Tuberous Sclerosis, the Kidneys, and Pregnancy

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Primer on Basic Kidney function

- Kidney is the body’s “processing plant”
- Made up of blood vessels and collection tubes
- Processes a huge amount of blood
  - Almost 20% of all the blood your heart pumps goes to the kidneys
    - More than any other organ except your brain
- Leaky capillaries filter the blood at a rapid rate
  - Roughly 100 ml each minute
  - Your entire blood volume is filtered every 45 minutes or so…

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Structure of the Kidney

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Basic kidney function

Most of that filtrate gets reabsorbed back into the bloodstream by tubules.

You don’t make a liter of urine every 10 minutes!

The tubules are responsible for fine tuning reabsorption to control the blood levels of many chemicals and electrolytes.

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Creatinine and Clearance

• Creatinine is made at a constant rate
• It is only removed from the blood by kidney filtration
• Once filtered, it gets excreted into the urine
• Measuring the blood levels gives a good estimation of the filtration, or GFR
• Decreased filtration is noted as an increase in creatinine.

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Kidney Function and Creatinine
Stages of Chronic Kidney Disease

1. **STAGE 1**
   - Kidney damage with normal or increased kidney function

2. **STAGE 2**
   - Kidney damage with mildly impaired kidney function

3. **STAGE 3**
   - Moderately impaired kidney function

4. **STAGE 4**
   - Severely impaired kidney function

5. **STAGE 5**
   - Kidney failure

### Glomerular filtration rate (mL/min/1.73 m²)

- **STAGE 1**: 130
- **STAGE 2**: 90
- **STAGE 3**: 60
- **STAGE 4**: 30
- **STAGE 5**: 15

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Kidney Features of Tuberous Sclerosis

Angiomyolipomas, Cysts, RCCs

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Age and Onset of Symptoms

Image courtesy of DN Franz, 2011.
Origin of TSC Renal Disease

Blood Vessels
- Angiomyolipoma

Epithelial Cell:
- Cyst
- RCC
- Oncocytoma

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Angiomyolipoma

- Solid tumors that grow from kidneys
- Made up of 3 distinct cell types
  - Blood vessel cells (Angio)
  - Muscle cells (myo)
  - Fat cells (lipoma)
- Loss of TSC gene function leads to deregulation of mTOR pathway
  - Overactivity of mTOR at center of AML growth
Pathobiology

Nutrients

PTEN

PI3K

Akt

Ras

Abl

mTOR

S6K1

4E-BP1

eIF-4E

Protein Synthesis

Cell growth and proliferation

Angiogenesis

Cell orientation and migration

Cell metabolism

Renal Angiomyolipomas in TSC

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• At the time of diagnosis, abdominal imaging should be obtained regardless of age. As for brain, MRI is the preferred modality for evaluation of angiomyolipomata because many can be fat-poor and hence missed when abdominal CT or US are performed.
• Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1-3 yr throughout lifetime.
• Assess kidney function and blood pressure at least annually.
Pathobiology

Nutrients

PTEN

PI3K

Akt

Ras

Abl

TSC1

TSC2

mTOR inhibitor

mTOR

4E-BP1

eIF-4E

S6K1

S6

Protein Synthesis

Cell growth and proliferation

Angiogenesis

Cell orientation and migration

Cell metabolism

mTOR inhibitor

For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first line therapy.
EXIST-2 Long Term Follow up

- Everolimus (n = 101)
  - Decrease in best % change from baseline: 98 (97%)
  - Increase in best % change from baseline: 3 (3%)

Fig 2. Best percentage reduction in the sum volume of target renal angiomyolipomas each individual patient reported at any time point in the study in 101 evaluable patients.*11 patients were considered “non-evaluable” due to missing overall angiomyolipoma response status at each radiological assessment. Among the 12 patients with a best overall response with the status “not evaluable”, only one patient reported at least one radiological assessment with a non-missing overall angiomyolipoma response status.

https://doi.org/10.1371/journal.pone.0180939.g002


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With TSC, most young women who are of childbearing age will have kidney tumors but still have normal kidney function (CKD 1 or 2)

- Likely means normal pregnancy
- Will HAVE to stop mTOR inhibition BEFORE pregnancy
  - Risk of angiomyolipoma growth during pregnancy
  - Risk of CKD progression during pregnancy
- MAY need to adjust blood pressure medications
  - Risk of high blood pressure during pregnancy
Kidney function = pregnancy

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Kidney function = pregnancy

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Changes during pregnancy

Changes in kidney function

Changes in body composition

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Kidney function = pregnancy

- Some women with TSC have large kidney lesions and suffer from diminished kidney function (CKD 3-5)
  - More difficult to get pregnant
  - More difficult to stay pregnant
- During pregnancy, CKD can have multiple effects
  - On mother
  - On baby

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Impact of pregnancy in women with CKD

**Maternal**
- Worsening kidney function
- Hypertensive disorders of pregnancy
  - Gestational HTN
  - Preeclampsia
  - HELLP
- Miscarriage

**Fetal**
- Preterm birth
- Stillbirth or neonatal death
- Low birthweight
  - SGA
  - Fetal growth restriction

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Interactions: Kidneys and Placenta

From the placenta to the kidney
PE may induce permanent kidney damage, via
AKI, tubular damage, podocyte loss

Placenta and kidney are highly vascularized; filter blood; divide compartments; are sophisticated metabolic machines
Pregnancy is a precious occasion to diagnose CKD.

From the kidney to the placenta
CKD may induce placental dysfunction with an increased risk of pre-term delivery, hypertensive disorders of pregnancy and PE
# Pregnancy complications in CKD

Adverse maternal outcomes: Hypertension, pre-eclampsia, eclampsia, mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>CKD Events</th>
<th>Total</th>
<th>No CKD Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>M-H, Random, 95% CI</th>
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<tr>
<td>Piccoli</td>
<td>1</td>
<td>36</td>
<td>3</td>
<td>297</td>
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<td>2.80 [0.28, 27.65]</td>
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<td>2</td>
<td>9</td>
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<td>Nagai</td>
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<td>11</td>
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<tr>
<td>Leppert</td>
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<td>88</td>
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<td>57</td>
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<td>Gladman</td>
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<td>50</td>
<td>2</td>
<td>70</td>
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<td>8.50 [1.77, 40.76]</td>
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<tr>
<td>Trevisan</td>
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<tr>
<td>Kimmerlee</td>
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<td>3</td>
<td>110</td>
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<tr>
<td>Murakami</td>
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<td>19</td>
<td>18</td>
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<td>4.4%</td>
<td>10.21 [2.99, 34.86]</td>
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<tr>
<td>Rosenn</td>
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<td>73</td>
<td>54</td>
<td>335</td>
<td>14.3%</td>
<td>4.06 [2.35, 7.01]</td>
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<tr>
<td>Fink</td>
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<td>169</td>
<td>31</td>
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<td>Gazarek</td>
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<td>3.98 [2.85, 5.56]</td>
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<tr>
<td>Fischer</td>
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<td>4606</td>
<td>25.8%</td>
<td>3.56 [2.81, 4.51]</td>
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</tr>
</tbody>
</table>

Risk higher in no CKD

Risk higher in CKD

Nevis CJASN (2011) 6: 2587–2598

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Clinical practice guideline on pregnancy and renal disease

Kate Wiles, Lucy Chappell, Katherine Clark, Louise Elman, Matt Hall, Liz Lightstone, Germin Mohamed, Durba Mukherjee, Catherine Nelson-Piercy, Philip Webster, Rebecca Whybrow and Kate Bramham
Guideline 3.3.1 We suggest women with CKD considering pregnancy are offered pre-pregnancy counselling by a multidisciplinary team including a consultant obstetrician and nephrologist or expert physician (2D).

Guideline 3.3.2 We recommend women with CKD are advised there is an increased risk of complications in pregnancy including pre-eclampsia, preterm birth, fetal growth restriction, and neonatal unit (NNU) admission, and that they are more likely to require caesarean delivery (1C).
Guideline 3.3.3 We recommend women with known or suspected inheritable renal diseases are offered genetic counselling including inheritance risk, prognosis, and intervention options including pre-implantation genetic diagnosis (1C).

Guideline 3.2.4 We recommend single-embryo transfer is performed to reduce risk of complications associated with multi-fetal pregnancies in women with CKD (1C).
Guideline 3.3.4 We recommend pre-pregnancy counselling for the optimization of maternal and neonatal outcomes in women with CKD, which may include:

- Stabilizing disease activity in advance of pregnancy on minimized doses of pregnancy-appropriate medications (1B).
- Optimizing blood pressure control (< 140/90 mmHg) on pregnancy-appropriate medications (1B).
- Minimizing risk of exposure to teratogenic medications (1C) (see section 2).
Guideline 4.3.1 We recommend women with CKD are offered low-dose aspirin (75-150 mg) in pregnancy to reduce the risk of pre-eclampsia (1B).

Guideline 4.4.1 We recommend that the target blood pressure during pregnancy for women with CKD is 135/85 mmHg or less, which should be documented in the woman’s healthcare record (1D).
Summary

- Kidneys are an important target of damage in TSC
- Some medications require discontinuation before pregnancy
- With normal kidney function, pregnancy often normal
- With diminished kidney function, pregnancy often complicated
- Regardless of fetal/baby outcomes, pregnancy is a strenuous metabolic process for mother and kidney function may decline
- Pregnancy brings many growth factors which may accelerate kidney tumor growth
Questions

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