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
Case 1

- 28 yo P0
- 12 weeks pregnant
- PMHx- Polycystic kidney disease
- Baseline creatinine- 2.0mg/dL
- CHTN
- Treatment for CHTN?
- Counseling re: genetic risk to fetus?
Case 2

• 32 yo P1001 – 22 weeks
• PMHX – Hx of Lupus nephritis, CHTN
• Presents due to uncontrolled HTN in office, 3+ proteinuria
• DDx – Lupus nephritis exacerbation vs early onset severe SI preeclampsia vs other etiology
• How do you tell which one?
Physiologic changes - Renal
Normal pregnancy renal physiology

- Blood volume expansion by 30-50%, CO increased by 30-50%

- 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
Cardiac Output Across Gestation

Cardiac Output Increased by 30-50%
Twin Pregnancy: Add another 15%
Starts Early and Peaks at 20 Weeks
FIGURE 5-11 Sequential changes (±SEM) in blood pressure throughout pregnancy in 69 women in supine (blue lines) and left lateral recumbent positions (red lines). PP = postpartum. (Adapted from Wilson and colleagues, 1980.)
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
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.)
Creatinine clearance (CrCl)

- **Estimation of glomerular filtration rate**
- **GFR = CrCl (assumptions in notes)**
  - \( \text{GFR} \times \text{SCr} = \text{UCr} \times V \)
  - \( \text{GFR} = \frac{\text{UCr} \times V}{\text{SCr}} \)
  - \( \text{CrCl} = \frac{\text{UCr}(\text{mg/dL}) \times \text{vol(ureine flow rate per unit time L/day})}{\text{SCr}(\text{mg/dL})} \)
  - Collection for 24hrs, multiply above by 1000 to convert to mL and divide by 1440 (minutes in a day) = mL/min
  - \( \text{CrCl} = \left\{\frac{\text{UCr}(\text{mg/dL}) \times \text{vol(L/day)}}{\text{SCr}(\text{mg/dL})}\right\} \times 1000 \) / 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:
      - \( \text{CCr} \times 1.73/\text{BSA} = \left[70 \text{ mL/min} \times 1.73\right] / 1.5 = 80 \text{ mL/min per 1.73 m2} \)
Urine protein/creatinine ratio

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

<table>
<thead>
<tr>
<th>TABLE E-1. Diagnostic Criteria for Preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
</tr>
<tr>
<td>• 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</td>
</tr>
<tr>
<td>• 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</td>
</tr>
<tr>
<td>and</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
</tr>
<tr>
<td>• Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>• Protein/creatinine ratio greater than or equal to 0.3*</td>
</tr>
<tr>
<td>• Dipstick reading of 1+ (used only if other quantitative methods not available)</td>
</tr>
<tr>
<td>Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
</tr>
<tr>
<td>• Platelet count less than 100,000/microliter</td>
</tr>
<tr>
<td><strong>Renal insufficiency</strong></td>
</tr>
<tr>
<td>• Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease</td>
</tr>
<tr>
<td><strong>Impaired liver function</strong></td>
</tr>
<tr>
<td>• Elevated blood concentrations of liver transaminases to twice normal concentration</td>
</tr>
<tr>
<td><strong>Pulmonary edema</strong></td>
</tr>
<tr>
<td><strong>Cerebral or visual symptoms</strong></td>
</tr>
</tbody>
</table>

*Each measured as mg/dL.*
### 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
Renal Disease

- Diabetic Nephropathy
- Nephrotic syndrome
- Lupus Nephritis
- Glomerulonephritis
- Polyarteritis nodosa - CI to pregnancy
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

http://www.learningradiology.com/notes/che...
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
Hydroxychloroquine

- Hydroxychloroquine (antimalarial/antirheumatic; binds DNA, interferes with vesicle functions, inhibits phospholipid metabolism; immunosuppressive by inhibiting rheumatoid factor, acute phase reactants, enzymes)
  - Stopping this in pregnancy is associated with increased risk of lupus flares, continuing this drug is recommended if needed to control lupus (prospective study by cortes-hernandez showed the increased risk)
  - Large series show no increased risk of anomalies
  - Used in prevention of malaria with increase of fetal anomalies
  - Not associated with increased r/o fetal malformations

- Class C
- Chloroquine possible teratogenic in initial studies
  - Ototoxicity, eye development

- Decreased risk of CHB (SSA/B + patients)

Buchanan, 1996; Khamashta 1996
Klinger 2001; Motta 2002

<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</td>
</tr>
<tr>
<td></td>
<td>LM with mesangial immune deposits. A few subendothelial or subepithelial deposits may</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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>
</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 VI 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;
  - 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 pregms, 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>

Foley OB ICU care manual
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 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.)
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.
Uterine Artery Notching – Present in Preeclampsia
Dialysis
Dialysis patients

• HD vs PD – no difference in pregnancy outcomes – HD (needs thromboppx)
• Frequency/duration of dialysis times should increase – daily, longer hours
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
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 –
  - 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

- 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
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  
(Villalobos, Obstet Gynecol, 2005, p639 – CC OB 4\textsuperscript{th} 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
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
Tacrolimus

- **Tacrolimus** (inhibits T lymphocyte activation, immunosuppressant)
- **Dose in liver transplant**
  - 0.1-0.15mg/kg/d po divide q12 hr
- **Preg class C**
- **Therapeutic drug levels** 5-20 ng/ml just before next dose; time to steady state 3 days
- **Monitor creatinine, K, fasting blood glucose, serum drug levels**
Azathioprine

- Azathioprine (inhibits T lymphocytes)
- Class D
- Teratogenic in animals, appears safe in humans
- Associated with IUGR
- Neonatal immunosuppression
- Indicated in pregnancy if chronic high doses of steroids is not controlling symptoms or to lower steroid dose
- One approach – titrate to normal WBC counts in preg
Cyclosporine

- Cyclosporine A (inhibits T lymphocytes)
- Preg class C
- Data comes from use in renal transplant patients, not an animal teratogen, appears safe in humans, long term follow up studies are limited
Glucocorticoids

- Glucocorticoids (antiinflammatory, glucocorticoid, mineralocorticoid)
- Preg class C
- Avoid fluorinated glucocorticoids b/c they cross the placenta
  - Hydrocortisone, prednisone, prednisolone inactivated by 11-beta hydroxysteroid dehydrogenase in the placenta allowing <10% of active drug to reach fetus
- High dose associated with maternal/fetal A/E
  - Osteoporosis (tx with vit D, ca2+); glucose intolerance, sodium, h2o retention; hypertension, infection; avascular necrosis
  - Preg complications – GDM, preeclampsia, PPROM, IUGR
  - Incidence of fetal adrenal suppression with maternal tx is low
- Avoid empiric treatment, use at lowest possible dose
- Stress dose steroids (hydrocortisone 100mg IV q8hr in labor and for 24 hr PP)
  - Use if chronic steroids (>5mg/day for >2-4 weeks prior to delivery)
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 (dixa, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob
  - Stress dosing at delivery
Cyclophosphamide

• Cyclophosphamide (alkylates and cross links DNA)

• Preg class D
  – Cleft palate, skeletal abnormalities, abnormal renal function
  – Avoid, esp in first trimester
  – May be needed in cases of severe proliferative nephritis (drug of choice in nonpregnant patients with proliferative lupus nephritis)
  – Crosses placenta
Pregnancy - FDA classes

- **A** – controlled studies show no fetal risk in any trimester, probability of fetal harm is remote
- **B** – animal studies, no risk; if risk in animal studies, controlled human studies do not confirm harm
- **C** – harm in animal studies with no controlled human studies; no available human or animal studies
- **D** – human studies show fetal risk but r/b relative to medical state of mother may support use
- **X** – animal/human studies show fetal risk or abnormalities, use is contraindicated during pregnancy or in women who may become pregnant
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).
PKD
Case 1

- 28 yo P0
- 12 weeks pregnant
- PMHx- Polycystic kidney disease
- Baseline creatinine- 2.0mg/dL
- CHTN
- Treatment for CHTN?
- Counseling re: genetic risk to fetus?
Autosomal Dominant

• Males and females equally affected
• Affected person has an affected parent
• Many are structural
• Many are new mutations
• Penetrance and expressivity are important
  – Penetrance – If you inherit the gene, will you show the disease
  – Expressivity – If you show the disease, how severe will you show it
• Age of onset is important
• 50% recurrence risk
Autosomal Dominant Pedigree
Case 2

- 32 yo P1001 – 22 weeks
- PMHX – Hx of Lupus nephritis, CHTN
- Presents due to uncontrolled HTN in office, 3+ proteinuria
- DDx – Lupus nephritis exacerbation vs early onset severe SI preeclampsia vs other etiology
- How do you tell which one?
## 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>
Maternal Mortality

- Maternal death is defined as one that occurs during pregnancy or within 42 days of the end of a pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by a woman's pregnancy, but not from accidental or incidental cause. Maternal mortality rates are calculated as the number of maternal deaths in a calendar year divided by the number of live births for the same period, multiplied by 100,000. The number of live births used in the denominator is an approximation of the population of pregnant women who are at risk of a maternal death. The numerator is calculated using data from the Final Mortality File from NCHS, included in these deaths assigned an underlying cause of death ICD-10 code of A34, O00-O95, or O98-O99. The denominator is calculated using data from the Natality File from NCHS.
Average
Peristats

Rate per 100,000 live births

15
10
7.9
5
13.3
Total

Kansas
US
Maternal Mortality Rates, by Race/Ethnicity, 2006

Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System

US Dept of Health and Human Services,
Health Resources and Services Administration
Maternal Mortality Rates, by Age, 2006
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System

US Dept of Health and Human Services,
Health Resources and Services Administration
THE FIVE MAIN CAUSES OF MATERNAL DEATH IN THE USA

**Embolism 20%**
A blood clot that blocks an essential blood vessel, for example in the lungs

**Hemorrhage 17%**
Severe blood loss

**Pre-eclampsia and eclampsia 16%**
Disorders associated with excessively high blood pressure

**Infection 13%**

**Cardiomyopathy 8%**
Heart muscle disease

Disturbing as these figures are, they probably significantly understate the problem. There are no federal requirements to report maternal deaths and US authorities
Table 2. Estimated Maternal Mortality Rates, 48 States and the District of Columbia, 2000–2014*

<table>
<thead>
<tr>
<th>Year</th>
<th>Maternal Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>18.8</td>
</tr>
<tr>
<td>2001</td>
<td>19.2</td>
</tr>
<tr>
<td>2002</td>
<td>19.5</td>
</tr>
<tr>
<td>2003</td>
<td>19.9</td>
</tr>
<tr>
<td>2004</td>
<td>20.3</td>
</tr>
<tr>
<td>2005</td>
<td>20.6</td>
</tr>
<tr>
<td>2006</td>
<td>21.0</td>
</tr>
<tr>
<td>2007</td>
<td>21.3</td>
</tr>
<tr>
<td>2008</td>
<td>21.7</td>
</tr>
<tr>
<td>2009</td>
<td>22.0</td>
</tr>
<tr>
<td>2010</td>
<td>22.4</td>
</tr>
<tr>
<td>2011</td>
<td>22.8</td>
</tr>
<tr>
<td>2012</td>
<td>23.1</td>
</tr>
<tr>
<td>2013</td>
<td>23.5</td>
</tr>
<tr>
<td>2014</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Rates back-estimated from reported 2014 rate for states with the standard pregnancy question using a weighted average of the slopes from groups 1–4; see “Materials and Methods.”

* Excludes California and Texas.

It would be preferable to analyze data individually for each state; however, maternal death is a rare event, and the number of cases (396 U.S. deaths in 2000 and 856 in 2014) was not sufficient to support individual state analysis for all but the most populous states (California and Texas). Rather, states needed to be grouped by some mechanism to create groups large enough for analysis. However, states varied
Recent Increases in the U.S. Maternal Mortality Rate

Disentangling Trends From Measurement Issues

Marian F. MacDorman, PhD, Eugene Declercq, PhD, Howard Cabral, PhD, and Christine Morton, PhD

Fig. 4. Adjusted maternal mortality rates, Texas, 2000–2014. Texas revised to the U.S. standard pregnancy question in 2006. The unrevised question asked about pregnancies within the past 12 months.


Fig. 5. Unadjusted combined maternal and late maternal mortality rates, California, 2000–2014. Includes pregnancy-related deaths occurring within 1 year of pregnancy. California revised their death certificate in 2003 to a non-standard question that asks about deaths within 1 year of pregnancy. Before 2003, California did not have a pregnancy question on their death certificate.

Maternal Mortality

- Maternal Mortality = death occurring within 42 days after delivery and are directly related to pregnancy or childbirth. Ratio is per 100,000 live births.
- Etiologies –
  - Venous-thromboembolic disease
  - Hemorrhage (0.9/100,000)
  - Hypertension (1.3/100,000)
- 2006 – 13.3/100,000 (vs. 7/100,000 in 1996) – goal was 3.3
  - California – 16.9/100,000 in 2006 (vs. 5.6/100,000 in 1996)
- Reasons for increase –
  - Increase in cesarean rate
  - Pregnancies in women > 30 years old
  - Obesity and associated hypertension and diabetes
- Black women – 3-4x more likely to die from pregnancy complications than white women.
- US women higher risk of dying during pregnancy than 40 other countries
  - 3-5x > Greece, Germany, Spain
- For every maternal death, about 50 additional women experience serious complications during pregnancy or delivery

WHO, 2010; MMWR 2006
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)