AKI IN PREGNANCY
2.23.16

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Nephrology Fellow
Case Presentation

33 yo Asian Indian Renal Fellow, at 41+3 weeks gestation, presents to NYU labor and delivery for induction of labor on 12/15/15

HPI:
- Uneventful pregnancy
- No spontaneous onset of labor, hence decision to induce
Case Presentation

- PMH: None, 2 miscarriages
- PSH: None
- Allergies: None
- Meds: Prenatal vitamins
- SH: Lifetime non smoker, non alcoholic, no illicit drug use
- FH: Father HTN, Mother Psoriasis
Physical Exam

Vitals: BP 100/60, HR 90, RR 22, O2 sat 100% RA
Gen: ANOX 3, pleasant, comfortable
HEENT: mmm, no jaundice
Resp: mild tachypneic, CTABL
CV: s1s2+, functional SM
Abd: distended with fetus, non tender
Ext: edema 2+ bilateral ankles
Hospital Course

- Induction started with insertion of balloon catheter
- Co-fellow comes to visit
- Pain starts, Epidural anesthesia given
- 6 hours later ARM done and Pitocin started
- Labor progresses as expected
Hospital Course

- 16 hours after induction, patient starts having severe headaches, has intermittent irrelevant conversations, lethargic
- Urine output starts to decline
- Vomiting progressively worsens, becomes projectile
- Fever 102, fetal tachycardia (FHR 180s-200), maternal tachycardia (HR 130-140s) ensues
- Clinical suspicion of chorioamnionitis, given a dose of ampi-genta and Tylenol
- HR improves, fever subsides
Hospital Course

- However symptoms persist

- Urine output further declines, BP 90/50s

- OB thinks all symptoms related to the labor process and asks patient to bear down at near full Cx dilatation

- Patient’s husband worried “something is not right, can we have labs please?” OB reluctant but gets labs
Hospital Course

While awaiting labs, urine output declines to 0-5 cc/hr, gross hematuria+ (anuria for > 6 hours despite 3L NS bolus), mental status worse, FHR again in 180s

Meanwhile labs come back

Diagnosis of HELLP syndrome made (atypical as no HTN and only mild drop in Hb initially)
Labs

LFTs: AST/ALT: 44/23, ALP 108, T bil 0.9, Albumin 1.9
Uric Acid 6.8
LDH 1132

UA: trace glucose, neg ketones, 4+ Blood, 4+ Protein, neg nitrite, neg leuk esterase

Urine Micro: 30-40 RBCs

Urine Protein/Cr: 9.9 gm/gm
Hospital Course

- Decision made for emergency C section
- Healthy baby delivered 23 hours after induction of labor
- Baby sent to NICU for observation and prophylactic Abx in lieu of suspected chorio
- Maternal post op course complicated
  - hypovolemic shock (1.5L blood loss intraop), requiring neosynephrine
  - R temporal binocular diplopia, CT scan of head negative for hemorrhage or ischemia
    - Anasarca
- Urine output improved immediately after delivery of the placenta, symptoms improved
- Patient and baby discharged on post op Day 5
Outline

- Renal Adaptive Mechanisms in Pregnancy
- DDs AKI in Pregnancy
- HELLP Syndrome
Renal Adaptive Mechanisms in Pregnancy
Renal Anatomy and Functional Changes of Urinary Tract

Kidney length increases by ~ 1 cm in secondary to:

- Increase in renal vascular volume
- Hypertrophy of kidney
- Increased capacity of dilated urinary collecting system (physiologic hydronephrosis of pregnancy):
  - Estrogen and progesterone influence
  - Inhibition of ureteral peristalsis by PGE2
  - Mechanical obstruction of ureters in pregnancy
  - Increased GFR

AJKD, Vol 49, No 2 (February), 2007: pp 336-345
Clinical Nephrology, Vol. 78 – No. 6/2012 (478-486)
Cardiovascular and Renal Physiology

Blood Pressure Regulation

- BP falls shortly after conception
  - Peripheral vasodilatation and resistance to angiotensin II secondary to high prostacyclin and prolactin levels
  - Nitric oxide synthesis increases
  - RAAS stimulated during pregnancy secondary to vasodilatation and vascular resistance to angiotensin II

AJKD, Vol 49, No 2 (February), 2007: pp 336-345
Clinical Nephrology, Vol. 78 – No. 6/2012 (478-486)
JNEPHROL 2012; 25(01): 19-30
Circulating blood volume increases by 50%

RBC mass begins to increase in 1st trimester and rises by 20% - 30% (on iron supplements), 15% to 20% (not on Fe supplements)

Cumulative Na retention (500 to 900 mEq [mmol]) stimulated by decreased PVR leads further to increased ECF volume, weight gain, and “benign” edema of lower extremities
Renal Hemodynamics

- GFR rises immediately after conception
  - Reaches ~ 50% above baseline, resulting in significant hyperfiltration in 2\textsuperscript{nd} trimester
  - GFR then falls by ~ 20% in last trimester, returning to prepartum levels within 3 months of delivery

- Normal plasma creatinine falls to 0.5 mg/dL, value > 0.8 mg/dL abnormal

- RBF increases by ~ 85% in 2nd trimester secondary to:
  - Increased cardiac output (30% to 40% above nonpregnant level by midgestation)
  - Increased renal vasodilatation of both afferent and efferent arterioles

AJKD, Vol 49, No 2 (February), 2007: pp 336-345
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Water Metabolism

Downward resetting of osmotic threshold for both AVP secretion and thirst (? hcg) begins early in 1st trimester with a new steady-state plasma osmolality maintained until term

- Osmotic thresholds for thirst and ADH release decrease ~ 10 mOsm/kg during initial weeks → hypoosmolality and lower Na+

- Water balance maintained by ability to dilute or concentrate urine maximally, despite increased RBF and high PG E2, an AVP antagonist

- Transient DI secondary to high placental vasopressinase activity occurs at term, short lived
Mineral Metabolism

- Na+ balance is maintained, despite 50% ↑ in GFR and respective ↑ filtered Na →↑Na reabsorption in PCT and distal tubules

- K+ metabolism remains unchanged, despite cumulative retention of about 350 mEq of K and increased aldosterone levels
  - Progesterone competes with aldosterone for binding to mineralocorticoid receptor causing natriuresis
  - Progesterone may play role in preventing kaliuresis

- Calcium absorption GIT increases secondary to high 1,25(OH)$_2$ produced by both kidney and placenta leading to hypercalciuria
Acid-Base Regulation

- Progesterone stimulates central nervous system respiratory center

- Causing increased ventilation resulting in mild chronic respiratory alkalosis (hypocapnia with lower serum bicarbonate)

- Early morning urine is more alkaline than in nonpregnant women, but acid excretion ability is unchanged
AKI in Pregnancy

- AKI in pregnancy remains a cause of significant fetomaternal mortality and morbidity.

- Definition and hence incidence, varies widely from mild increase in serum creatinine > 0.8 mg/dl to dialysis requirement.

- Incidence < 1% in the Western world.

- New cases of pregnancy related AKI have declined from ~ 1/3,000 to 1/15,000 – 20,000 since the 1960s.
  - Improved pre-natal care
  - Decline of illegal, septic abortions

References:
Clinical Nephrology, Vol. 78 – No. 6/2012 (478-486)
JNEPHROL 2012; 25(01): 19- 30
JNEPHROL 2011; 24(05): 554-563
Figure 1. Main causes of pregnancy-related AKI depending on their predominant timing of occurrence during pregnancy.
<table>
<thead>
<tr>
<th>Causes</th>
<th>Prerenal</th>
<th>Intrarenal</th>
<th>Postrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>Hemorrhage</td>
<td>Acute tubular necrosis</td>
<td>Obstruction</td>
</tr>
<tr>
<td>Prerenal</td>
<td>Hyperemesis gravidarum</td>
<td>Pyelonephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td>Renal cortical necrosis</td>
<td></td>
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<tr>
<td></td>
<td>Sepsis</td>
<td>Thrombotic microangiopathy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Preeclampsia/HELLP syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute fatty liver of pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medications</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE I**

**ACUTE KIDNEY INJURY ETIOLOGY IN PREGNANCY**
HELLP SYNDROME

- Hemolysis, Elevated Liver Enzymes and Low Platelets
- Described and coined by Weinstein in 1982
- Multisystem disease characterized by abnormal vascular tone, vasospasm and coagulation defects
- Occurs in about 0.2–0.8% of pregnancies
- A/W increased risks of maternal and fetal adverse complications

*Journal of Obstetrics and Gynaecology, May 2013*
*European Journal of Ob & Gyn and Reproductive Biology 166 (2013)*
Pathophysiology

- Remains partially unknown

- Severe form of preeclampsia VS totally different expression of the rejection of the fetus in the late due to materno – fetal immune imbalance

- Final manifestation of insults that leads to microvascular endothelial damage and intravascular platelet activation.
Placental Pathogenesis of HELLP

- Antiangiogenic factors: sFlt1 and sEng

- sFlt1 in pregnant rats induced a syndrome similar to human PE but did not produce hemolysis and thrombocytopenia

- Semiquantitation in blood from women with HELLP showed higher soluble endoglin (sEng) values in HELLP than in PE

sEng and sFlt1 concentrations

Nature Medicine June 2006
Pregnant rats treated with sEng and sFlt1

Nature Medicine June 2006
ADAMTS13 Endopeptidase Protects against Vascular Endothelial Growth Factor Inhibitor–Induced Thrombotic Microangiopathy

Luise Erpenbeck, † Melanie Demers, † Zsuzsanna K. Zsengellér, ‡ Maureen Gallant, * Stephen M. Cifuni, * Isaac E. Stillman, § S. Ananth Karumanchi, ‡ and Denisa D. Wagner* †
Hypothesis and Methods

- Deficiency of the VWF-cleaving ADAMTS13 endopeptidase contributes to the development of VEGF inhibitor–related TMA

- Mice

- WT-Ad-sFlt1
- ADAMTS13−/−-Ad-sFlt1
- ADMATS13−/− Ad-Null
Table 1. sFlt-1 plasma levels in WT and ADAMTS13−/− mice at days 7 and 10 after adenovirus injection

<table>
<thead>
<tr>
<th>Day/Group</th>
<th>WT Ad-sFlt-1</th>
<th>ADAMTS13−/− Ad-null</th>
<th>ADAMTS13−/− Ad-sFlt-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>6345.91±576.13 ng/ml</td>
<td>0.63±0.15 ng/ml</td>
<td>7177.26±286.91 ng/ml</td>
</tr>
<tr>
<td></td>
<td>n.s. to ADAMTS13−/− Ad-sFlt-1 day 7</td>
<td></td>
<td>a to ADAMTS13−/− Ad-sFlt-1 day 10</td>
</tr>
<tr>
<td></td>
<td>n.s. to WT Ad-sFlt-1 day 10 (P=0.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 10</td>
<td>4995.59±388.71 ng/ml</td>
<td>0.69±0.12 ng/ml</td>
<td>4813.54±307.73 ng/ml</td>
</tr>
<tr>
<td></td>
<td>n.s. to ADAMTS13−/− Ad-sFlt-1 day 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are average ± SEM, n=7–13. There was no significant difference between sFlt-1 plasma levels of WT and ADAMTS13−/− Ad-sFlt-1 mice on day 7 or day 10, respectively. From day 7 to day 10, sFlt-1 levels declined significantly in the ADAMTS13−/− Ad-sFlt-1 mice and showed a trend toward lower sFlt-1 levels in the WT Ad-sFlt-1 mice. n.s., not significant.

*P<0.05.
Table 2. Organs positive for VWF-rich thrombi in WT and ADAMTS13<sup>−/−</sup> mice, at day 7 after Ad-sFlt-1 or Ad-null injection and after treatment with rhADAMTS13 or PBS (as vehicle)

<table>
<thead>
<tr>
<th>Group/Organ</th>
<th>Liver</th>
<th>Kidney</th>
<th>Lung</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT Ad-sFlt-1</td>
<td>0/6 (0%)</td>
<td>1/6 (16%)</td>
<td>1/6 (16%)</td>
<td>0/6 (0%)</td>
</tr>
<tr>
<td>ADAMTS13&lt;sup&gt;−/−&lt;/sup&gt; Ad-null</td>
<td>0/6 (0%)</td>
<td>0/6 (0%)</td>
<td>0/6 (0%)</td>
<td>1/6 (16%)</td>
</tr>
<tr>
<td>ADAMTS13&lt;sup&gt;−/−&lt;/sup&gt; Ad-sFlt-1</td>
<td>5/6 (83%)</td>
<td>6/6 (100%)</td>
<td>4/6 (66%)</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>ADAMTS13&lt;sup&gt;−/−&lt;/sup&gt; Ad-sFlt-1+PBS</td>
<td>4/5 (80%)</td>
<td>5/5 (100%)</td>
<td>2/5 (40%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>ADAMTS13&lt;sup&gt;−/−&lt;/sup&gt; Ad-sFlt-1+rhADAMTS13</td>
<td>3/9 (33%)</td>
<td>2/9 (22%)</td>
<td>1/9 (11%)</td>
<td>3/9 (33%)</td>
</tr>
</tbody>
</table>

Last two rows: treatment of ADAMTS13<sup>−/−</sup> Ad-sFlt-1 mice with PBS (as vehicle) or rhADAMTS13 was carried out from day 4 to day 7 after Ad-sFlt-1 or Ad-null injection. Statistical comparison between the groups was performed by chi-squared test between the indicated groups. n.s., not significant.

<sup>a</sup>P<0.05.
<sup>b</sup>P<0.01.
<sup>c</sup>P<0.001.
Organs positive for VWF rich thrombi at D7
KO mice rescued with rhADAMTS13
TMAs often result from the synergism of multiple factors driving endothelial dysfunction.

Pregnancy is an ideal situation for the existence of synergism.

Treat specific factors that work in synergy to cause TMA.

Maintain healthy endothelium.
# Genetics

## Table 1

Genetic variants associated with an increased risk of HELLP syndrome.

<table>
<thead>
<tr>
<th>Gene variant</th>
<th>HELLP compared to</th>
<th>HELLP (n)</th>
<th>OR (95% CI), p</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid receptor gene (GCCR), Bell SNP polymorphisms</td>
<td>Healthy pregnant</td>
<td>17</td>
<td>2.89 (1.45–5.74) p=0.004</td>
<td>Altered immune sensitivity and glucocorticoid sensitivity</td>
</tr>
<tr>
<td>Toll-like receptor 4 gene (TLR4), D299G, T3991 polymorphisms</td>
<td>Severe PE</td>
<td></td>
<td>2.56 (1.26–5.23) p=0.013</td>
<td>Uncontrolled or harmful inflammation</td>
</tr>
<tr>
<td>VEGF gene (VEGFA), C-460T, G+405C polymorphisms</td>
<td>Healthy pregnant</td>
<td>177</td>
<td>4.7 (2.0–1.9)</td>
<td>Ineffective immunity</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td></td>
<td>2.3 (1.3–4.3)</td>
<td></td>
</tr>
<tr>
<td>FAS (TNFRSF6) gene, homozygous polymorphism in A-670G</td>
<td>Healthy pregnant</td>
<td>81</td>
<td>2.7 (1.2–5.9)</td>
<td>Immune regulation, apoptosis. Lipid metabolism</td>
</tr>
<tr>
<td>FV Leiden</td>
<td>Healthy pregnant</td>
<td>71</td>
<td>4.5 (1.31–15.31)</td>
<td>Thrombophilia</td>
</tr>
</tbody>
</table>
Development of Maternal HELLP

- Cytokines, NKB
- sFlt1, sEng, Cytokines
- TNFα, sEng, FasL

- EC dysfunction
- Glomerular endotheliosis
- Arterial hypertension

- MAHA
- Thrombotic microangiopathy

- Active WVF, TNFα

- Liver damage
- Preeclampsia
- HELLP

- Activate EC: Inflammation, response, hypercoagulation, activated complement
- Activate Platelets, Leukocytes
Clinical Features

Nonspecific symptoms: nausea, vomiting, malaise/fatigue and viral-like symptoms

Specific:

- mid-epigastric/RUQ discomfort
- blurred vision, altered consciousness, clonus
- bleeding diathesis
- pulmonary edema
- Hypertension

Up to 30 – 60% women: headache and about 20% visual symptoms
Clinical Features

Absence of proteinuria and HTN in 15-20% patients
<table>
<thead>
<tr>
<th>HELLP class</th>
<th>Tennessee classification</th>
<th>Mississippi classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PLTs $\leq 100 \times 10^9$/l</td>
<td>PLTs $\leq 50 \times 10^9$/l</td>
</tr>
<tr>
<td></td>
<td>AST $\geq 70$ IU/l</td>
<td>AST or ALT $\geq 70$ IU/l</td>
</tr>
<tr>
<td></td>
<td>LDH $\geq 600$ IU/l</td>
<td>LDH $\geq 600$ IU/l</td>
</tr>
<tr>
<td>2</td>
<td>PLTs $\leq 100 \times 10^9$/l and $\geq 50 \times 10^9$/l</td>
<td>AST or ALT $\geq 70$ IU/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDH $\geq 600$ IU/l</td>
</tr>
<tr>
<td>3</td>
<td>PLTs $\leq 150 \times 10^9$/l and $\geq 100 \times 10^9$/l</td>
<td>AST or ALT $\geq 40$ IU/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDH $\geq 600$ IU/l</td>
</tr>
</tbody>
</table>
TMA: ADAMTS13 deficient / CAP dysregulation
Preeclampsia
Thrombocytopenia
Synergism
Treatment and Prognosis

- Delivery of the fetus and placenta

- Glucocorticoids: just for fetal maturity, can improve LFTs and platelet count but no impact on mortality, morbidity

- Once placental delivered, generally good prognosis, most abnormalities normalize by 3 months post partum