Prenatal Diagnosis & Counseling

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Prenatal Renal Disease

-Consider

- Family History
- Associated anomalies
- Renal size, normal, big, small, #SD?
- Cysts, macro? Cortical?
- Amniotic fluid- normal, increased or decreased?
- Hydronephrosis?
  - Severity
  - Unilateral or bilateral
  - Ureter seen or not?
  - Bladder function?
**Audience Participation Case**

- Family had previous newborn with Congenital Nephrotic Syndrome, Finnish type. NPHS1 mutation confirmed.
- Baby had very difficult course, spent the first 3 months in hospital and succumbed to sepsis.
- Mom is 20 weeks pregnant with second child.
- Maternal alpha fetoprotein screen is reported “elevated”
  - 40 Multiples of the Median (normal MOM <2.5)
- Fetal ultrasound shows no abnormalities.

**Abnormal Function - high AFP**

- What is the likelihood she is carrying a child affected with CNS?
  - A ~2-5%
  - B ~33%
  - C ~50%
  - D ~99%

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In measurement of AFP. These findings are surprising since NPHS1 is clearly an autosomal recessive disorder, and individuals heterozygous for nephrin gene mutations do not have renal problems. Nephrin is a major extracellular component of the glomerular slit diaphragm, and its synthesis is probably reduced when only one NPHS1 allele is functioning properly. During glomerulogenesis, this shortage seems to cause temporary dysfunction of the slit diaphragm and protein leakage. After glomerulogenesis is finished, the amount of nephrin synthesis is no longer critical. Many non-Finnish mutations lead to lack of...
Abnormal Function - high AFP

- What is the likelihood she is carrying a child affected with CNS
  - A ~2-5%
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  - C ~50%
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Abnormal Structure - Renal Dysplasia

- Increased kidney echogenicity
- Loss of normal architecture
- Small subcapsular cysts

Fetal Renal Cysts: Ultrasound vs MRI

<table>
<thead>
<tr>
<th></th>
<th>Prenatal US</th>
<th>Fetal MRI</th>
<th>Postnatal US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small subcapsular</td>
<td>5/16 (5/11*)</td>
<td>8/16 (8/11*)</td>
<td>8/11</td>
</tr>
<tr>
<td>cysts in duplex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>4/16 (4/11*)</td>
<td>5/16 (4/11*)</td>
<td>4/11</td>
</tr>
<tr>
<td>Large cysts</td>
<td>8/16 (5/11*)</td>
<td>8/16 (5/11*)</td>
<td>8/11</td>
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</tbody>
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*11 patients had postnatal follow up ultrasound

- In 4/16 patients fetal MRI diagnosed subcapsular cysts not seen on prenatal US
Fetal MRI more sensitive than ultrasound for cysts

Prenatal US

28 weeks of gestational age

MCDK and Early Dysplasia – Prenatal Imaging

Fetal MRI

23 weeks of gestational age

Cystic Kidney Disease

Multicystic-dysplastic

Autosomal Recessive PKD
Source of amniotic fluid

- Fetal Transudate
  - 12 weeks

- Urine up to ~15ml/kg/hr

- Lung ~3ml/kg/hr

Swallowing accounts for majority of absorption in normal pregnancy

You don’t need kidneys to have normal lungs… If you have a twin...

Lung Volume Estimation

MRI Calculation of Lung Volumes to Predict Outcome in Fetuses with Genitourinary Abnormalities
Lung Volume Estimation

CONCLUSION. After 20 weeks’ gestation, the predictions of outcome in fetal pneumonitis data analysis using the MRI T1 V: gestational age ratio is comparable to the previous analysis of echocardiography.

Fetal Echogenic Kidney

Table X: Sonographic features and outcome

| Feature                      | Termination of pregnancy | Normalised | Survive | Symptomatic
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<tbody>
<tr>
<td>Optic radiation &lt; 12 D</td>
<td>15</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Normal or increased amniotic fluid volume &lt; 250 mL</td>
<td>3</td>
<td>1</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Kidney length &gt; 3.6 mm above the mean (n = 250)</td>
<td>3</td>
<td>2</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Kidney height &gt; 3.6 mm above the mean (n = 250)</td>
<td>8</td>
<td>3</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Eggshell thickness &lt; 3.6 mm above the mean (n = 250)</td>
<td>5</td>
<td>5</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

In conclusion, our results suggest that prenatal counseling following the diagnosis of isolated bilateral hyperechogenic kidneys should emphasize that establishing the etiology is difficult, especially when renal cysts are found in one of the parents. While patients with very large kidneys and severe oligohydramnios are likely to have a poor outcome, the chances to survive without significant morbidity in infancy are high when anatomic fluid volume remains normal and when the kidneys are moderately enlarged.
How about the REALLY enlarged kidneys?

TCF/HNF-1 abnormalities implicated
- 62 pregnancies with echogenic kidneys
- Studied those unlikely to be ARPKD or ADPKD
- Kidneys not 'too big'
- No oligohydramnios

TCF2 accounted for 1/3 of all hyperechogenic kidneys in their series

If you exclude ARPKD and ADPKD based on size and presence of oligohydramnios
TCF2 accounts for 60% of the remainder
Spectrum of HNF1B Mutations in a Large Cohort of Patients Who Harbor Renal Diseases

Laurence Heidt,1 Stéphane Decoster,1 Audrey Paternotte,1 Vincent Mottez,1,2 Florence Sandoz,3 Bernard Roudot-Thoraval,1 Anne-Catherine Labeeuw,1,3 Naomius Pagès,3 Vincent Gaugier,3 Gérard Antignac,1,2,4,5 and René Salomon1,2

Results: We studied a heterogeneous cohort of 78 (100%) index cases, consisting of a diverse group of the whole gene, 17q12, deletions of chromosome, and small mutations in 31. Eighteen mutations were novel. HNF1B mutations account for 61% of deletions and 40% of small mutations. In patients who carried HNF1B mutations and for whom we were able to study parental ultrasonography (50 probands), isolated hypertensive kidneys with normal or slightly enlarged size were the most frequent (48% of 50 genotypes). In 15 other prenatal renal phenotypes were associated with HNF1B mutations, at a low frequency. Echographies in four probands, 17q12 microdeletions and hypertension, although not systematically investigated, were frequently associated.

Conclusions: This large cohort confirmed that the severity of the renal disease associated with HNF1B mutations was extremely variable from prenatal renal failure to normal renal function in adulthood and was not correlated with the genotype.


HNF 1b mutation variable phenotype

• Mother with renal dysplasia and bicornuate uterus

Oldest boy
R MCDK

Oldest boy
L Dysplasia

Sister has dysplasia & cysts

3rd pregnancy
fetal US
enlarged echogenic kidneys

17q12 microdeletion -> TCF2 -> HNF-1ß-mutations

• 17q12 microdeletion eliminates the gene, TCF2
• TCF2 is the gene that encodes for HNF-1ß (Hepatocyte Nuclear Factor 1B)
• HNF-1ß regulates expression of Umodulin, PKHD-1, PKD-2
• Mutations in HNF-1ß therefore cause renal cystic disease that mimics
  - Umod-medullary cystic kidney disease
  - PKHD-1- ARPKD
  - PKD2-ADPKD
• HNF-1ß mutations are found in up to 30% of unselected children with renal hypodysplasia and urogenital abnormalities (uterine agenesis, bicornuate uterus, hypospadias)
• Maturity Onset Diabetes of the Young #5 (MODY5)
Other causes of echogenic kidneys

- Any ciliopathy
  - Ivermark, Meckel-Gruber, Bardet-Biedel
- Renal tubular dysgenesis
  - Primary
  - Secondary to fetal ACE inhibitor exposure
- Some forms of Congenital Nephrotic Syndrome

Recommendation

- Post delivery
- Detailed physical exam
- Genetics consultation
- Consider
  - 17q12 microdeletion testing
  - Ciliopathy panel testing

Cameron et al. Obstetrics & Gynecology 1994
**Bilateral Renal Agenesis (1)**

1.23 kg 2.5 years old

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**Bilateral Renal Agenesis (2)**

1.23 kg 2.5 years old, transplanted

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**Successful In Utero Intervention for Bilateral Renal Agenesis**

Jessica L. Bienstock, MD, MPP, Meredith L. Bernier, MD, Fred Coleman, MD, and Nancy A. Hueppehem, MD, MPP

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**Obstetrics & Gynecology, August 2014**

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**A Cautionary Note on New Fetal Interventions**

Aside from the fact that this novel approach was, in fact, reported in this very journal 20 years ago (with an unfortunate outcome for the newborn). It is quite rare to suggest that this intervention should be considered as an option for parents who are faced with a fetus with renal agenesis.
2.5 years old, transplanted

10 months old, PD

Succumbed to Barotrauma & hypoxia, Day of Life #2

5+ weeks

12 days old on conventional Ventilator, hypotensive

Coordination between Maternal/Fetal Medicine (MFM) & Nephrology

- Case at another institution.
  - Multiple amniotic fluid infusions
  - Baby born below local cutoff for PD
    - 2kg
    - Baby died without dialysis attempt
In BRA- Preterm PD is anticipated

- Coordination between MFM and Nephrology Team
- Timing of Delivery
- Place of Delivery
- Committed surgeon, nephrology and nursing

What not to do

- 1.1 kg
Preterm PD

• Be willing to do “inadequate dialysis” for a while
• i.e. 1.4 kg patient
• Start 10 cc / fill, (80 cc/M²)
• 4.25%, 30 minute cycles, continuous
• Gradual increase Fill Volume by 2 cc/day
• Yes, we know it shouldn’t work because you are just running fluid back and forth in the tubing
• But it does

Prenatal Counseling - Nephrology Alone?

• In clinic
• Non-life threatening conditions
  • Solitary normal kidney
  • Hydronephrosis with adequate renal function
• Normal amniotic fluid volume
• No indication for early delivery
• No additional significant anomalies
Prenatal Counseling - Multidisciplinary format preferred?

- Life threatening issues
- Significant anomalies involving more than just the kidney
- Need / expectation of premature delivery
- Need for operations / dialysis immediately post delivery
- Pulmonary insufficiency
- Decision pressure
  - Termination easier on mom earlier in gestation
  - Legal parameters

Multidisciplinary Prenatal Counseling - Format

- Prenatal Diagnostic Center
- Review Images
- Maternal Fetal Medicine (Perinatologist)
- Neonatologist
- Social Worker
- ±Surgeon
  - Urology, General Surgery, Cardiac

Parental Phenotype

- “Do everything/save my baby”
- High information seeking
  - May still default to “Do everything/save my baby”
- Conscious decision making
  - Educated, engineer approach (work the problem)
  - Quality of research varies (Google, social media etc)
- Watch for evidence of being ‘overwhelmed’
Planning around decision

• Relocation prior to delivery
• Prolonged hospitalization after delivery
• Implications
  • Financial
  • Other children
  • Social support
  • Marital stress

Don’t be afraid to ask for help

And don’t be afraid to say you don’t know

Classification

Hereditary (ciliopathies)
  • ARPKD
  • ADPKD
  • Glomerulocystic kidney disease
    • Isolated
    • Familial
  • Medullary cystic kidney disease (MCKD)
  • Nephronophthisis
    • Isolated
    • Syndromic
  • Syndromes
  • Other
    • Tubero-cortical dysplasia
    • Von Hippel-Lindau disease

Non-hereditary
  • Multicystic dysplastic kidney disease (MCDK)
  • Cystic renal dysplasia (dysplastic kidneys with cysts)
  • Isolated renal cysts
    • Simple
    • Complex
  • Acquired renal cysts
    • In ESRD
    • After liver transplant
Algorithm for Evaluation of the Newborn with Antenatal Hydronephrosis

Fetal Renal Pelvis Anti-Post Diameter:
- ≥ 4 mm at 15-32 weeks GA
- ≥ 7 mm at > 33 weeks GA
- Presence of caliectasis

SFU 2 or 3
- Follow-up US in 2 weeks
- US abnormal
- Start Antibiotics
- VCUG in 3-4 weeks
- Urology referral after VCUG

SFU 0 or 1
- Follow-up US in 2 weeks
- US normal
- No further testing indicated

SFU 4 or Bladder outlet obstruction
- Start Antibiotics
- VCUG at birth before hospital discharge
- Urology consult (telephone okay) before discharge
- Urology referral

SFU 2 or 3
- Start Antibiotics
- VCUG at birth before hospital discharge
- Urology referral after VCUG

What if postnatal renal U/S is normal?
- U of Toronto - 68 children with any prenatal pelviectasis &
  ≤ 10 mm AP pelvis diameter on ultrasound done > 48 hrs post delivery (mean 12 days)
- Ped. Nephrol 2003;18:1224