PREGNANCY AND RENAL DISEASE
Pathophysiology, diagnosis and clinical management
Kathleen Claes
Core curriculum BVN-SBN 2014

Pregnancy and renal disease
- Physiological changes
- Renal complications of “normal” pregnancy
- Pregnancy in a renal patient
  - Chronic Kidney Disease
  - Transplantation
- The role of the kidney in pre-eclampsia

BMJ 2008; 336: 211–215; Williams D, and Davison J
In renal grafts, male kidneys show equal changes.
Changes independent of graft age.

Figure 1. Renal length in relation to body height, determined from mammograms taken during the immediate postpartum. (From Bailey, R. R., and Bellman, G. L.: Kidney length and urinary dilatation in the postpartum. J. Obstet. Gynaecol. Br.)

Kidney function and disease in pregnancy. Lindheimer. Eds. 1977

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Renal hemodynamics
- Renal blood flow (27%)
- Pelvic kidney (17%)
- Intramural arteriolar resistance (30%)
- Glomerular filtration rate (20%)
- Proteinuria (200 mg/24 h)

Tubular function
- Bladder infection
- Metabolic acidosis
- Cardiac
- Plasma cortisol (40 ng/mL)

Endocrine function
- Renins
- Erythropoietin
- Active vitamin D

BMJ 2003; 326: 211-215, Williams D. and Davison J.
Pregnancy and renal disease

- Physiological changes
- Renal complications of “normal” pregnancy
- Pregnancy in a renal patient
  - Chronic Kidney Disease
  - Transplantation

Renal complications

- Urinary tract infections/pyelonephritis
- Urolithiasis
- Hypertension
- Novel renal diagnosis/ Acute kidney injury
INFECTIONS: UTI

- Untreated → 30-40% pyelonephritis
- Risk ↓ 70-80% after R/
- Treat if
  - >100,000 CFU if asymptomatic
  - w/ symptoms
- Pre-eclampsia:
  - OR 1.22 (1.03-1.45)
- Preterm delivery
  - OR 1.3 (1.2-1.5)

Nicolle LE, Clin Infect Dis. 2005
Minassian C, Plos One 2013
Wing DA, Am J Obstet Gynecol 2000

Amoxycillin: risk for necrotising enterocolitis end of pregnancy
Quinolones: CI do not use

UROLITHIASIS

- Same prevalence as in non-pregnant population
- DD with the physiological dilatation

HYPERTENSION
HYPERTENSION (6%-8%)

- Pre-existing hypertension
- Pregnancy induced hypertension
- Pre-eclampsia/eclampsia

Target blood pressure < 160/105 mm Hg
Renal patients ≤ 140/90 mm Hg

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative rest</td>
<td>No salt restriction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Low dose ASA in all| 60-100 mg/d             | Start 12 weeks   | First choice
|                    |                         |                  | No long term follow-up children hepatotoxicity |
| Labetalol (Trandate)| α-β-adrenergic receptor antagonists | 100-400 mg (2-4/d) maximum dose 1200 mg | First choice
|                    |                         |                  | No long term follow-up children hepatotoxicity |
| Methyldopa (Aldomet)| α2-adrenergic receptor agonists | 250-500 mg (2/d) maximum dose 2 g/d | Maternal side effects: fatigue, nasal congestion, dry mouth, postural hypotension, hepatotoxicity |
| Nifedipine LA (Adalat)| Ca2+ block | 30-120 mg/d | Mildly tocolytic?
|                    |                         |                  | Aggravate oedema                                  |
| Ketanserin         | Sandozine-2 receptor blocker | In combination w/ aspirin & PET |                                               |

HYPERTENSION: NOT RECOMMENDED

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>β-adrenergic receptor antagonists</td>
<td>Side effects: bradycardia, apnoe, hypoglycemia, IUGR, etc.</td>
</tr>
<tr>
<td>ACE-inhibitor or ARB</td>
<td>May be used until pregnant recent data no increase in teratogenicity if stopped in first trimester</td>
<td>Teratogenic in second and third trimester</td>
</tr>
<tr>
<td>Diuretics</td>
<td>May be continued if intake pre-pregancy</td>
<td>Avoid (may limit physiological increase in plasma volume)</td>
</tr>
</tbody>
</table>
**ACUTE KIDNEY INJURY**

- Any renal disorder similar to non-pregnant patients
- Early in pregnancy
  - Prerenal: hyperemesis gravidarum
  - Acute tubular necrosis: septic abortion
- Late in pregnancy
  - Severe pre-eclampsia w/ or w/o HELLP
  - Acute fatty liver of pregnancy
  - Thrombotic micro-angiopathy (HUS)
  - Cortex necrosis (abruptio placentae/placenta praevia)
  - Pyelonephritis

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**NOVEL RENAL DISEASES**

Evaluation during pregnancy

- Immunological testing
- Ultrasound
- Biopsy <32 weeks
  - Complication rate similar as non-pregnant? <-> morbid procedure (7% complications in pregnancy)
  - Limited to women in need for diagnosis
  - Rapidly progressive with active sediment
  - Nephrotic syndrome ? Steroidresponsive?
  - No coagulation abnormalities

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**NOVEL RENAL DISEASES**

- ADPKD
- Focal Sclerosis
- Refluxnephropathy
- IgA nephropathy
- HUS
“Acute post-partum renal failure is one of the strongest complications of an apparently uncomplicated pregnancy and delivery .... Occasionally the same syndrome strikes during pregnancy... Renal failure is usually irreversible although Finkelstein saw 2 patients make an excellent recovery... heparin improved some cases but not others”

Lancet, 1975,801-802

---

**DIFFERENTIAL DIAGNOSIS**

<table>
<thead>
<tr>
<th>Thrombotic microangiopathy: HUS</th>
<th>Severe PET HELLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>mostly PP, every trimester (TPP mostly 3rd trimester)</td>
<td>&gt;20/40, third trimester, intrapartum</td>
</tr>
<tr>
<td>No pre-existing hypertension</td>
<td>Pre-existing hypertension at higher risk</td>
</tr>
<tr>
<td>No DIC</td>
<td>DIC</td>
</tr>
<tr>
<td>Hemolysis, thrombocytopenia, LDH=1000 U/L</td>
<td>Hemolysis, thrombocytopenia, LDH=800 U/L</td>
</tr>
<tr>
<td>Liver function tests: normal</td>
<td>Liver function tests abnormal, subcapsular hematoma</td>
</tr>
</tbody>
</table>

---

**DIAGNOSTICS PREECLAMPSIA**

**Guidelines of ACOG**

- **Blood pressure**
  - ≥140 mm Hg Systolic or 90 mm Hg diastolic on two occasions (4 h apart)
  - >20/40 w with previous normal blood pressure
  - ≥150 mm Hg systolic or ≥110 mm Hg diastolic

- **Proteinuria**
  - >300 mg/24 h or P/C ratio ≥0.3 (Dipstick 1+)
  - Or in the absence of proteinuria, new-onset hypertension with the onset of any of the following:
    - Thrombocytopenia
    - Renal insufficiency
    - Impaired liver function
    - Pulmonary oedema or cerebral or visual symptoms

>100,000/µl

=1.1 mg/dl or doubling

Transaminases >2times ULN

www.acog.org
Differential Diagnosis

<table>
<thead>
<tr>
<th>Signs</th>
<th>Intrinsic renal problem</th>
<th>Pre-eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>&gt;1 mg/dL (variable)</td>
<td>0.8-1.2 mg/dL</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>variable</td>
<td>&gt;300 mg/d</td>
</tr>
<tr>
<td>Uric acid</td>
<td>variable</td>
<td>&gt;5.5 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>variable</td>
<td>&gt;140/90 mm Hg</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>normal</td>
<td>(+)</td>
</tr>
<tr>
<td>Blood platelets</td>
<td>normal</td>
<td>(+)</td>
</tr>
<tr>
<td>Angiogenic factors</td>
<td>sFlt-1 low/PIGF high</td>
<td>S-FB-1 high/PIGF low</td>
</tr>
</tbody>
</table>

Angiogenic Factors

Proteinuria

Proteinuria: P/C ratio is sufficient
Misclassification: 250-400 mg/24h → 24h proteinuria
Pregnancy and renal disease

- Physiological changes
- Renal complications of “normal” pregnancy
- Pregnancy in a renal patient
  - Chronic Kidney Disease
  - Transplantation

“Children of women with renal disease used to be born dangerously or not at all - not at all if their doctors had their way…”

“Nature takes a helping hand by blunting fertility as renal function falls”

Lancet, 1975,801-802

Chronic kidney disease

- What is the underlying disease?
- Impact CKD on pregnancy
- Impact pregnancy on CKD
GENETIC COUNSELLING

ADPKD, familial focal sclerosis, CAKUT, Alport, VUR, ...
But also postpregnancy FU if mother or father VUR: ultrasound postpartum

Renal insufficiency
Chronic hypertension
Proteinuria

Maternal risks
Foetal risks
Impact CKD on Pregnancy

- Renal insufficiency
- Chronic hypertension
- Proteinuria

Maternal risks

Foetal risks
IMPACT PREGNANCY ON CKD

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Dx</th>
<th>Creat mg/dl</th>
<th>Renal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz (1990)</td>
<td>121</td>
<td>GN</td>
<td>Scr 1.4 mg/dl</td>
<td>16%</td>
</tr>
<tr>
<td>Abe (1985)</td>
<td>244</td>
<td>GN</td>
<td>CCr=70mL/min</td>
<td>idem</td>
</tr>
<tr>
<td>Jungers (1995)</td>
<td>360</td>
<td>GN</td>
<td>nd</td>
<td>idem</td>
</tr>
<tr>
<td>Jones (1996)</td>
<td>82</td>
<td>GN</td>
<td>Scr 1.9 mg/dl</td>
<td>31% irrev</td>
</tr>
</tbody>
</table>

Pregnancy in CKD Stages 3 to 5: Fetal and Maternal Outcomes:

- N = 49
- Dx = Ig A nephropathy
  - Mean serum creatinine at conception: 2.1 +/- 1 (SD) mg/dL (186 +/- 88 micromol/L)
  - Mean GFR at conception 35 +/- 12 mL/min/1.73 m² (0.58 +/- 0.2 mL/s/1.73 m²)
- Mean GFR after delivery was less than before conception
- The rate of GFR decrease did not change (0.55 +/- 0.8 versus 0.50 +/- 0.3 mL/min/1.73 m²; 0.0092 +/- 0.013 versus 0.0083 +/- 0.005 mL/s/1.73 m²; P = 0.661)

Impact Pregnancy on CKD

Simbic E. AJKD, 2007
**Pregnancy in chronic kidney disease: need for a common language**

Giovanna S. Pizzol1, Marie-Cécile1, Rosella Attiei1,
Marina Bilocchi1, Carolina Bruschi1, 
Valentino Cornelli1, Maria Chiara De Cossio1, 
Tulio Testa2

1IS Nephrology, Biological and Clinical Sciences, University of Turin, Torino, Italy
2Maternal-Fetal Unit, University of Turin, Turin, Italy

**GENERAL RULES**

- Counselling: patient tailored

**TABLE 1**

<table>
<thead>
<tr>
<th>Women with renal disease who should be referred for pre-pregnancy counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with CKD stage 1-2 and adverse risk factors:</td>
</tr>
<tr>
<td>Significant proteinuria</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Systemic diseases such as lupus or vasculitis</td>
</tr>
<tr>
<td>Previous adverse obstetric history</td>
</tr>
<tr>
<td>Women with CKD stage 3 to 5 including women on dialysis</td>
</tr>
<tr>
<td>Women with renal transplants</td>
</tr>
<tr>
<td>Women with a family history of hereditary renal disease</td>
</tr>
<tr>
<td>CKD = chronic kidney disease.</td>
</tr>
</tbody>
</table>

Lightstone L. J nephrol 2012
GENERAL RULES: CKD stages 1 and 2

- Risk of pre-eclampsie (10%-20%) (5% normal)
- Risk of preterm delivery (11%-40%)
- Low birth weight (5-26%)
- Risk increase with presence of:
  - Proteinuria:
    - No PU: 30% develops PU
    - Nephrotic: thrombophrophylaxis
  - Hypertension:
    - Dd preeclampsia: difficult
    - FU of foetal growth to guide decision about delivery

GENERAL RULES: CKD stages 3 and 4

- Fetal loss is greater
- Preeclampsia: 40%-60%
- Prematurity: 39%-64%
- No creatinine reduction in the first trimester: suggestive of future complications
- Predictors: <40 ml/min/1.73 m² and proteinurie >1 g/24h
- Reduction in fertility

Therapeutic approach

- Timing of conception
  - Diabetes: adequately controlled blood pressure and glucose
  - Lupus nephritis: 6 m quiescent disease
  - Woman: <35y and CKD 4-5 with deteriorating renal function: delay conception until transplantation
  - Woman: >35y and CKD 4-5 with deteriorating renal function: discuss with patient
Therapeutic approach

- ACE-inhibitor and angiotensin 2 receptor blockers
  - Beyond first trimester: CONTRA-indicated
  - Blood pressure control with minimal proteinuria: switch to save therapy preconception
  - Proteinuria: stop while trying to conceive
  - Heavy proteinuria: discontinue after pregnancy confirmed

<table>
<thead>
<tr>
<th>Risk level</th>
<th>History of preeclampsia, especially when accompanied by an adverse outcome</th>
<th>Moderate risk</th>
<th>Consider low-dose aspirin if the patient has several of these moderate-risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Multifetal gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 1 or 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Multiparity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity (body mass index &gt;30 kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family history of preeclampsia (mother or sister)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sociodemographic characteristics (African American race, low socioeconomic status)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ≥35 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, &gt;10-year pregnancy interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>Previous uncomplicated full-term delivery</td>
<td></td>
<td>Do not recommend low-dose aspirin</td>
</tr>
</tbody>
</table>

Doppler of a uterinae at 20 weeks (Resistive and pulsatility index)

Persistence of the notch
• ‘Show me a method of birth control more effective than end stage renal disease’, Roger Rodby MD, 1991

• ‘Even if a woman on CAPD ovulates, doesn’t the egg just float away?’, Rodby, 1992
Higher RRF increases the probability of a successful pregnancy.
Better outcome with increase of dialysis dose
Slow flow, slow ultrafiltration

Piscoll GB. Nephrol Dial Transplant 2014

Pregnancy and renal disease
- Physiological changes
- Renal complications of “normal” pregnancy
- Pregnancy in a renal patient
  - Chronic Kidney Disease
  - Transplantation
Restoration of fertility. **Talk** about it

- 2-8% conceive
- Contraception
  - Barrier methods
  - IUD (intact immune system for efficacy)
  - Hormonal therapy
  - Progestin only: Cerazette
  - Depot progesterone

Consult gynecologist

- Risk of renal transplant on pregnancy and risk of pregnancy on graft survival
- Immunosuppressive therapy
- Antihypertensive therapy (as in non-transplant CKD)
- Hereditary risk (CKD)


**Timing of Pregnancy**

- Stable transplant function
- >1 y after transplantation (guidelines differ)
- 6 m after stop of cellcept (stable graft function)

**What is the effect on the graft?**

![Graph showing graft survival](image)

*FIGURE 2. Kaplan-Meier survival curve comparing postpregnancy graft survival for patients with and those without drug-treated hypertension during pregnancy.*
What is the effect on the graft?

Bramham K et al. CJASN 2013

Pregnancy Outcomes In Renal Transplant Recipients: A Single-Centre

Kaplan-Meier analysis of graft survival

Stoumpos, ERA-EDTA 2014

Pregnancy Outcomes In Renal Transplant Recipients: A Single-Centre Study

Baseline characteristics

Stoumpos, ERA-EDTA 2014
Pregnancy Outcomes In Renal Transplant Recipients: A Single-Centre Study

Stoumpos, ERA-EDTA 2014

Delivery and renal outcomes

<table>
<thead>
<tr>
<th>Delivery and renal outcomes</th>
<th>Programme n (%)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>132</td>
<td>58.6</td>
</tr>
<tr>
<td>Premature birth (&lt; 37 weeks)</td>
<td>41</td>
<td>11.5</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>12</td>
<td>4.8</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>8</td>
<td>3.2</td>
</tr>
<tr>
<td>Low birth weight*</td>
<td>44</td>
<td>18.6</td>
</tr>
<tr>
<td>Very low birth weight##</td>
<td>6</td>
<td>2.6</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>80</td>
<td>78.9</td>
</tr>
<tr>
<td>Emergency Caesarean section</td>
<td>31</td>
<td>38.4</td>
</tr>
<tr>
<td>Renal outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All during pregnancy</td>
<td>6</td>
<td>6.2</td>
</tr>
<tr>
<td>Graft loss within 3 y*</td>
<td>13</td>
<td>5.4</td>
</tr>
<tr>
<td>All graft##</td>
<td>96</td>
<td>11.6</td>
</tr>
<tr>
<td>sCr &gt; 2x upper limit##</td>
<td>58</td>
<td>27.9</td>
</tr>
</tbody>
</table>

*includes 16 cases with missing data; 1 from conception to 2 years after delivery.
All: acute rejection

Sibanda transplantation 2007

TABLE 1: Results for multiple logistic regression model selection for the outcome variables: "increase of pregnancy" and "live birth delivery" for kidney transplant recipients

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Analysis of proportion (%)</th>
<th>Regression coefficient</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>111 (24)</td>
<td>0.098</td>
<td>0.003-0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum blood pressure (mm Hg)</td>
<td>111 (24)</td>
<td>0.039</td>
<td>-0.019-0.008</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognostic factor</th>
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<th>Regression coefficient</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic serum creatinine (µmol/L)</td>
<td>111 (24)</td>
<td>0.2</td>
<td>0.096-0.12</td>
<td>0.007</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>111 (24)</td>
<td>0.9</td>
<td>0.0-1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Drug treated hypertension during pregnancy</td>
<td>111 (24)</td>
<td>0.9</td>
<td>0.0-1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Yes</td>
<td>111 (24)</td>
<td>0.9</td>
<td>0.0-1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>No</td>
<td>111 (24)</td>
<td>0.9</td>
<td>0.0-1.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*All regression coefficient indicates that an increase in the factor is associated with a greater risk of being an uneventful pregnancy.
##All regression coefficient indicates that an increase in the factor is associated with a lower risk of being an uneventful pregnancy.
###All regression coefficient indicates that the factor level is associated with a lower risk of a protocol delivery compared to the baseline factor level.

Sibanda transplantation 2007
### IMMUNOSUPPRESSIVE THERAPY

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Transplacental passage</th>
<th>Comments</th>
<th>safe</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>Limited</td>
<td>(increase in oral clefts?) High dose: cataract</td>
<td>Y</td>
<td>Y (not if prednisolone &gt;60 mg)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Y</td>
<td>Sporadic congenital abnormalities</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>MMF</td>
<td>Y</td>
<td>Contia-indicated hypoplastic nails, shortened fifth finger, microthia, micrognathia, cleft lip and palate, heart defects</td>
<td>ND</td>
<td>NO</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Y</td>
<td>Hyperkalemia, renal impairment, Diabetes mother, increase in dose</td>
<td>Y</td>
<td>? Possibly safe</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Y</td>
<td>Increase in dose</td>
<td>Y</td>
<td>? Possibly safe</td>
</tr>
<tr>
<td>sirolimus</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

### MULTIDISCIPLINARY APPROACH

- **Keep calm and call a gynecologist**
- **Keep calm and call a nephrologist**
- **Keep calm and call a genetic counselor**
- **Keep calm and call a neonatologist**

### The end