Renal Disease through the Ages: From Childbearing years to Old Age

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Renal Physician, General Physician, Obstetric Physician.
Learning Outcomes:

• Understand the presentation of renal disease
  – Including aspects of treatment

• Understand how some medical illnesses can be effected by pregnancy and how pregnancy can affect medical illnesses

• Understand long term health outcomes after preeclampsia

• Understand aspects of Hypertension
  – Including treatment – when and with what
Summary

• Renal disease is an important cause of morbidity in all age groups
  – Often undetected for many years
• Renal disease and other medical illnesses have important implications for pregnancy
• Preeclampsia carries significant short-term and long-term morbidity
  – More common than usually appreciated
• Hypertension is common and carries significant risk
  – Usually undertreated
  – Thiazide, CCB or ACE-I/ARB.
Mrs C.B.

• 28 y.o. woman
• Presented to GP August 2010 with ankle swelling and dyspnoea
  – Background history of asthma and borderline subclinical hypothyroidism
• What are possible diagnoses?
  – Fluid overload
    • Renal disease
    • Cardiac disease
    • Other
Investigations

• What would you be looking for on laboratory findings?
  – FBC, ELFTs, urine

• Results
  – Hb 130
  – Creat 105µmol/L
  – Alb 20
  – Cholesterol 8.5
  – 24 hour urine 4.5g protein and PCR 338g/mol creat (normal <15)
  – Renal biopsy showed FSGS
Treatment Options

• ACE-I +/- ARB
• Lasix
• Heparin (DVT/PE prophylaxis)
• Statin
• Consider immunosuppressive therapy: – long term steroids, cyclosporin, cyclophosphamide
No Response to Initial Treatment

• Steroids given and monitored over next 4 months with no response
  – with significant side-effects (cushingoid, mood effects)
  – Unable to work

• Treatment changed to cyclosporin
  – Dose monitored with trough levels

• Partial response to treatment but creatinine deteriorates to baseline of 130-150µmol/L
Pregnancy…

• Comes to clinic stating that she wants to have a baby
• What general advice would you give her about a pregnancy given her diagnosis?
• Are her medications contraindicated in pregnancy?
• What are the risks associated with her renal disease?
• Is she at risk for preeclampsia?
Pre-pregnancy Counselling

- Medications discussed: ACE-I/ARB, statin, lasix, cyclosporin, ?heparin
- Preeclampsia prophylaxis:
  - aspirin, calcium (PPIs?, statin?)
- Effects of pregnancy on renal disease
- Effects of renal disease on pregnancy
- Asthma in pregnancy
- Subclinical hypothyroidism
Specific Aspects of Drugs: Use vs timing for cessation

• ACE-I/ARB contraindicated in pregnancy
  – ACE-I can be used up to 6 weeks gestation

• Statin – avoid in first trimester
  – upcoming research in late second trimester

• Lasix
  – use cautiously
  – discuss with physician/obstetrician

• Heparin
  – often used in pregnancy for a variety of indications
Specific Aspects of Drugs: Use vs timing for cessation

• Steroids
  – able to be used
  – issues include indications for use, dose used bearing in mind indication and dose which crosses placenta

• Cyclosporin
  – able to be used in pregnancy but needs monitoring by someone with experience because of changes in metabolism associated with pregnancy
Where there is an increased risk for Preeclampsia...

- Prophylaxis
  - Aspirin, calcium, LMWH
  - Depending on risk assessment and background medical problems
    - e.g. renal disease, T1DM/T2DM, thrombophilia

- PPIs?, statin? – upcoming research looking at this
Asthma Management in Pregnancy

• Asthma still kills in pregnancy
  – Deaths every year in the UK

• General principle: continue medications on which the patient was stable prior to pregnancy
  – Able to use short courses of high dose steroids as needed bearing in mind the goal of maternal health
Hypothyroidism and Subclinical Hypothyroidism in Pregnancy

• TSH targets in pregnancy:
  – TSH<2.5 in 1\textsuperscript{st} trimester,
  – <3.0 in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters

• Where thyroxine is supplemented pre-pregnancy:
  – T4 requirements frequently increase in pregnancy
  – Increase total weekly dose presumptively by ~30% with confirmation of pregnancy
Effects of Subclinical and Overt Hypothyroidism

• Overt hypothyroidism is associated with:
  – ↑ risk of adverse pregnancy complication (miscarriage, preeclampsia, premature birth, low birth weight infants)
  – detrimental effects on neurocognitive development

• Association between maternal subclinical hypothyroidism, adverse pregnancy outcome and fetal neurocognitive development:
  – Some evidence for this; thought likely but not clearly demonstrated
  – Less evidence that treatment improves outcome
    • But we do treat
## Effects of Pregnancy on Renal Disease

<table>
<thead>
<tr>
<th>Degree of Renal Impairment</th>
<th>Mild Cr &lt;125 umol/L</th>
<th>Moderate Cr125-180 umol/L</th>
<th>Severe Cr &gt;180 umol/L</th>
<th>On dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of function (%)</td>
<td>2</td>
<td>40</td>
<td>70</td>
<td>n/a</td>
</tr>
<tr>
<td>Reduced function persisting postpartum (%)</td>
<td>0</td>
<td>20</td>
<td>50</td>
<td>n/a</td>
</tr>
<tr>
<td>End-stage renal failure (%)</td>
<td>2</td>
<td>35</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>
## Effects of Renal Disease on Pregnancy

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</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia (%)</td>
<td>22</td>
<td>40</td>
<td>60</td>
<td>75%</td>
</tr>
<tr>
<td>FGR (%)</td>
<td>25</td>
<td>40</td>
<td>65</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Preterm delivery (%)</td>
<td>30</td>
<td>60</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Neonatal mortality (%)</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>
How common is renal disease in pregnancy?

- It is surprisingly common with potentially significant adverse outcomes in both pregnancy and long-term:
  - affect up to 3% of women of child-bearing age (20-39 years)
  - estimated 1 in 750 pregnancies is complicated by CKD stages 3-5
  - Some women are found to have CKD for the first time during pregnancy.
  - ~20% of women who develop early PET (≤30 weeks), especially those with heavy proteinuria, have undiagnosed CKD
She falls pregnant...

- Progresses well through pregnancy
- At 34-35 weeks her creatinine starts to rise
  - (it can be really hard to determine when there is a rising creatinine – primary disease vs super-imposed PET)

<table>
<thead>
<tr>
<th>Date</th>
<th>5/11</th>
<th>9/11</th>
<th>10/11</th>
<th>12/11 am</th>
<th>12/11 pm</th>
<th>13/11</th>
<th>15/11</th>
<th>16/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creat µmol/L</td>
<td>141</td>
<td>163</td>
<td>165</td>
<td>194</td>
<td>194</td>
<td>204</td>
<td>177</td>
<td>156</td>
</tr>
</tbody>
</table>
What does a Diagnosis of Preeclampsia mean for Mrs C.B. into the future?

• Increased risk of HT and vascular events
  – RR 3.7 of HT after 14 years
  – RR 2.16 of IHD after 12 yrs, RR 1.81 for stroke after 10 yrs
• Overall mortality after PET was increased by 1.5 fold after 14 yrs
• Suggest yearly monitoring of BP (minimum)
  – target <140/90,
• 1 to 2 yearly monitoring of other risk factors (lipids)
• If GDM:
  – needs weight loss if appropriate
  – 2nd yearly OGTTs for rest of life
Moving forward 2 years...

- Presents to clinic wanting another baby
- Baseline creatinine now 160-180umol/L:
  - Have her risks changed?
    - Yes
  - What are her chances of conceiving?
    - Reduced compared to last pregnancy
  - What is her recurrence risk of preeclampsia?
    - Need to consider gestation of onset of preeclampsia and new risks from deterioration of underlying medical problem
## Recurrence Risk of Preeclampsia

<table>
<thead>
<tr>
<th>Delivery due to PET in preceding pregnancy</th>
<th>Recurrence Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-28 weeks</td>
<td>40%</td>
</tr>
<tr>
<td>29-32 weeks</td>
<td>30%</td>
</tr>
<tr>
<td>33-36 weeks</td>
<td>20%</td>
</tr>
<tr>
<td>37+ weeks</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Other factors to consider:**
- Time since last affected pregnancy,
- New vs same partner
What about her Kidney Disease Long Term?

• Basics of management of CKD
  – Avoid obesity
  – If diabetic control BSLs
  – Tight control of HT - critical
  – Smoking cessation
  – ACE-I/ARB
ESKD – HT is still a common cause

*These disease categories were treated as being mutually exclusive.

Figure 7. Trends in incident rates of ESRD, by primary diagnosis (adjusted for age, gender, race).

Hypertension

• Guidelines
  – Who writes them
  – Recent changes
  – Treatment
    • Non-pharmacological
    • Pharmacological

• Authors all highlight the importance of HT in their respective populations
  – WHO “leading global risk for mortality”
The Breadth of the Problem… the European Perspective

• Affects 30-45% of the population
• Lack of awareness of potential problems of untreated HT amongst patients
• Lack of compliance with medications
• Target BPs are rarely achieved
• “Inertia” of doctors in treatment
Who puts out the Guidelines

• USA
  – Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines: JNC 7 and JCN 8
  – American Heart Association/American College of Cardiology
  – American Society of HT

• European
  – ESH/ESC Clinical Guidelines for the management of arterial HT 2013

• British
  – HT: Clinical Management of primary HT in adults (NICE guidelines)

• Other (most countries, ISH)
What changes have taken place?

- **JNC 8**
  - Age targets for 140/90
    - 60 vs 80 years of age (controversial-AHA, ACC, ASH, ISH)

- **European**
  - Increasing role for home BP/ambulatory BP monitoring
  - BP targets for almost all patients:
    - recommends a single SBP target of 140 mmHg
      - 2007 ESH/ESC target of 140/90 mmHg target for moderate to low risk patients, and 130/80 mmHg target for high risk patients
  - BP targets for diabetics
    - DBP<85mmHg for diabetics
Treatment Choices

• JCN 7/8
  – Thiazide, CCB, ACE-I or ARB
  – Recommend a diuretic
  – Other agents as 3\textsuperscript{rd}/4\textsuperscript{th} line

• EHS/ECS
  – No specific drug recommendations
    • Most people have other organ damage or considerations which help guide treatment
  – Highlights the evidence that the beneficial effect of HT depends largely on blood pressure lowering

• “ACE or bust”
## Lifestyle Modifications to Prevent and Manage Hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction (Range)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (body mass index 18.5–24.9 kg/m²).</td>
<td>5–20 mm Hg/10 kg</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.</td>
<td>8–14 mm Hg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).</td>
<td>2–8 mm Hg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week).</td>
<td>4–9 mm Hg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks (eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter-weight persons.</td>
<td>2–4 mm Hg</td>
</tr>
</tbody>
</table>

DASH indicates Dietary Approaches to Stop Hypertension.

*For overall cardiovascular risk reduction, stop smoking.

†The effects of implementing these modifications are dose- and time-dependent and could be greater for some individuals.
Hypertension Guidelines - USA

• 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) JAMA. 2014;311(5):507-520
  – 9 specific recommendations for initiating and modifying pharmacotherapy for patients with elevated BP

• Changes to BP targets for those >60 years of age

• American Heart Association argues that the JCN 7 report is still the national standard (until it releases its own guidelines later in 2014 or 2015)
  – 80 years of age: BP target to 150mmHg systolic
  – States that even as it stands 1 in 3 Americans have under-diagnosed and undertreated HT
## Classification of BP in Adults

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>Systolic BP mmHg</th>
<th>Diastolic BP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td>Pre-hypertension*</td>
<td>120-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>

*No longer exists with JCN 8

### TABLE 2. Changes in Blood Pressure Classification

<table>
<thead>
<tr>
<th>JNC 6 Category</th>
<th>JNC 7 Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 120/80</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129/80–84</td>
</tr>
<tr>
<td>Borderline</td>
<td>130–139/85–89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>≥ 140/90</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140–159/90–99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160–179/100–109</td>
</tr>
<tr>
<td>Stage 3</td>
<td>≥ 180/110</td>
</tr>
</tbody>
</table>


Who, When and How

• General population (<60 or 80 years depending on guidelines)
  – initiate treatment at SBP >140mmHg and/or DBP >90mmHg with same goal of treatment

• Ages ≥60/80 years
  – initiate treatment SBP >150mmHg and/or DBP >90mmHg
  – NOTE: ESH/ESC state consider goal of SBP 140-150mmHg if they are fit elderly >80 and if <80 and fit then 140mmHg is reasonable

• If treatment results in lower achieved SBP and no associated with adverse effects, treatment does not need to be adjusted
Who, When and How

- >18 years with DM or CKD, initiate treatment at SBP>140 mmHg or a DBP>90 mmHg
  - Treat to goals below these thresholds
- General pop’n, includ DM, initial treatment:
  - thiazide-type diuretic,
  - CCB,
  - ACE-I or ARB
- Ages ≥18 with CKD and HT:
  - initial (or add-on) treatment should include an ACE inhibitor or an ARB to improve kidney outcomes
- ↑ treatment every month until goal reached
  - Increase dose of drug one
  - Add second agent
Role for Ambulatory Monitoring

• Suspected white-coat “effect” in patients with hypertension and no target organ damage
• Apparent drug resistance (office resistance)
• Hypotensive symptoms with antihypertensive medication
• Episodic hypertension
• Autonomic dysfunction
Ambulatory or Home BP monitoring is an important adjunct

- Prediction of CV events is significantly better with out-of-office BP than with office BP
- Cut-offs for the definition of hypertension are:
  - 130/80 mmHg for 24-hour BP
  - 135/85 mmHg for daytime ambulatory BP and home BP
  - 120/70 mmHg for night-time BP
- EHS/ECS
Errors in Measurement of BP

- Natural variation
  - $\geq 14\%$
- Incorrect measurement technique (technique, single reading etc)
  - $\geq 60\%$
- White coat HT
  - 20\%
- Office-based measurement
  - $\sim 100\%$
- Global cardiovascular risk not assessed
  - $\sim 100\%$
Figure 16. Algorithm for treatment of hypertension.

Lifestyle Modifications

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for those with diabetes or chronic kidney disease)

Initial Drug Choices

Without Compelling Indications

Stage 1 Hypertension (SBP 140–159 or DBP 90–99 mmHg)
Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination

Stage 2 Hypertension (SBP ≥160 or DBP ≥100 mmHg)
Two-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB)

With Compelling Indications

Drug(s) for the compelling indications (see Table 12)
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed

Not at Goal Blood Pressure

Optimize dosages or add additional drugs until goal blood pressure is achieved. Consider consultation with hypertension specialist.
Figure 8. Residual lifetime risk of hypertension in women and men aged 65 years.

Figure 9. Ischemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade.

Figure 10. Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade.

Figure 11. Impact of high normal blood pressure on the risk of cardiovascular disease.

Figure 15. Systolic blood pressure distributions.
