Urology Challenges in Infants with Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

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Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

• Constitute approximately 20-30% of all anomalies identified in the prenatal period

• Play a causative role in 30 to 50 percent of cases of end-stage renal disease (ESRD) in children

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

• Defects can be unilateral or bilateral and different defects often coexist in an individual child

• Patients with a reduction in kidney numbers or size are most likely to have a poor renal prognosis

CAKUT and ESRD

• Important to diagnose these anomalies early and initiate therapy to minimize renal damage

• Prevent or delay the onset of ESRD, and provide supportive care to avoid complications of ESRD

Sanna-Cherchi Set al. Kidney Int 2009; 76:528
Prenatal US: Urinary Tract Anomalies

• Urologic abnormalities: in up to 1.5% of all pregnancies

• At least 50% represent some form of hydronephrosis

• Prenatal US has completely changed the face of pediatric urology/nephrology practice

Prenatal Hydronephrosis

• In most cases, fetal renal pelvic dilation is a transient physiologic state

• Excessive concern may lead to unnecessary testing of the newborn infant and anxiety for parents and health care providers
Prenatal Hydronephrosis

• However, congenital anomalies of the kidney and urinary tract (CAKUT) can present with fetal hydronephrosis

• Goal: to detect cases that may affect the health and require antenatal and postnatal evaluation and management
## Prenatal Hydronephrosis: Causes

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Transient hydronephrosis of fetal development</td>
<td>41–88</td>
</tr>
<tr>
<td>Ureteropelvic junction obstruction</td>
<td>10–30</td>
</tr>
<tr>
<td>Vesicoureteral reflux</td>
<td>10–20</td>
</tr>
<tr>
<td>Ureterovesical junction obstruction</td>
<td>5–10</td>
</tr>
<tr>
<td>Duplex collecting system</td>
<td>5–7</td>
</tr>
<tr>
<td>Posterior urethral valves</td>
<td>4–6</td>
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</tbody>
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Prenatal US: Diagnosis

• How do we deal with the large number of prenatally detected urinary tract abnormalities?

• How do we selectively evaluate them perinatally?

• How do we avoid over-testing, without under-testing those who may benefit?
Renal pelvic diameter (RPD): method to define and grade fetal hydronephrosis (maximum AP diameter of the renal pelvis)

<table>
<thead>
<tr>
<th>Classification of Prenatal Hydronephrosis</th>
<th>Second Trimester APD (mm)</th>
<th>Third Trimester APD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>4-7</td>
<td>7-9</td>
</tr>
<tr>
<td>Moderate</td>
<td>7-10</td>
<td>9-15</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;10</td>
<td>&gt;15</td>
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Grading Prenatal Hydronephrosis

SFU

Guidelines – sort of...

An attempt to permit a more consistent communication about prenatal hydronephrosis
UTD Grading: Prenatal

- 16-27 wks: AP RPD ≥ 7 mm
- ≥ 28 wks: AP RPD ≥ 10 mm

- Peripheral calyceal dilation*
- Parenchymal thickness abnl
- Parenchymal appearance abnl
- Ureters abnormal
- Bladder abnormal
- Unexplained oligohydramnios**

UTD A2-3: INCREASED RISK
Postnatal Management

- APRPD > 15mm
- Peripheral calyceal dilation
- Parenchymal thickness normal
- Parenchymal appearance normal
- Ureters abnormal
- Bladder normal

UTD P2: INTERMEDIATE RISK

FOLLOW UP US:
1 to 3 months
VCUG:
Discretion of clinician
ANTIBIOTICS:
Discretion of clinician
FUNCTIONAL SCAN:
Discretion of clinician
Prenatal Hydronephrosis

• UPJO increased in frequency with severity of hydronephrosis

• In contrast, VUR was not associated with the severity of fetal hydronephrosis

• However, moderate to severe reflux (grades III through V) appears to be associated with a greater degree of renal pelvic dilation (RPD >10 mm) and ureter, both in utero and postnatally

Correlation of degree of hydronephrosis with postnatal outcomes – meta-analysis

from Lee et al., Pediatrics 2006, 118(2):586
Postnatal longitudinal evaluation of children with prenatal hydronephrosis

• 1034 charts of fetuses with PNH

• At last follow-up (mean age 20.6 months), hydronephrosis persisted in children with:
  • Mild: 10%
  • Moderate: 24%
  • Severe: 63%

Risk for CAKUT and Postnatal Surgical Intervention with Increasing Severity of Fetal Hydronephrosis

- Meta-analysis of 1678 infants from 17 studies:
  - **Mild hydronephrosis**: ($\leq 7 \text{ mm in 2}\text{nd and/or } \leq 9 \text{ mm in 3}\text{rd}$): **12 %**
  - **Moderate**: (7-10 mm in 2\text{nd} / 9-15 mm in the 3\text{rd} third trimester): **45 %**
  - **Severe**: (>10 mm in 2\text{nd} / >15 mm in 3\text{rd} third trimester): **88 percent**

Ureterocele: Prenatal detection

- Duplex system with upper pole hydronephrosis
- Hydroureter
- Intravesical cystic structure

Ureteroceles can cause bladder outlet obstruction if closely located to the urethra
How should we evaluate obstruction?

• When hydronephrosis is severe (SFU 3-4), functional testing (MAG 3 renal scan) should be used.
Severe unilateral UPJO

Need for surgery: Ultrasound dilation of pelvis predicts functional decline - Dhillon, 1997
Ultrasound evaluation of hydronephrosis

- Calyceal dilation may be best indicator of severity

- “Thinning” of parenchyma may reflect only dilation

- Extra-renal pelvis may look more severe than it is functionally
Serial MAG-3 scans for UPJO

Age: 2 months

Differential uptake
Left: 61%
Right: 39%

T ½ minutes
Left: <3
Right: 11.5

Age: 7.5 months

Differential uptake
Left: 68%
Right: 32%

T ½ minutes
Left: 9
Right: 26

“Function”: 39% to 32%

Washout time (t ½): 11.5 min to 26 min
Observation of infants with SFU 3-4 hydronephrosis
Ross, et al., 2011, J Ped Urol 7:266-71

• 115 pts (125 kidneys) / Overall operative rate of 38%
• Delayed surgery in 21 (21%) at mean of 500 days, 3 showed < DRF
• Cost of multiple studies / Limited F/U in some patients
Management for UPJO (SFU gr. 3-4 hydronephrosis)

- If US confirms moderately severe dilation: MAG3
- If function >45% and washout < than 30 min – repeat US at 4-6 ms
- Repeat MAG3 at 6-12 months - re-assess “function”
Initial Evaluation of prenatally detected hydronephrosis

From Swords and Peters, Arch Dis Child Fetal Neonatal Ed 2015; 100:F460-64
Isolated Fetal Hydronephrosis:
The Every-day Question

• Should we screen for vesicoureteral reflux?
Isolated Fetal Hydronephrosis:
Incidence of Reflux

In the context of prenatal hydronephrosis, VUR is present in a significant number of patients

- Arena, et al. (2001): 382 pts - VUR in 68 (17.8%)
- Brophy, et al. (2002): 234 pts - VUR in 40 (17.1%)
Isolated Fetal Hydronephrosis: Screening for Reflux

• Benefits of screening:
  ✓ identify those patients with reflux before they have an infection and damage their kidneys

• Burden of screening:
  ✓ we may identify patients with low grade reflux with little risk of renal injury and therefore over-test
Is this Reflux Clinically Important?

• Ismaili, et al. (2002): 264 infants with prenatal hydro
  • Had 2 neonatal US images
  • If both normal (74), VCUG abnormal in 5 (6.7%)
  • Can select low risk population with post-natal imaging
Not screening for Reflux

• If a VCUG is not to be obtained, the family should be made aware of the clinical signs and symptoms of UTI

• A follow-up US is useful to assess renal growth and ensure the child has been well

• The chance of missing significant reflux is small (postnatal SFU 1-2)
Amniotic fluid (AF)

- Fetal urine becomes significant at the start of the second trimester

- By 20 weeks gestation, fetal urine accounts for > than 90 % of the amniotic fluid volume

- Oligohydramnios at or beyond 20 week of gestation is consistent with a decreased production of fetal urine and CAKUT

Fetal LUTO

Three main diagnoses:

• Posterior urethral valves (PUV)
• Urethral atresia
• Prune belly syndrome

• Other: anterior urethral valves, megalourethra, megacystis-microcolon-hyperparastalsis syndrome, cloacal malformations, and prolapsing cecoureterocele

Anumba et al, 2005 / Heihhila et al 2011
PUV

• Most common cause of LUTO (approx. 1/8000 live male births)

• Up to 28% of boys with PUV maintain a lifetime risk for ESRD

Prenatal US: PUV

• PUV: most common cause of bilateral hydronephrosis in males

• Fetal US:
  - Distended bladder, thickened detrusor, posterior urethral dilatation (key hole sign)
  - Oligohydramnios
  - Severe hydroureteronephrosis (renal cysts)
• Severe cases, mortality up to 45%

• Postnatal: severe morbidity and mortality, independent of treatment type
Prenatal Intervention

Vesicoamniotic shunt placement

- Overwhelmingly, VAS placement is the most common procedure with the largest dataset to analyze.
VAS: Lung Hypoplasia

- AF levels are critical for proper lung development during the canalicular phase (between weeks 16 and 24)
- Most severe fetal complication and cause of perinatal mortality
- VAS: ameliorate pulmonary hypoplasia

Smith LJ. Paediatr Respir Rev. 2010;11(3):135–42
Prenatal VAS (PLUTO)

- Randomised women (UK, Ireland, and Netherlands) whose pregnancies were complicated by LUTO

- Randomly assigned to receive either the intervention (VAS) or conservative management.

31 women (16 VAS – 15 CM)

- Survived to 28 days:
  - **VAS**: 8/16 (50%)
  - **Conservative management**: 4/15 (26.5%) (intention-to-treat relative risk [RR] 1.88, 95% CI 0.71–4.96; p=0.27)

- All deaths were caused by pulmonary hypoplasia

Overall outlook in both trial groups at 2 years was poor (only 2 babies surviving without renal impairment)

VAS improves perinatal survival (long-term renal function was poor)

(Morris et al, Lancet 2013; 382: 1496–506)
Prenatal Intervention: Results

• Updated meta-analysis (2017): 112 fetuses with VAS - 134 treated conservatively

• VAS improved perinatal survival (from birth up to 6 months of age) (57% VAS v. 39% conservative treatment)

• 2-year renal function outcomes, VAS placement did not improve postnatal renal function

Prenatal VAS
(Univ. Miami – Jackson Memorial Hospital)

Prenatal renal parenchymal area as a predictor of early end-stage renal disease in children with vesicoamniotic shunting for lower urinary tract obstruction.


• Retrospective study of 15 male fetuses (01/2009 and 12/2015) with LUTO who survived VAS placement

• Diagnoses included: PUV (8), PBS (4), urethral atresia (2), and megacystis microcolon intestinal hypoperistalsis syndrome (1)
Prenatal Renal Parenchyma area

• Analyze renal parenchymal area (RPA) in fetuses with LUTO and, its use as a predictor of postnatal renal function

• Shunts were placed at 21.39 ± 3.58 weeks of gestation

Prenatal Renal Parenchyma area

- Patients were divided into 2 groups according to renal function in the last follow-up:
  - **Group 1**, ESRD: 8 patients (53.3%)
  - **Group 2**, non-ESRD: 7 patients (46.7%)

Prenatal Renal Parenchyma area

Prenatal US of a 22wk fetus with LUTO before VAS placement

A) Total renal area measurement (cm²)  B) Area of hydronephrosis (cm²)

Mean Renal parenchyma area was significantly smaller in patients with ESRD (p<0.05)

Even with early VAS, postnatal morbidity remain high, emphasizing role of renal dysplasia, in postnatal renal failure.

Prenatal RPA measurement could have an important role as a non-invasive tool to predict postnatal renal function.
Prenatal VAS: Conclusions

• From SRs and data from PLUTO trial, VAS increase early survival rates in patients with an initial poor prognosis

• Interventions do not have significant benefit on renal function

• “Renal Dysplasia”, insult is too early and led to postnatal renal failure
Postnatal management
PUV – Endoscopic valve ablation

- Cystoscopy: 6.5 - 7.5 - 9-Fr.
  - Laser Fiber
  - Bugbee Electrode
  - Resectoscope 9.5-Fr with Collins knife

WOLF 4.5 Fr (6.5)
SHORT URETEROSCOPE
110MM WL, 3 FR WC
PUV – Endoscopic Valve Resection
Goal

• Evaluate efficacy of PUV resection during early postnatal period

• Compare results between premature/low weight babies and term neonates
• 2004 - 2015, 130 patients underwent endoscopic PUV resection

• 44 neonates (< 28 days), divided in 2 groups:
  • Group 1 (n=25): premature (<37 wks) / low weight (<2.5 Kg)
  • Grupo 2 (n=19): term / weight >2.5 Kg
## PUV Endoscopic Resection in Neonates

### Results

<table>
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<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age surgery (days)</td>
<td>7</td>
<td>7</td>
<td>0.910</td>
</tr>
<tr>
<td>Time to follow up (months)</td>
<td>71.4 ± 39.1</td>
<td>57.6 ± 34.2</td>
<td>0.230</td>
</tr>
<tr>
<td>Initial mean serum Cr (mg/dL)</td>
<td>2.19 ± 1.53</td>
<td>1.1 ± 0.62</td>
<td>0.004</td>
</tr>
<tr>
<td>Initial mean eGFR (mL/min per 1.73m²)</td>
<td>11.4 ± 7.4</td>
<td>23.7 ± 15.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Follow-up nadir Cr (mg/dL)</td>
<td>1.18 ± 1.31</td>
<td>0.50 ± 0.45</td>
<td>0.030</td>
</tr>
<tr>
<td>eGFR at last follow-up (mL/min per 1.73m²)</td>
<td>78.1 ± 52.3</td>
<td>118.2 ± 54.3</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Podium Presentation, Fall Meeting SPU, Montreal, September 2017
Elevated serum creatinine in Group 1

No other significant differences between the 2 groups (RVU, hydronephrosis, redo valves resection, urethral stenosis)
Conclusion

• PUV resection is a safe and effective surgical option in premature and low weight babies

• Preterm/Low birth weights boys had a worse initial and 1 year renal function when compared with term neonates
Observations

• The major value of prenatal diagnosis is education for the expectant parent

• Perinatal decision-making should be based upon postnatal clinical outcomes

• CAKUT: Identify those patients at risk for renal injury, develop prevention strategies, and intervene when appropriate
Thanks...

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