Living with Atypical HUS

PREGNANCY AND ATYPICAL HUS

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Pregnancy and Atypical HUS

Pregnancy and Kidney Disease (PreKID) Clinic
• Collaborative approach – High Risk OB & nephrology

Patients Counseled >1000
• Number of Pregnancies 65%
> 50 new patients consulted at clinic undergo pregnancy annually

• < 10 have had aHUS
Pregnancy Counseling

Pregnancy Risk Assessment

- Risk of Deterioration in Kidney Function
- Risk of Adverse Pregnancy Outcomes
  - Preeclampsia, Poor fetal growth, Pre-term Delivery

Risk of a Flare
Optimization Strategies

Pregnancy Management

Differentiating aHUS from TTP and Preeclampsia/HELLP Syndrome

Postpartum Care
Disease Flare

- Pregnancy Exacerbated
  - Lupus
    - Present or Flare in any trimester or early postpartum
    - Nephritis is the biggest risk for a bad outcome
    - Antiphospholipid Antibody Syndrome
    - Severe Morbidity and Mortality reported
      - 6-12 months of disease quiescence recommended
  - ANCA
  - TTP/Atypical HUS
  - Diabetic Nephropathy
    - ? Mechanism
  - ? MCD, FSGS, MN, IgA
    - Deserves further study
Complement System

- Innate immune system - protect
- 3 distinct pathways (classical, lectin and the alternate)
- Alternate pathway (C3 convertase) can be initiated spontaneously so it is tightly regulated

Chiang and Inagi, Nat Rev Immunol 2010
aHUS-associated complement abnormalities

- **Loss of function mutations:**
  - Factor H (CFH)
  - Factor I (CFI)
  - Membrane cofactor protein (MCP/CD46)
  - Thrombomodulin (THBD/CD141)

- **Gain of function mutations:**
  - CFB
  - C3

- **Autoantibodies:**
  - CFH (in combination with CFHR3/CFHR1 deletion: DEAP-HUS


Chiang and Inagi, Nat Rev Immunol 2010
Multiple hit theory of TMA pathogenesis

- **At Risk for TMA**
  - Complement mutations increase risk and some may be more important eg CFH

- **Safe Zone**

- **Disease becomes manifest as risk factors accumulate**
  - Additional triggers eg, CNI, toxin, IRI or pregnancy
  - Risk allele
  - Trigger

- **CFH**

- **MCP**

© Damien
Multiple hit theory of TMA pathogenesis
TMA Phenotype

At Risk

1st Hit

2nd Hit

Safe

Pregnancy

MCP

CFH

TMA
Pregnancy and Atypical HUS

- Series of 21 pregnancies/100 women with aHUS
- Pregnancy is the trigger in ≈ 20% of women with aHUS
- Most commonly presented in the second pregnancy

Fakhouri F et al JASN 2010;21:859-867
Pregnancy and Atypical HUS

- 74% with documented complement abnormalities had at least one pregnancy before the pregnancy related aHUS

Fakhouri F et al JASN 2010;21:859-867
Pregnancy and Atypical HUS

- 79% presented postpartum
- Presumed the complement system is activated to help cleanup placental debris

Fakhouri F et al JASN 2010;21:859-867
Pregnancy and Atypical HUS

• Outcomes were poor for mom
  • 62% reaching ESRD by one month
  • 76% reaching ESRD by last follow-up
  • Despite majority receiving PLEX

• Outcomes were reasonable for baby

Table 5. Pregnancy outcome in 44 women with aHUS and genetic defects (CFH = 23, CFI = 9, MCP = 4, C3 = 3, CFB = 2, more than one mutation = 3) and in 10 patients with aHUS and no detectable genetic defect

<table>
<thead>
<tr>
<th></th>
<th>Number of Pregnancies</th>
<th>Fetal Loss</th>
<th>Preeclampsia</th>
<th>P-aHUS</th>
<th>Uneventful Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with genetic abnormality (n = 44)</td>
<td>103</td>
<td>5 (4.8%)</td>
<td>8 (7.7%)</td>
<td>18 (17.4%)</td>
<td>77 (74.7%)</td>
</tr>
<tr>
<td>Patients with no genetic abnormality (n = 10)</td>
<td>15</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (20%)</td>
<td>12 (80%)</td>
</tr>
</tbody>
</table>

Fakhouri F et al JASN 2010;21:859-867
Pregnancy and Atypical HUS

Table 4. Frequency of P-aHUS according to the type of complement dysregulation

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of Pregnancies</th>
<th>P-aHUS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH mutations (n = 23)*</td>
<td>49</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Mutations in SCR19-20 (n = 6)</td>
<td>10</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Mutations in other SCR (n = 17)</td>
<td>38</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>CFI mutations (n = 8)</td>
<td>26</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>MCP mutations (n = 4)</td>
<td>6</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>C3 mutations (n = 3)</td>
<td>7</td>
<td>2 (28%)</td>
</tr>
<tr>
<td>CFB mutations (n = 2)</td>
<td>7</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>More than one mutation (n = 4)**</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>No mutation (n = 10)</td>
<td>15</td>
<td>3 (20%)</td>
</tr>
</tbody>
</table>

*Three patients with two mutations in CFH (SCR 9 and 19)—in C3/CFH and in MCP/CFH—were excluded from the analysis.

**Patients with two mutations in CFH (SCR 9 and 19)—in C3/CFH (patient 8), in MCP/CFH (P3), and in CFI/CFH (patient 4)

1st pregnancy presentation 4/7 CFH Mutation

Fakhouri F et al JASN 2010;21:859-867
Pregnancy Counseling

- Women with a history of aHUS or a genetic preponderance ≈ 20%
- CFH mutation may be the worst to have
- Subsequent Pregnancies potentially more dangerous than the 1st pregnancy
- Disease is aggressive
Characteristics and Outcomes of AKI treated with Dialysis During Pregnancy

- Analyzed data from 1.9 million pregnancies in ON over 15 years (1997 to 2011)
- Incidence of AKI treated with dialysis: 1 in 10,000 pregnancies (95% CI 0.8 to 1.1) (N=188)
- Women treated with acute dialysis in pregnancy were older, had a lower neighborhood income, fewer prenatal visits, and were more likely to have preexisting hypertension or chronic kidney disease compared with the general population
  - Preexisting medical condition (RR 2.24, 95% CI 1.42-3.52)
  - Medical complication of pregnancy (RR 5.55, 95% CI 4.16-7.38)

Hildebrand, Hladunewich and Garg JASN 2015
Diagnosis

Postpartum

- Septic abortion
- Abruptio placentae
- Severe haemorrhage / DIVC
- Sepsis
- PE/E
- HELLP syndrome
- Acute fatty liver
- ADAMTS13 deficiency-TMA
- CAP dysregulation-TMA
- TMA of unknown mechanism

Fakhouri F et al CJASN 2012
THROMBOTIC MICROANGIOPATHY

A pathology that results in thrombosis in capillaries and arterioles due to an endothelial cell injury
Diagnosis

- Preeclampsia/ HELLP Syndrome
  - Disease of the placenta
- TTP
  - Estrogen effect on ADAMTS13
    - Decreases throughout pregnancy to nadir in postpartum
    - Pro-coagulant state
- Atypical HUS
  - genetic mutations activation or regulation of the alternative complement pathway triggered by pregnancy
Treatment

- Preeclampsia/HELLP Syndrome
  - Delivery
- TTP
  - PLEX
- aHUS
  - PLEX
  - Eculizumab
Treatment

- Eculizumab
  - Has been used during pregnancy in PNH
  - Does not appear to cross the placenta
  - Does not appear to enter breast milk
  - Case report in pregnancy of a women with a homozygous mutation in Factor H treated from 26 weeks onward
    - 38 weeks gestation
    - 3650 g baby

Ardissino et al ACOG 2013
In Summary

• Patients need to be aware of their potential risks entering a pregnancy
• Clinicians need to be educated as this is a difficult clinical diagnosis to make
• Availability of Eculizumab will make child bearing a safer potential for patients with aHUS