 16 weeks gestation; maintained until 34 weeks gestation, then declines by 25%

• **Glomerular filtration rate (GFR)**
  – Measured by inulin clearance
  – Increases by 5-7 weeks to 50% above nonpregnant levels by end of first trimester and this is maintained t/o pregnancy
  – 3 months PP goes to normal

• **ERPF/GFR = filtration fraction** falls from nonpregnant levels until late 3rd trimester (due to ERPF increasing more than GFR in early pregnancy)
  – Nonpregnant values of 20-21%
Normal pregnancy renal physiology

- **GFR = endogenous creatinine clearance**
  - Normal in pregnancy to be increased to 150-200 mL/min (nonpregnant 120 mL/min)
  - Reliable predictor of renal function provided complete urine collection is taken during a specific time period

- **BUN**
  - Decreases from 12 to 9 mg/dL (14 mg/dL is suggestive of underlying pathology)

- **Creatinine**
  - Decreases from 0.7 to 0.5 mg/dL (0.9 is suggestive of underlying renal impairment)

- **BUN, Cr will likely not be elevated even with severe proteinuria**
Normal pregnancy renal physiology

- **Serum uric acid**
  - Declines in early pregnancy
  - Nadir 2-3 mg/dL at 24 weeks after which rise until the end of pregnancy (close to nonpregnant values)
  - Rise is caused by increased renal tubular absorption of urate
  - ? Diagnostic value in preeclampsia

- **Urine protein excretion**
  - Increases from nonpreg values of 60-90 mg/24 hrs to 180-250 mg/24 hrs in 3rd trimester
  - Absorption of filtered protein in proximal tubule is reduced
  - Screening method – urine dipstick
    - 1+ ~ 30mg/dL ~ 300mg/24 hr
  - 24 hr urine does not change much trimester to trimester (Higby et al)
  - Abnormal when >300mg/24 hr period
  - 20 weeks as cutoff for determining if underlying renal impairment or pregnancy related

- **Preexisting proteinuria tends to increase in 2nd and 3rd trimesters**
  - Study of pts with diabetic nephropathy
    - Amount of proteinuria increased from mean of 1.74 g/24 hr to 4.82 g/24 hr irrespective of presence of pre-eclampsia
Creatinine clearance (CrCl)

- Estimation of glomerular filtration rate
- \( GFR = CrCl \) (assumptions in notes)
  - \( GFR \times SCr = UCr \times V \)
  - \( GFR = \frac{UCr \times V}{SCr} \)
  - \( CrCl = \frac{UCr(mg/dL) \times vol(\text{urine flow rate per unit time L/day})}{SCr(mg/dL)} \)
  - Collection for 24hrs, multiply above by 1000 to convert to mL and divide by 1440 (minutes in a day) = mL/min
  - \( CrCl = \frac{[UCr(mg/dL) \times vol(L/day)] / SCr(mg/dL)}{1440} \)
  - Adjust to body surface area
    - As an example, a creatinine clearance of 70 mL/min in a small woman with a weight and height of 50 kg and 160 cm, who has a BSA of 1.5 kg/m2, is corrected to a body surface area of 1.73 m2 as follows:
      - \( CCr \times 1.73/BSA = \frac{[70 \text{ mL/min} \times 1.73]}{1.5} = 80 \text{ mL/min per 1.73 m2} \)
Glomerular filtration rate changes with pregnancy in normal women, those stable after unilateral nephrectomy, and those with a successful renal transplant. (Data from Newcastle-upon-Tyne, 1974–2006, courtesy of Dr. John Davison.)
Comparison of blood volume expansion in 44 normally pregnant women at term with 29 who had eclampsia; 10 with moderate chronic renal insufficiency (CRI)—serum creatinine 1.5 to 2.9 mg/dL; and 4 with severe CRI—serum creatinine ≥3.0 mg/dL. (Data from Zeeman and colleagues, 2009, and Cunningham and associates, 1990.)
Chronic Renal Insufficiency and Pregnancy Outcomes (vs serum creatinine mg/dL)

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Queenan 2007
Renal Disease

- Diabetic Nephropathy
- Nephrotic syndrome
- Lupus Nephritis
- Glomerulonephritis
• In contrast to lupus nephritis, the outcome of pregnancy in women with renal involvement as a result of periarteritis nodosa is very poor, largely because of the associated hypertension, which frequently is malignant. Many cases in the literature have involved maternal demise. However, this dismal prognosis is based primarily on selected anecdotal studies, and a few successful pregnancies have been reported. Still, until more data are available (perhaps through a registry), consideration of early therapeutic termination must be made in the best interests of maternal health.
Periarteritis Nodosa

Multiple aneurysms of renal vessels in Polyarteritis

Diabetic Nephropathy
Diabetic nephropathy

- Diagnosis
  - White classification - >500mg /24hr
  - Macroalbuminuria (300mg/24 hours) – cleveland clinic def
    - http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/diabetic-nephropathy/#cesec1
  - Abnormal renal function as represented by an abnormality in serum creatinine, CrCl, GFR
  - ‘clinically – diabetic nephropathy is characterized by a progressive increase in proteinuria and decline in GFR, hypertension, and a high risk of CV morbidity and mortality’
- ADA 2009 - Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD).
  - Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes.
  - Microalbuminuria is also a well-established marker of increased CVD risk.
  - Patients with microalbuminuria who progress to macroalbuminuria (300 mg/24 h) are likely to progress to ESRD
- Landon 2007 – 30-299mg/24hr (incipient nephropathy ‘pre’); overt = 500mg/24 hr ;–
Glucose + NH₂-R → K₁ → Schiff base → K₂ → Amadori product → Kₙ → Intermediate glycosylation products → K₂ → Advanced glycosylation endproducts

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{C} & \quad \text{(CHOH)}₄
\end{align*}
\begin{align*}
\text{H} & \quad \text{N} \cdot \text{R} \\
\text{C} & \quad \text{(CHOH)}₄
\end{align*}
\begin{align*}
\text{CH₂-NH-R} & \quad \text{C} = \text{O} \\
\text{(CHOH)}₃ & \quad \text{(CHOH)}₂
\end{align*}
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{CH₂OH} & \quad \text{CH₂OH}
\end{align*}
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\begin{align*}
\text{O} & \quad \text{N} \cdot \text{N} \\
\text{O} & \quad \text{N} \cdot \text{N}
\end{align*}
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis. Courtesy of Helmut Rennke, MD.

Advanced nephropathy

Normal glomerulus

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows). Courtesy of Helmut G Rennke
Diabetic nephropathy

• Management
  – Optimizing glucose control
  – Renoprotective medications – diltiazem, nifedipine, amlodipine
    • CI – Right heart failure
  – If also chronic hypertensive –
    • BP goals – 110-129/65-79 (ADA, 2009)
  – Monitoring for preeclampsia
  – Fetal surveillance
  – Ophthalmic surveillance
Lupus Nephritis
Glomerular and interstitial nephritis (e.g. lupus nephritis)

- Diagnosis (Gupta 2005)
  - WHO classifications 1974, 1982, ; 2005 Gupta review
  - Morphological diagnosis – 6 levels of classification; latest study from 2005
  - Level of proteinuria and serum creatinine - used more to follow progression

- LN is thus divided into 6 classes according to severity of the lesions observed\cite{16}: (Mariani 2004 from renal pathology society working group conf in 2002)

  - Class I, minimal mesangial LN;
  - Class II, mesangial proliferative LN;
  - Class III, focal LN;
  - Class IV, diffuse segmental LN;
  - Class V, membranous LN; and
  - Class VI, advanced sclerosing LN.
Lupus Nephritis

Table 1. WHO 1974 Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Normal glomeruli by LM, IF, EM</td>
</tr>
<tr>
<td>Class II</td>
<td>Purely mesangial disease</td>
</tr>
<tr>
<td>IIa</td>
<td>- Normocellular mesangium by LM but mesangial deposits on IF and EM</td>
</tr>
<tr>
<td>IIb</td>
<td>- Mesangial hypercellularity with mesangial deposits by IF or EM</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal proliferative glomerulonephritis (&lt;50%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse proliferative glomerulonephritis (&gt;50%)</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous glomerulonephritis</td>
</tr>
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</table>

and vascular lesions were also not included in this classification.

This classification was first modified in 1982 by the International Study of Kidney Diseases in Children group (Table 2). In this classification, class II was divided into IIa and IIb.
Fig 5. Renal biopsy showing enlarged glomerulus displaying thickening of glomerular basement membrane and epimembranous spikes consistent with SLE WHO class V (PAS).

Class V lupus nephritis may occur with class III or IV in which case both will be diagnosed.

Class VI lupus nephritis may show advanced sclerosis

\[ \geq 90\% \text{ glomeruli globally sclerosed without residual activity.} \]

Proliferative mesangial deposits

Identifying this and it is important to note is that for previously described cases or segmental or global

GUPTA 2005 – Rheum association lupus nephritis classes
Lupus nephritis

- Indications for a renal biopsy in nonpregnant SLE patients include:
  - Hematuria and proteinuria;
  - Renal dysfunction;
  - Hypertension;
  - Low levels of the complement factor C3;
  - The presence of chronic renal lesions;
  - Modifications in therapy: initiation, changes, or discontinuation.
Lupus nephritis (Foley ICU book)-Dr. Silver

- Preexisting renal disease
  - 50% of patients with SLE will develop renal disease
  - Results from immune complex deposition, complement activation, and inflammation of the kidney
  - Potential for permanent decrease in renal function after pregnancy with renal disease
    - Burkett 1985 – 242 pregns, 59% no change, 30% transient renal impairment, 7% permanent renal insufficiency
    - Serum creatinine of 1.5mg/dL; if greater – ‘correlation of deterioration of renal function during and after pregnancy; if <1.5, pt can reassured that pregnancy will not increase the rate of deterioration of renal function; specific type of renal disease documented histologically does not appear to influence pregnancy outcome or renal function
Lupus nephritis (Silver – ICU book)

- Pt with severe nephritis may present with acute renal insufficiency
  - DDX – preeclampsia, lupus flare, acute rejection (if transplanted kidney) – may require renal biopsy
  - Frequently respond to glucocorticoids (prednisone 1mg/kg/d)
  - If proliferative nephritis – may require cyclophosphamide
  - If not responsive to medical therapy, serum cr >3.5mg/dL, dialysis should be started to optimize pregnancy outcome
**Glomerular and interstitial nephritis (e.g. lupus nephritis)**

- **Management**
  - **Baseline labs** – 24 hr urine analysis; metabolic profile/serum creatinine, CBC,
  - **If also chronic hypertensive** –
    - **BP goals** – 110-129/65-79 (extrapolated from ADA, 2009)
  - **Monitoring for preeclampsia**
  - **Fetal surveillance**
  - **Renoprotective medications** – diltiazem, nifedipine, amlodipine; No ACE inhibitors, ARBS
**Lab tests that may be used to distinguish preeclampsia from lupus flare** (Silver, ICU book)

<table>
<thead>
<tr>
<th>Lab test to differentiate lupus vs preeclampsia</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement levels</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased dsDNA</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Increased serum cr</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
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Objective: Our aim was to review our experience with renal biopsy in pregnancy. Study Design: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case. Results: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosi confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy. Conclusion: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term. (Am J Obstet Gynecol 2001;184:1093-6.)
A – Normal kidney
B – Endotheliosi
C – electron micrograph of B
http://www.nature.com/ki/journal/v67/n6/fig_tab/4495287f2.html
Lupus Nephritis

**Figure 1.** Glomerular tuft with proliferation of mesangial cells, segments with endocapillary proliferation, and a small circumscribed crescent (arrow). In lupus nephritis active proliferation and glomerular changes are frequently segmental; nevertheless, to determine if it is class III (focal) or IV (diffuse) it is necessary to quantify the percentage of glomeruli with lesions.

http://www.kidneypathology.com/English_version/Lupus_nephritis.html
# Lupus Flare vs. Preeclampsia

<table>
<thead>
<tr>
<th>Finding/test</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
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<tbody>
<tr>
<td>Decreased complement</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased anti-ds DNA Ab</td>
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<td>+++</td>
</tr>
<tr>
<td>Antithrombin III decreased</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
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<td>Increased serum creatinine</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
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Uterine Artery Notching – Present in Preeclampsia
Indications for PA Catheter in Hypertensive Disease

- Severe preeclampsia with refractory oliguria or pulmonary edema
- Ineffective IV antihypertensive therapy
- Intraoperative or intrapartum cardiac failure
- Significant cardiac disease
Pulmonary Edema in Preeclampsia – 3 subsets

- **Management**
  - Intravascular volume depletion (oliguria), low PCWP, high CO, high SVR, low CVP –
    - fluids
  - Renal Vasoconstriction (High PCWP, Normal CO and SVR, uroconcentration):
    - Dopamine – 1-5µg/kg/min; furosemide
  - LV Dysfunction/Failure with Vasospasm (high PCWP, high SVR, low CO <5 L/min, NL-high CVP) :
    - Needs Afterload Reduction (Sodium nitroprusside 0.25-0.5µg/kg/min IV infusion)
    - Volume Restriction
    - Diuretics (max acute dose of furosemide is 120mg, start with 20-40mg)
  - Mechanical Ventilation for Respiratory Failure (If still Pregnant, Intubate Early rather than Late)
Renal Biopsies in Pregnancy

• Complications -
  – Hematoma formation
  – Bleeding
  – Death

• Usually does not help change management

• If steroids are the change in management, then steroid administration is of lower risk than a renal biopsy
Renal Biopsy

- **Risks in pregnancy**
  - Hematoma formation
  - Renal dysfunction

- **Lupus Nephritis**
  - Increased mesangial matrix and mesangial hypercellularity (increased leukocytes)

- **Preeclampsia - Endotheliosis**
Renal Biopsy

• Preeclampsia
  - A – endothelial swelling
  - B – Glomerular necrosis
  - C – sloughing of tubular epithelial cells
<table>
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<tr>
<th>Diagnostic index</th>
<th>Prerenal azotemia</th>
<th>Ischemic intrinsic renal azotemia/ acute tubular necrosis</th>
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<tbody>
<tr>
<td>FENA (%)</td>
<td>&lt;1</td>
<td>&gt;1 -2(1 = obstructive)</td>
</tr>
<tr>
<td>Urine Na conc (meq/L)</td>
<td>&lt;10 (&lt;20 CCOB 4th ed)</td>
<td>&gt;10 (&gt;40 CCOB)</td>
</tr>
<tr>
<td>Urine cr / plasma cr ratio</td>
<td>&gt;40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Urinary urea nitrogen / plasma urea nitrogen ratio</td>
<td>&gt;8’</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Urine spec gravity</td>
<td>&gt;1.018</td>
<td>&lt;1.012</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/Kg H2O)</td>
<td>&gt;500</td>
<td>&lt;250-350</td>
</tr>
<tr>
<td>Plasma BUN/ cr ratio</td>
<td>&gt;20</td>
<td>&lt;10-15</td>
</tr>
<tr>
<td>Renal failure index (Una/Ucr/Pcr)</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Hyaline casts</td>
<td>Muddy brown granular casts</td>
</tr>
</tbody>
</table>
Renal Failure
Acute and chronic renal failure

- Management
  - Establish etiology
  - Attempts to reverse or treat underlying process
  - Nephrology consultation
  - Supportive therapy
  - Correction of metabolic acidosis with bicarbonate or dialysis (p153 Foley ICU book)
  - Prevent hyperphosphatemia (diet restriction, calcium binders with meals)
  - Prevent hyperkalemia (avoid in diet, kayexalate – cation/exchange resin)
    - If associated ECG changes (peaked T waves) IV calcium gluconate (1gm); infusion of glucose/insulin; inhaled beta agonist; dialysis
  - Fluid balance !!
  - Dialysis (cr >3.5)
  - Control of HTN
  - Evaluation for preeclampsia, and continue basic principles to establish M-F wellbeing
Chronic Renal Insufficiency and Pregnancy Outcomes (expressed by serum creatinine mg/dL)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
<th>Cr 1.5-3</th>
<th>Cr &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>13%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5%</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>IUGR</td>
<td>10%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Abortion</td>
<td>11%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Surviving infants</td>
<td>84%</td>
<td>62%</td>
<td>50%</td>
</tr>
</tbody>
</table>

— Williams Obstetrics
Birthweight percentiles of infants born to 29 women at Parkland Hospital with mild to moderate renal insufficiency—serum creatinine 1.4–2.4 mg/dL (black points) and severe renal insufficiency—serum creatinine ≥2.5 mg/dL (red points). (Data are from Cunningham and colleagues, 1990; and Stettler and Cunningham, 1992. Growth curves are those reported by Alexander and co-workers, 1996.)
Dialysis
Indications for dialysis (in pregnancy)

• AEIOU (acidosis, electrolytes, Intox, overload/volume, uremia)
• Clinical evidence of uremia (pericarditis, encephalopathy, metabolic, neurologic, GI, cardiac – arrythmias)
  – BUN > 50-70mg/dL (lower than for nonpreg)
  – Serum creatinine >6-7mg/dL (lower than for nonpreg)
• Volume overload - Intractable intravascular volume overload (despite diuresis)
• Hyperkalemia (>5.0) or severe acidosis (<7.2) resistant to conservative measures
• Above Conditions not responsive to conservative measures
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- Needed for acute renal failure, ESRD, deterioration of chronic renal function, possible prophylactic dialysis
  - Pregnant women that have progressive loss of renal function represent ~20% of women undergoing dialysis (Hou 1999)

- In CRF – cutoff of GFR (if 24 hr urine CrCl gets <5-10ml/min), then hyperkalemia, metabolic acidosis, fluid overload, uremia is likely to develop (<15ml/min in diabetics with end organ disease)
Dialysis — p191 CC OB 4th ed (Gail Seiken)

• Modes
  – Hemodialysis
  – Peritoneal dialysis
    • Continuous ambulatory PD
    • Continuous cycling PD
    • Nocturnal intermittent PD
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- Advantage in pregnancy of
  - Hemodialysis – less work intensive for patient
    - No risk if peritoneal catheter-related complications (laceration of uterine vessels, infection, peritonitis, PTL, but PTL is also observed in HD pts)
    - No interruption in therapy needed after Csection
  - Peritoneal Dialysis – stable biochemical environment
    - Continuous fluid removal avoids hypotension
    - Allows liberal fluid intake
    - Permits continuous insulin administration in DM
    - No anticoagulation needed
    - Permits administration of intraperitoneal MgSO4 in pree (ideally better steady state, but still IV bolusing and rates in patients with renal failure is typically needed)
    - HTN easier to control; Less severe anemia
Mode of dialysis and fetal outcome

- Initially improved with peritoneal
- National Registry for pregnancy in Dialysis pts
  - N=184; ~40% HD and 40% PD – identical fetal survival rates (Okundaye 1998)
- Chou – 2008 – Preg outcome –
  - Avg GA of delivery – 31 wks
  - HD – 70% success ; PD 64.2% success
  - BW not different
Dialysis – p191 CC OB 4th ed (Gail Seiken)

- Intensive dialysis
  - Daily dialysis in pregnancy to minimize fetal exposure to uremic toxins and improve outcome
  - NPDR – infant survival 73% in women needed to start dialysis in pregnancy vs being dialyzed at the beginning (40%)
  - Initiate dialysis at BUN 60-70mg/dL and creatinine of 6-7mg/dL with goal of BUN <50, cr <5
    - Fetal urea production 540mg/d in 3rd trim
    - HD – daily – 5+ hours /day
    - Best outcomes if >20+ hours of dialysis weekly
    - Low level of azotemia prevents hydramnios, PTL – based on urea diuresis that normally occurs in utero due to high fetal BUN
  - Avoids large dialytic weight gains and fluid shifts and labile BPs, less hypotension, also better HTN control
Dialysis in pregnancy (CCOB 4th ed)

- Maternal – Fetal complications
  - Accelerated decline in renal function – 1/3 (Imbasciata 1991, n=80pt)
  - Accelerated HTN – 50%
  - Superimposed preeclampsia – 60% (Cunningham 1990, n=37)
  - PTL
  - Worsening anemia
  - HD access thrombosis
  - Placental abruption
  - Pregnancy loss – 50%
  - PTB - >90%
  - IUGR – 20%
  - Polyhydramnios
Dialysis changes
- Less Na taken off due to hyponatremia of preg; less HCO3 to avoid untoward alkalosis that exists in pregnancy
- No acetate dialysis b/c of hypotension?
- Monitor K and Ca to avoid hypokalemia and hypercalcemia (b/c of placental calcitriol increasing the absorption of calcium for fetal stores)
Dialysis – p191 CC OB 4th ed (Gail Seiken)

- Fetal monitoring? - Before and after?
  - Uptodate – ‘Careful uterine and fetal monitoring during hemodialysis, such as assessment of the fetal heart rate (particularly during the last portion of a session), combined with measures aimed at preventing dialysis-induced hypotension should be performed. Maternal hemodynamic instability may compromise the uteroplacental circulation and may be associated with the induction of uterine contractions
  - N=5 Bamburg Germany – ‘intensive fetal surveillance not well defined’
  - NSTs twice weekly; serial growth scans q 4weeks
Dialysis – p191 CC OB 4th ed (Gail Seiken)

• Mode of delivery – CD for obstetric indications
  – If CD performed and peritoneal dialysis is mode – will need to interrupt dialysis regimen to allow healing or switch to HD temporarily
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- **Anemia** –
  - Increase in plasma volume without a corresponding increase in Red cell mass
  - Deficient EPO production, short red cell survival, bone marrow suppression by uremia toxins
  - Need for erythropoietin to get hct to 30%, transfusion to > 21%, higher if delivery imminent
  - EPO - low chance of birth defects, minimal gets to fetus; doses needed during pregnancy increase
  - Chao (2002 – retrospective – 18 pregnancies) used hgb 6 as cutoff for transfusion,
  - CCOB – 4th ed- ‘It is accepted by most obstetricians that hgb <6g/dL is associated with increased perinatal mortality and maternal morbidity secondary to high output cardiac failure)
  - Iron supplementation oral, IV if persistent deficiency
Dialysis

• Diet –
  – Protein – 1g/kg/d HD; 1.5 for PD; add 20g/d for pregnancy
  – Supplement water soluble vitamins, folate, zinc, iron
  – Avoid standard prenatal vitamins b/c of too much vit A
  – Rx, consult with Pharmacist
  – Folic acid 2mg/d
Table 48-4. Pregnancy Outcomes in 118 Women Undergoing Dialysis during Pregnancy – Williams - Textbook

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Delivery (wks)</th>
<th>Birthweight (g)</th>
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<tr>
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<td>Approximate averages</td>
<td>118</td>
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<td>1500</td>
<td>40–50</td>
<td>40</td>
<td>25–30</td>
<td>70–80</td>
</tr>
</tbody>
</table>
Pregnancy after Kidney Transplant
Renal transplantation – Scott

- 1 in 20 women of childbearing age with a functioning renal allograft becomes pregnant, >10,000 pregnancies have occurred
- Ideal if serum creatinine is <1.5mg/dL
- Risks of deterioration of renal function, rejection, maternal death; no direct evidence that pregnancy has a deleterious effect on the transplanted kidney
- Risk of graft rejection and permanent renal dysfunction is 10-20% (same for nonpregnant pt)
- Signs of rejection – fever, oliguria, deteriorating renal function, enlargement of kidney, tenderness to palpation - need to rule out infection, preeclampsia, glomerulonephritis, nephrotoxicity from immunosuppressant meds
- Risks of PTB, IUGR, fetal death – from CHTN, pree
- BP goal <140/90, ACE inhib good, but not in pregnancy, CCB (nifedipine) help counter vasoconstrictive effect of cyclosporine
Optimal pregnancy outcome – prognostic factors (p639 – CC OB 4th ed)

- 1-2 years since transplant
- Good general health and prognosis
- Satisfactory graft function with no evidence of rejection
- Stable immunosuppressive regimen
- No/minimal HTN or proteinuria
- Serum cr <1.5-2mg/dL
- Family support
Prenatal care in allograft recipients

- PRENATAL care – close surveillance for allograft rejection, infection, HTN, anemia, preeclampsia, fetal growth, monitoring for UTIs (esp in kidney transplant); Asx bacteruria tx for 2 weeks with f/u cultures, poss suppression doses
  - Other infections of note – bacterial/fungal endometritis, wound infection, skin abscesses, pneumonia (aspergillus, Pneumocystis, Mycobacterium TB, listeria)
  - Poss for Rh sens from graft;
  - CMV infection (usually ppx 3 mo after transplant, poss primary or recurrent CMV can cause congenital infection)
  - HBV, HCB – HBIG, HBV vaccine to newborn are 90% effective at preventing chronic HBV hepatitis
  - ACV for HSV
Immunosuppressants in transplant pt (Scott CC OB)

- All drugs cross placenta, diffuse to fetus
- No convincing evidence that prednisone, azathioprine, cyclosporine, tacrolimus produce congenital abnormalities;
- Drugs of choice in preg transplant pts
- a/e IUGR, PTB, o/w neonates do well
  - Short term ‘prematurity issues of infection, hypoglycemia, bone marrow hypoplasia, leukopenia, reduced IGM, IGG, elevated serum cr’ hard to know if it’s the drug or prematurity
- Long term – poss infertility, autoimmune disease, neoplasia – need for long term f/u
Immunosuppressants
Azathioprine
per Dr. Scott in CC in OB book 4th ed

- Azathioprine – MOA – inhibits T-lymphocytes; D
  - More toxic metabolite 6-mercaptopurine - purine analog that decreases delayed hypersensitivity and cellular cytotoxicity
  - a/e – infection, neoplasia, liver tox, bone marrow suppression
  - 64-90% of azathioprine crosses the placenta, majority if inactive thiouric acid
  - D b/c increased anomaly rate of 9 and 6.4%, not found in recent series, no specific pattern, possible bone marrow suppression in fetus, with anemia, leukopenia, thrombocytopenia
  - One approach – titrate to normal WBC counts in preg
Immunosuppressants

per Dr. Scott in CC in OB book 4th ed

• Tacrolimus – MOA – inhibits T-lymphocytes; C
  – FK506 – macrolide abx from streptomyces;
  – Incidence of post transplant DM with tacrolimus is 11-20%; median time to onset is 68d; 50% reversible
  – Nephrotoxicity, hyperkalemia in 1/3; HA, tremor, motor fxn, sensory fxn are neuro a/e
  – Cord blood concentrations 50% of maternal levels, no proven association with anomalies to date
Immunosuppressants - Cyclosporine per Dr. Scott in CC in OB book 4th ed

- Cyclosporine – MOA – inhibits T-lymphocytes; C
  - Fungal metabolite, inhibits Tcell response by inhibiting IL2
  - Improved survival in transplant pt, in most regimen
  - a/e – nephrotoxicity, HTN; others hirsutism, tremor, gingival hyperplasia, hepatotoxicity, risk of lymphomas
  - Cyclosporine levels drop in pregnancy, but graft function remains stable in most pts (Bumgardner Matas 1992)
  - Readily crosses placenta, no evidence of teratogenicity
Immunosuppressants - prednisone

- Prednisone- IV used to tx acute rejection reactions
  - MOA – inhibit humoral and cell mediated immune response
  - a/e – glucose intolerance, PPROM, hirsutism, acne, wt gain, cushinoid appearance, striae, osteonecrosis, osteoporosis, fluid retention, HTN, infection, impaired wound healing, mood changes
  - Metabolized by placental 11-hydroxyxygenase to inactive 11-keto form – fetus is exposed to 10% of maternal dose
  - Dose – 10-30mg/d
  - a/e preg – poss PPROM, PTB, pree, IUGR
  - Prolonged courses of fluorinated steroids (dexa, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob
Immunosuppressants -

**Cyclophosphamide** per Dr. Scott in CC in OB book 4th ed

- Cyclophosphamide – MOA – alkylating agent; D
  - cancer chemotherapy and as an immunosuppressant
  - In human pregnancies, cyclophosphamide exposures that occurred during the first trimester have been associated with skeletal and palate defects, as well as malformations of the limbs and eyes
  - Cyclophosphamide is excreted into human milk (34). Two reports indicates that the platelet and leukocyte counts of a nursing infants were reversibly depressed during maternal cyclophosphamide therapy (35,48). Cyclophosphamide was classified among the cytotoxic drugs that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics (36).
Renal Biopsies in Pregnancy

• Complications -
  – Hematoma formation
  – Bleeding
  – Death

• Usually does not help change management

• If steroids are the change in management, then steroid administration is of lower risk than a renal biopsy
PKD
Polycystic Kidney Disease

- AD disease of kidneys
- 1 in 800 live births
- Cause of 10% of end-stage renal disease in the United States
- 85% due to \textit{PKD1} gene mutations (C16)
- 15% due to \textit{PKD2} (C4), Salant 2008
- Variable penetrance and expressivity
- PNDX possible if mutation is known (family member or linkage studies)
PKD

• Renal complications M>F, 20s and 30s
• HTN in 75%
• Flank pain, hematuria, nocturia, proteinuria, calculi, infection, progression to renal failure, superimposed acute renal failure may also develop from infection or obstruction from ureteral angulation by cyst displacement
• Other organs –
  – Hepatic (F>M), 1/3 of patients
  – Cardiac – Valve lesions, mitral, aortic, and tricuspid incompetence
  – CNS – 10% of patients with PKD die from rupture of associated intracranial berry aneurysm
PKD

• Pregnancy
• Pregnancy outcome depends on the degree of associated hypertension and renal insufficiency.
• UTIs are common
• Chapman -1994
  – 235 affected women, 605 pregnancies vs 108 unaffected family members, 244 pregnancies
  – Composite perinatal complication rates were similar—33 versus 26 percent—but hypertension, including preeclampsia, was more common in women with polycystic kidneys.
• Pregnancy does not seem to accelerate the natural disease course (Lindheimer and colleagues, 2007).
Take home points

• CCBs for HTN in renal patients
• PKD – check head MRI, echo; GHR
• Dialysis – Outcomes similar re: mode, extra folic acid, increase dialysis time
• Transplant – Outcomes better >2yr of Cr <1.5, on immunosuppressants, no HTN, no rejection
• Polyarteritis nodosa – CI to pregnancy
Cases - 1

- 30 yo P1001 at 28 weeks – Admitted for pyelonephritis
  - Describe management
Cases - 1

• 30 yo P1001 at 28 weeks – Admitted for pyelonephritis
  – Describe management
  – Worsening at 72h of hospitalization – febrile, tachycardic, tachypneic
    • Describe evaluation, management
A series of anterior-posterior projection chest radiographs of improving acute respiratory distress syndrome (ARDS) in a second-trimester pregnant woman with severe pyelonephritis. A. An extensive infiltrative process and complete obliteration of the diaphragm (white arrows) is seen. B. Improved aeration of lung fields bilaterally is noted as pleural disease resolves (arrows). C. Markedly improved visualization of the lungs fields with residual platelike atelectasis and normal appearance of the diaphragm.

Legend:

From: Chapter 48. Renal and Urinary Tract Disorders
Williams Obstetrics, 23e, 2010
Cases - 2

- 35 yo P0000, PPC, Hx of lupus nephritis, desiring pregnancy
  - HTN – On lisinopril
  - Describe evaluation, management, counseling
Cases – 3

• 25 yo P0000 - Hx of PKD
  – Describe evaluation, management in setting of prepregnancy counseling/evaluation

  – Comes back 12 weeks later and is pregnant, describe counseling re: genetics and inheritance risk
Notes
End
Williams
Glomerular filtration rate changes with pregnancy in normal women, those stable after unilateral nephrectomy, and those with a successful renal transplant. (Data from Newcastle-upon-Tyne, 1974–2006, courtesy of Dr. John Davison.)
Williams - UTI
A series of anterior-posterior projection chest radiographs of improving acute respiratory distress syndrome (ARDS) in a second-trimester pregnant woman with severe pyelonephritis. A. An extensive infiltrative process and complete obliteration of the diaphragm (white arrows) is seen. B. Improved aeration of lung fields bilaterally is noted as pleural disease resolves (arrows). C. Markedly improved visualization of the lungs fields with residual platelike atelectasis and normal appearance of the diaphragm.

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Legend:
Nephrolithiasis -
Chronic Renal Disease and Dialysis
Comparison of blood volume expansion in 44 normally pregnant women at term with 29 who had eclampsia; 10 with moderate chronic renal insufficiency (CRI)—serum creatinine 1.5 to 2.9 mg/dL; and 4 with severe CRI—serum creatinine ≥3.0 mg/dL. (Data from Zeeman and colleagues, 2009, and Cunningham and associates, 1990.)

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Glomerular nephropathies
**Williams Obstetrics, 23e**  
**Table 48-5. Causes of Acute Nephritic Syndrome**

<table>
<thead>
<tr>
<th><strong>Poststreptococcal infection</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacute bacterial endocarditis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Antiglomerular basement membrane disease</td>
</tr>
<tr>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>ANCA small vessel vasculitis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Mesangioproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Causes</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Minimal change disease (MCD) (10–15%)</strong></td>
</tr>
<tr>
<td>primary idiopathic (most cases),</td>
</tr>
<tr>
<td>drug-induced (NSAIDs), allergies, viral</td>
</tr>
<tr>
<td>infections</td>
</tr>
<tr>
<td><strong>Focal segmental glomerulosclerosis (FSGS)</strong></td>
</tr>
<tr>
<td>(33%): viruses, hypertension, reflux</td>
</tr>
<tr>
<td>nephropathy, sickle-cell disease</td>
</tr>
<tr>
<td><strong>Membranous glomerulonephritis (30%)</strong></td>
</tr>
<tr>
<td>idiopathic (majority), malignancy,</td>
</tr>
<tr>
<td>infection, connective-tissue diseases</td>
</tr>
<tr>
<td><strong>Diabetic nephropathy</strong>: most common cause</td>
</tr>
<tr>
<td>of ESRD</td>
</tr>
<tr>
<td><strong>Amyloidosis</strong></td>
</tr>
</tbody>
</table>
Acute Renal Failure
Williams
From MFM fellow didactic series

- Each disease – criteria for diagnosis; overall management
- Prediction of disease on pregnancy and vice versa slide
- Indications for dialysis slide
- Interpretation of FeNa, osmolality slide
Diabetic nephropathy

- **Diagnosis**
  - White classification - >500mg /24hr
  - Macroalbuminuria (300mg/24 hours) –cleveland clinic def
    - http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/diabetic-nephropathy/#cesec1
  - Abnormal renal function as represented by an abnormality in serum creatinine, CrCl, GFR
  - ‘clinically – diabetic nephropathy is characterized by a progressive increase in proteinuria and decline in GFR, hypertension, and a high risk of CV morbidity and mortality

- **ADA 2009** - Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD).
  - Persistent albuminuria in the range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes.
  - Microalbuminuria is also a well-established marker of increased CVD risk.
  - Patients with microalbuminuria who progress to macroalbuminuria (300 mg/24 h) are likely to progress to ESRD

- **Landon 2007** - 30-299mg/24hr (incipient nephropathy ‘pre’); overt =
Glucose + NH$_2$-R $\overset{K_1}{\longrightarrow}$ Schiff base $\overset{K_2}{\longrightarrow}$ Amadori product $\overset{K_n}{\longrightarrow}$ Intermediate glycosylation products $\overset{K_2}{\longrightarrow}$ Advanced glycosylation endproducts
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis. Courtesy of Helmut Rennke, MD.

Normal glomerulus

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows). Courtesy of Helmut G Rennke
Diabetic nephropathy

• Management
  – Optimizing glucose control
  – Renoprotective medications – diltiazem, nifedipine, amlodipine
  – If also chronic hypertensive –
    • BP goals – 110-129/65-79 (ADA, 2009)
  – Monitoring for preeclampsia
  – Fetal surveillance
  – Ophthalmic surveillance
Glomerular and interstitial nephritis (e.g. lupus nephritis)

- Diagnosis (Gupta 2005)
  - Morphological diagnosis – 6 levels of classification; latest study from 2005
  - Level of proteinuria and serum creatinine - used more to follow progression

- LN is thus divided into 6 classes according to severity of the lesions observed\textsuperscript{16}: (Mariani 2004 from renal pathology society working group conf in 2002)
  - Class I, minimal mesangial LN;
  - Class II, mesangial proliferative LN;
  - Class III, focal LN;
  - Class IV, diffuse segmental LN;
  - Class V, membranous LN; and
  - Class VI, advanced sclerosing LN.
Lupus Nephritis

Table 1. WHO 1974 Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Normal glomeruli by LM, IF, EM</td>
</tr>
<tr>
<td>Class II</td>
<td>Purely mesangial disease</td>
</tr>
<tr>
<td>IIa</td>
<td>- Normocellular mesangium by LM but mesangial deposits on IF and EM</td>
</tr>
<tr>
<td>IIb</td>
<td>- Mesangial hypercellularity with mesangial deposits by IF or EM</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal proliferative glomerulonephritis (&lt;50%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse proliferative glomerulonephritis (≥50%)</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous glomerulonephritis</td>
</tr>
</tbody>
</table>

and vascular lesions were also not included in this classification.

This classification was first modified in 1982 by International Study of Kidney Diseases in Children group\(^4\,^{15}\) (Table 2). In this classification, there is normal, divided into five classes A to E.


<table>
<thead>
<tr>
<th>Class</th>
<th>Morphological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial lupus. Normal glomeruli by LM but mesangial immune deposits by IF.</td>
</tr>
<tr>
<td>Class II</td>
<td>Mesangial proliferative lupus nephritis. Purely mesangial hypercellularity of any degree or mesangial matrix expansion on LM with mesangial immune deposits. A few subendothelial or subepithelial deposits may be visible by IF or EM but not by LM.</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal lupus nephritis.</td>
</tr>
<tr>
<td>III (A)</td>
<td>Active or inactive, segmental or global, endo or extracapillary</td>
</tr>
<tr>
<td>III (A/C)</td>
<td>Glomerulonephritis involving ≤50% of all glomeruli typically with focal</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse lupus nephritis.</td>
</tr>
<tr>
<td>IV-S (A)</td>
<td>Active lesions: diffuse segmental proliferative lupus nephritis.</td>
</tr>
<tr>
<td>IV-G (A)</td>
<td>Active lesions: diffuse global proliferative lupus nephritis.</td>
</tr>
<tr>
<td>IV-S (A/C)</td>
<td>Active and chronic lesions: diffuse segmental proliferative &amp; sclerosing lupus nephritis.</td>
</tr>
<tr>
<td>IV-G (A/C)</td>
<td>Active and chronic lesions: diffuse global proliferative &amp; sclerosing lupus nephritis.</td>
</tr>
<tr>
<td>IV-S (C)</td>
<td>Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis.</td>
</tr>
<tr>
<td>IV-G (C)</td>
<td>Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis.</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous lupus nephritis.</td>
</tr>
</tbody>
</table>

This classification, while highly specific, does not include designation of distribution or segment of previous or crescentic involvement.
Lupus nephritis

- Indications for a renal biopsy in nonpregnant SLE patients include:
  - Hematuria and proteinuria;
  - Renal dysfunction;
  - Hypertension;
  - Low levels of the complement factor C3;
  - The presence of chronic renal lesions;
  - Modifications in therapy: initiation, changes, or discontinuation.
Lupus nephritis (Foley ICU book)-Dr. Silver
author ch

• Preexisting renal disease
  – 50% of patients with SLE will develop renal disease
  – Results from immune complex deposition, complement activation, and inflammation of the kidney
  – Potential for permanent decrease in renal function after pregnancy with renal disease
    • Burkett 1985 – 242 preg, 59% no change, 30% transient renal impairment, 7% permanent renal insufficiency
    • Serum creatinine of 1.5mg/dL; if greater – ‘correlation of deterioration of renal function during and after pregnancy; if <1.5, pt can reassured that pregnancy will not increase the rate of deterioration of renal function; specific type of renal disease documented histologically does not appear to influence pregnancy outcome or renal function
Lupus nephritis (Silver – ICU book)

• Pt with severe nephritis may present with acute renal insufficiency
  – DDX – preeclampsia, lupus flare, acute rejection (if transplanted kidney) – may require renal biopsy
  – Frequently respond to glucocorticoids (prednisone 1mg/kg/d)
  – If proliferative nephritis – may require cyclophosphamide
  – If not responsive to medical therapy, serum cr >3.5mg/dL, dialysis should be started to optimize pregnancy outcome
Glomerular and interstitial nephritis (e.g. lupus nephritis)

- **Management**
  - Baseline labs – 24 hr urine analysis; metabolic profile/serum creatinine, CBC,
  - If also chronic hypertensive –
    - BP goals – 110-129/65-79 (ADA, 2009)
  - Monitoring for preeclampsia
  - Fetal surveillance
  - Renoprotective medications – diltiazem, nifedipine?
## Lab tests that may be used to distinguish preeclampsia from lupus flare

(Silver, ICU book)

<table>
<thead>
<tr>
<th>Lab test to differentiate lupus vs preeclampsia</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement levels</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased dsDNA</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Increased serum cr</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Renal biopsy in pregnancy – N=18, Kuller 2001

Objective: Our aim was to review our experience with renal biopsy in pregnancy. Study Design: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case. Results: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosis confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy. Conclusion: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term. (Am J Obstet Gynecol 2001;184:1093-6.)
Acute and chronic pyelonephritis

• Diagnosis
  – Acute (2%) of all pregnancies – fever, flank pain, urine analysis, culture; recurrence rate 20%
  
  • Association with MR? (McDermott 2000 – 41000 medicaid pregnancy chart review)) – in patients not treated or noncompliant – association of fetal death and postnatal mental retardation
  
  – Chronic - tubulointerstitial disease – infectious or noninfectious (p908- Creasy), outcome is good if normotensive and
Acute and chronic pyelonephritis

Management

- **Acute** – IV hydration, IV antibiotics; imaging if no improvement after 48-72 hr
  - 10-20% rate of bacteremia
  - Monitor for preterm labor
  - Course of abx to treat infection
  - Oral suppression
  - Serial urine cultures (esp if no suppression)
- **Chronic** – surveillance of infections, acute infection
  - ? Suppression
  - Postnatal surveillance if acute infection develops during pregnancy, ck for persistent renal pelvis/calyceal dilation (Creasy p908, Twickler 1994)
Objective: Our aim was to review our experience with renal biopsy in pregnancy. Study Design: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case. Results: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosis confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy. Conclusion: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term. (Am J Obstet Gynecol 2001;184:1093-6)
Periarteritis nodosa

• Def - Polyarteritis nodosa is a rare multi-system disorder characterized by widespread inflammation, weakening, and damage to small and medium-sized arteries. Blood vessels in any organ or organ system may be affected, including those supplying the kidneys, heart, intestine, nervous system, and/or skeletal muscles. Damage to affected arteries may result in abnormally increased blood pressure (hypertension), "ballooning" (aneurysm) of an arterial wall, the formation of blood clots (thrombosis), obstruction of blood supply to certain tissues, and/or tissue damage and loss (necrosis) in certain affected areas.

• Guarded prognosis because of associated malignant hypertension

• Preconception, antenatal counseling – avoidance of pregnancy, recommendation for termination if pregnant

• Literature – case reports – mainly comprised of maternal deaths
  – Burkett G, Richards R. Pregnancy in patients with periarteritis resulted in maternal death in 7 of the 8 cases that have been reported. In the present case, periarteritis was in remission throughout the pregnancy; the patient was thus the second known maternal survivor. The infant also did well. It is suggested that pregnancy probably does not have as direct an effect on the course of the disorder as appears from the outcome of the previous cases. Extreme caution must prevail, especially as diagnosis is often difficult and experience so limited.
Systemic sclerosis

- **Def** – autoimmune systemic condition (Raynauds, hardening of skin, + anti centromere and anti topoisomerase ab, +ANA) – p 910

- Renal involvement in 60% of pt within 3-4 yrs of dx

- Treatment involves preventing pulmonary complications; treating hypertension

- Maternal deaths due to onset during pregnancy or pulmonary complication; pregnancy not common due to onset in 4-5th decades
Nephrotic syndrome

• Diagnosis – proteinuria (>3.5gm/day); hypoalbuminemia; hypercholesterolemia; hypertriglycerideridemia; edema

• Most common cause – preeclampsia late in pregnancy
  – Next is diabetic nephropathy
  – Membranoproliferative glomerulonephritis; Glomerular disease, lupus nephritis, minimal change disease
• Management
  - Rule out preeclampsia, define etiology
  - ?biopsy
  - Sudden appearance of nephrotic syndrome with any of the glomerular diseases should prompt evaluation of preeclampsia, renal vein thrombosis
  - If renal function is adequate, no hypertension, pregnancy should be tolerated
  - Hypoalbuminemia of pregnancy increases fluid retention, edema
  - Diuretics for massive fluid retention causing hypertension
  - Anticoagulation
Chronic undifferentiated renal disease (arteriolar nephrosclerosis)

- Diagnosis – ‘malignant hypertension’
  - Hallmark - Hypertension first
  - See on u/s, MRI – small kidneys
  - Renal failure (elevated creatinine and BUN, hyperphosphatemia) in a hypertensive pt; biopsy is rarely indicated per uptodate
  - Hypertensive end organ damage (eg, retinal changes, left ventricular hypertrophy)
  - No other cause of chronic kidney disease
  - The diagnosis may be suspected when routine blood tests indicate deteriorating renal function in a hypertensive patient.
  - Hypertension should be present before onset of proteinuria and renal failure, and there should be no other clinically suspected cause of renal failure. (vs nephrotic syndrome where hypertension is after massive proteinuria)
  - At risk groups – blacks, marked elevations of BP, diabetics with nephropathy
Chronic undifferentiated renal disease (arteriolar nephrosclerosis)

- **Management**
  - Baseline lab assessment, renal function assessment
  - BP control (DBP <90) and prevention of labile hypertension
  - Maternal surveillance for hypertension, close surveillance for superimposed preeclampsia esp if renal dysfunction is significant;
  - What drug is best for renal protection and what level of BP control best prevents progression of renal dysfunction; no definite answer per uptodate (ACE-, ARB, CCB)
  - Fetal surveillance (growth, biophysical testing)
Renal transplantation – Scott

• 1 in 20 women of childbearing age with a functioning renal allograft becomes pregnant, >10,000 pregnancies have occurred
• Ideal if serum creatinine is <1.5mg/dL
• Risks of deterioration of renal function, rejection, maternal death; no direct evidence that pregnancy has a deleterious effect on the transplanted kidney
• Risk of graft rejection and permanent renal dysfunction is 10-20% (same for nonpregnant pt)
• Signs of rejection – fever, oliguria, deteriorating renal function, enlargement of kidney, tenderness to palpation – need to rule out infection, preeclampsia, glomerulonephritis, nephrotoxicity from immunosuppressant meds
• Risks of PTB, IUGR, fetal death – from CHTN, pree
• BP goal <140/90, ACE inhib good, but not in pregnancy, CCB (nifedipine) help counter vasoconstrictive effect of cyclosporine
Optimal pregnancy outcome – prognostic factors (p639 – CC OB 4th ed)

- 1-2 years since transplant
- Good general health and prognosis
- Satisfactory graft function with no evidence of rejection
- Stable immunosuppressive regimen
- No/minimal HTN or proteinuria
- Serum cr <1.5-2mg/dL
- Family support
Prenatal care in allograft recipients

- PRENATAL care – close surveillance for allograft rejection, infection, HTN, anemia, preeclampsia, fetal growth, monitoring for UTIs (esp in kidney transplant); Asx bacteruria tx for 2 weeks with f/u cultures, poss suppression doses
  - Other infections of note – bacterial/fungal endometritis, wound infection, skin abscesses, pneumonia (aspergillus, Pneumocystis, Mycobacterium TB, listeria)
  - Poss for Rh sens from graft;
  - CMV infection (usually ppx 3 mo after transplant, poss primary or recurrent CMV can cause congenital infection)
Immunosuppressants in transplant pt (Scott CC OB)

- All drugs cross placenta, diffuse to fetus
- No convincing evidence that prednisone, azathioprine, cyclosporine, tacrolimus produce congenital abnormalities;
- Drugs of choice in preg transplant pts
- a/e IUGR, PTB, o/w neonates do well
  - Short term ‘prematurity issues of infection, hypoglycemia, bone marrow hypoplasia, leukopenia, reduced IGM, IGG, elevated serum cr’ hard to know if it’s the drug or prematurity
- Long term – poss infertility, autoimmune disease, neoplasia – need for long term f/u
Immunosuppressants

Azathioprine

per Dr. Scott in CC in OB book 4th ed

- Azathioprine – MOA – inhibits T-lymphocytes; D
  - More toxic metabolite 6-mercaptopurine- purine analog that decreases delayed hypersensitivity and cellular cytotoxicity
  - a/e – infection, neoplasia, liver tox, bone marrow suppression
  - 64-90% of azathioprine crosses the placenta, majority if inactive thiouric acid
  - D b/c increased anomaly rate of 9 and 6.4%, not found in recent series, no specific pattern, possible bone marrow suppression in fetus, with anemia, leukopenia, thrombocytopenia
  - One approach – titrate to normal WBC counts in preg
Immunosuppressants

per Dr. Scott in CC in OB book 4<sup>th</sup> ed

- **Tacrolimus** – MOA – inhibits T-lymphocytes; C
  - FK506 – macrolide abx from streptomykes;
  - Incidence of post transplant DM with tacrolimus is 11-20%; median time to onset is 68d; 50% reversible
  - Nephrotoxicity, hyperkalemia in 1/3; HA, tremor, motor fxn, sensory fxn are neuro a/e
  - Cord blood concentrations 50% of maternal levels, no proven association with anomalies to date
Immunosuppressants -

**Cyclosporine** per Dr. Scott in CC in OB book 4th ed

- Cyclosporine – MOA – inhibits T-lymphocytes; C
  - Fungal metabolite, inhibits T-cell response by inhibiting IL2
  - Improved survival in transplant pt, in most regimen
  - a/e – nephrotoxicity, HTN; others hirsutism, tremor, gingival hyperplasia, hepatotoxicity, risk of lymphomas
  - Cyclosporine levels drop in pregnancy, but graft function remains stable in most pts (Bumgardner Matas 1992)
  - Readily crosses placenta, no evidence of teratogenicity
Immunosuppressants - prednisone

- Prednisone - IV used to tx acute rejection reactions
  - MOA – inhibit humoral and cell mediated immune response
  - a/e – glucose intolerance, PPROM, hirsutism, acne, wt gain, cushinoid appearance, striae, osteonecrosis, osteoporosis, fluid retention, HTN, infection, impaired wound healing, mood changes
  - Metabolized by placental 11-hydroxygenase to inactive 11-keto form – fetus is exposed to 10% of maternal dose
  - Dose – 10-30mg/d
  - a/e preg – poss PPROM, PTB, pree, IUGR
  - Prolonged courses of fluorinated steroids (dexa, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob
Immunosuppressants - Cyclophosphamide per Dr. Scott in CC in OB book 4th ed

- Cyclophosphamide – MOA – alkylating agent; D
  - cancer chemotherapy and as an immunosuppressant
  - In human pregnancies, cyclophosphamide exposures that occurred during the first trimester have been associated with skeletal and palate defects, as well as malformations of the limbs and eyes
  - Cyclophosphamide is excreted into human milk (34). Two reports indicates that the platelet and leukocyte counts of a nursing infants were reversibly depressed during maternal cyclophosphamide therapy (35,48). Cyclophosphamide was classified among the cytotoxic drugs that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics (36).
Acute and chronic renal failure

- Diagnosis – decreased urine production, <400-500 cc/day
  - Elevated serum creatinine, BUN
  - Urine studies

- Acute kidney injury - rapidly progressive loss of renal function; oliguria; electrolyte imbalance; results from prerenal, intrinsic or post renal disease; goal is to identify the cause so as to halt the process or reverse it; dialysis may be needed in the meantime;

- Chronic kidney disease – long term result from an acute nonreversible insult or occurs from a chronic disease progression

- Acute-on-chronic renal failure – acute renal injury in a patient that has known or unknown chronic renal disease or insufficiency; goal is to identify the cause for the acute decompensation so as to reverse the process as measured by return of serum creatinine to baseline (difficulty arises when there is no baseline)
Acute renal failure in pregnancy DDx

- Preeclampsia (proteinuria, HTN, edema)
- HELLP syndrome (RUQ pain, proteinuria, hemolysis, elevated LFTs, thrombocytopenia, normal coags)
- TTP (microangiopathic hemolytic anemia - MAHA; thrombocytopenia; neurologic (confusion, HA, paresis, visual hallucinations, seizures); fever; renal dysfunction; All 5 in 40%; Anemia, thrombocytopenia, neuro in 75%)
- Prerenal azotemia (decreased renal perfusion...
Acute renal failure - DDX

- Acute tubular necrosis - brown granular casts, renal tubular cells, proteinuria <2g/d; FENA >2%; HTN uncommon rather hypotension, sepsis, hemorrhage
- Acute interstitial nephritis – hematuria, pyuria, eosinophils, WBC casts; proteinuria <2g/d; FENA >2%; HTN uncommon rather fever, skin rash, new medication
- Acute glomerulonephritis – hematuria RBC casts, oval fat bodies; >2g, but <3.5 gm proteinuria/day, poss nephrotic range, FENA <1%; HTN common, collagen vascular disease, infection
- Obstruction – mass, stone; exam, CT
Acute renal failure DDX

- Acute fatty liver of pregnancy (elevated LFTs, hyperbilirubinemia, coagulopathy, oliguria, nausea, abd pain, leukocytosis, hypoglycemia)
- Postpartum renal failure /HUS – PP, MAHA, severe HTN, prodromal illness, thrombocytopenia, CNS sx
- Pyelonephritis _ urine culture, fever, flank pain
- Bilateral renal cortical necrosis – hemorrhage, hypotension/shock, oliguria/anuria (<50ml/d), flank pain, gross hematuria; dx by renal arteriogram demonstrating virtual absence of cortical blood flow despite renal artery patency; high mortality
Acute tubular necrosis and renal cortical necrosis – see renal failure slides

• Diagnosis
Acute tubular necrosis and renal cortical necrosis – see renal failure slides

• Management
# Urine indices used in the DDX of prerenal and Ischemic intrinsic renal disease/azotemia

<table>
<thead>
<tr>
<th>Diagnostic index</th>
<th>Prerenal azotemia</th>
<th>Ischemic intrinsic renal azotemia/ acute tubular necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENA (%)</td>
<td>&lt;1</td>
<td>&gt;1 -2(1 = obstructive)</td>
</tr>
<tr>
<td>Urine Na conc (meq/L)</td>
<td>&lt;10 (&lt;20 CCOB 4th ed)</td>
<td>&gt;10 (&gt;40 CCOB)</td>
</tr>
<tr>
<td>Urine cr / plasma cr ratio</td>
<td>&gt;40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Urinary urea nitrogen / plasma urea nitrogen ratio</td>
<td>&gt;8’</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Urine spec gravity</td>
<td>&gt;1.018</td>
<td>&lt;1.012</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/Kg H20)</td>
<td>&gt;500</td>
<td>&lt;250-350</td>
</tr>
<tr>
<td>Plasma BUN/ cr ratio</td>
<td>&gt;20</td>
<td>&lt;10-15</td>
</tr>
<tr>
<td>Renal failure index (Una/Ucr/Pcr)</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Hyaline casts</td>
<td>Muddy brown granular casts</td>
</tr>
</tbody>
</table>
Acute and chronic renal failure

- Management
  - Establish etiology
  - Attempts to reverse or treat underlying process
  - Nephrology consultation
  - Supportive therapy
  - Correction of metabolic acidosis with bicarbonate or dialysis (p153 Foley ICU book)
  - Prevent hyperphosphatemia (diet restriction, calcium binders with meals)
  - Prevent hyperkalemia (avoid in diet, kayexalate – cation/exchange resin)
    - If associated ECG changes (peaked T waves) IV calcium gluconate (1gm); infusion of glucose/insulin; inhaled beta agonist; dialysis
  - Fluid balance !!
  - Dialysis (cr >3.5)
  - Control of HTN
  - Evaluation for preeclampsia, and continue basic principles to establish M-F wellbeing
Indications for dialysis (in pregnancy)  

Foley ICU book; CCOB 4th ed

• AEIOU (acidosis, electrolytes, Intox, overload/volume, uremia)

• Clinical evidence of uremia (pericarditis, encephalopathy, metabolic, neurologic, GI, cardiac – arrythmias)
  – BUN > 50-70mg/dL (lower than for nonpreg)
  – Serum creatinine >6-7mg/dL (lower than for nonpreg)

• Volume overload - Intractable intravascular volume overload (despite diuresis)

• Hyperkalemia (>5.0) or severe acidosis (<7.2) resistant to conservative measures

• Above Conditions not responsive to conservative measures
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- Needed for acute renal failure, ESRD, deterioration of chronic renal function, possible prophylactic dialysis
  - Pregnant women that have progressive loss of renal function represent ~20% of women undergoing dialysis (Hou 1999)

- In CRF – cutoff of GFR (24 hr urine CrCl gets <5-10ml/min hyperkalemia, metabolic acidosis, fluid overload, uremia is likely to develop (15ml/min in diabetics with end organ disease)
Dialysis

• Modes
  – Hemodialysis
  – Peritoneal dialysis
    • Continuous ambulatory PD
    • Continuous cycling PD
    • Nocturnal intermittent PD
Dialysis — p191 CC OB 4th ed (Gail Seiken)

- Advantage in pregnancy of
  - hemodialysis – less work intensive for patient
    - No risk if peritoneal catheter-related complications (laceration of uterine vessels, infection, peritonitis, PTL, but PTL is also observed in HD pts)
    - No interruption in therapy needed after Csection
  - Peritoneal D – stable biochemical environment
    - Continuous fluid removal avoids hypotension
    - Allows liberal fluid intake
    - Permits continuous insulin administration in DM
    - No anticoagulation needed
    - Permits administration of intraperitoneal MgSO4 in pree (ideally better steady state, but still IV bolusing and rates in patients with renal failure is typically needed)
    - HTN easier to control; Less severe anemia
Dialysis – p191 CC OB 4th ed (Gail Seiken)

• Mode of dialysis and fetal outcome
  – Initially improved with peritoneal
  – National Registry for pregnancy in Dialysis pts
    • N=184; ~40% HD and 40% PD – identical fetal survival rates (Okundayye 1998)
Intensive dialysis
- Daily dialysis in pregnancy to minimize fetal exposure to uremic toxins and improve outcome
- NPDR – infant survival 73% in women needed to start dialysis in pregnancy vs being dialyzed at the beginning (40%)
- Initiate dialysis at BUN 60-70mg/dL and creatinine of 6-7mg/dL with goal of BUN <50, cr <5
  - Fetal urea production 540mg/d in 3rd trim
  - HD – daily – 5+ hours /day
  - Best outcomes if >20+ hours of dialysis weekly
  - Low level of azotemia prevents hydramnios, PTL – based on urea diuresis that normally occurs in utero due to high fetal BUN
- Avoids large dialytic weight gains and fluid shifts and labile BPs, less hypotension, also better HTN control
Dialysis in pregnancy (CCOB 4th ed)

- Maternal – Fetal complications
  - Accelerated decline in renal function – 1/3 (Imbasciata 1991, n=80pt)
  - Accelerated HTN – 50%
  - Superimposed preeclampsia – 60% (Cunningham 1990, n=37)
  - PTL
  - Worsening anemia
  - HD access thrombosis
  - Placental abruption
  - Pregnancy loss – 50%
  - PTB - >90%
  - IUGR – 20%
  - Hydramnios
Dialysis changes

- Less Na taken off due to hyponatremia of preg; less HCO3 to avoid untoward alkalosis that exists in pregnancy
- No acetate dialysis b/c of hypotension?
- Monitor K and Ca to avoid hypokalemia and hypercalcemia (b/c of placental calcitriol increasing the absorption of calcium for fetal stores)
Fetal monitoring? - Before and after?

- Uptodate – ‘Careful uterine and fetal monitoring during hemodialysis, such as assessment of the fetal heart rate (particularly during the last portion of a session), combined with measures aimed at preventing dialysis-induced hypotension should be performed. Maternal hemodynamic instability may compromise the uteroplacental circulation and may be associated with the induction of uterine contractions

- N=5 Bamburg Germany – ‘intensive fetal surveillance not well defined’

- NSTs twice weekly; serial growth scans q 4weeks
Dialysis – p191 CC OB 4th ed (Gail Seiken)

• Mode of delivery – CD for obstetric indications
  – If CD performed and peritoneal dialysis is mode – will need to interrupt dialysis regimen to allow healing or switch to HD temporarily
• Anemia –
  – Increase in plasma volume without a corresponding increase in Red cell mass
  – Deficient EPO production, short red cell survival, bone marrow suppression by uremia toxins
  – need for erythropoietin to get hct to 30%, transfusion to > 21%, higher if delivery imminent
  – EPO- low chance of birth defects, minimal gets to fetus; doses needed during pregnancy increase
  – Chao (2002 – retrospective – 18 pregnancies) used hgb 6 as cutoff for transfusion,
  – CCOB – 4th ed- ‘It is accepted by most obstetricians that hgb <6g/dL is associated with increased perinatal mortality and maternal morbidity secondary to high output cardiac failure)
  – Iron supplementation oral, IV if persistent deficiency
Dialysis

- **Diet** –
  - **Protein** – 1g/kg/d HD; 1.5 for PD; add 20g/d for pregnancy
  - **Supplement** water soluble vitamins, folate, zinc, iron
  - **Avoid standard prenatal vitamins b/c of too much vit A**
### Chronic Renal Insufficiency and Pregnancy Outcomes (expressed by serum creatinine mg/dL)

— Williams Obstetrics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
<th>Cr 1.5-3</th>
<th>Cr &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>13%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5%</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>IUGR</td>
<td>10%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Abortion</td>
<td>11%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Surviving infants</td>
<td>84%</td>
<td>62%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Antihypertensives

- **Procardia** (nifedipine) – CCB - C
- **Diltiazem** – CCB - C
• See ppt slides in folder of renal disease in preg

• Physiology
• DM nephropathy
• Lupus nephritis
• Renal transplant
• Indications for Dialysis
• Oliguria in severe preeclampsia
Renal Disease in Pregnancy

• END

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