Antenatal aspects of CAKUT / Ciliopathies

Paul Winyard
Overview

Define CAKUT

Illustrate with a range of cases

Highlight important prognostic factors

Increase confidence in counselling future families
Cautions

Limited information, and from ultrasound rather than traditional sources

Aneuploidy has to be considered

Timely decisions essential, but time changes decisions
CAKUT

- Congenital Anomalies of the Kidney and Urinary Tract (Ichikawa)
- Diverse spectrum including
  - Cystic / Multicystic = containing cysts
  - Dysplastic kidneys = abnormal structures
  - Hypoplastic kidneys = reduced normal structures
  - Lower urinary tract dysfunction such as pelvi-ureteric junction (PUJ), vesico-ureteric junction (VUJ), posterior urethral valves (PUV) and reflux
Causes of end-stage renal failure in UK children

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>N</th>
<th>%</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysplasia ± reflux</td>
<td>240</td>
<td>34.2</td>
<td>147</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>128</td>
<td>18.2</td>
<td>121</td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>74</td>
<td>10.5</td>
<td>32</td>
</tr>
<tr>
<td>Congenital nephrotic syndrome</td>
<td>68</td>
<td>9.7</td>
<td>37</td>
</tr>
<tr>
<td>Tubulo-interstitial diseases</td>
<td>46</td>
<td>6.6</td>
<td>19</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>32</td>
<td>4.6</td>
<td>19</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>31</td>
<td>4.4</td>
<td>11</td>
</tr>
<tr>
<td>Metabolic</td>
<td>27</td>
<td>3.8</td>
<td>14</td>
</tr>
<tr>
<td>Uncertain aetiology</td>
<td>25</td>
<td>3.6</td>
<td>11</td>
</tr>
<tr>
<td>Malignancy &amp; associated disease</td>
<td>16</td>
<td>2.3</td>
<td>5</td>
</tr>
<tr>
<td>Missing</td>
<td>15</td>
<td>2.1</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>702</strong></td>
<td><strong>100</strong></td>
<td><strong>425</strong></td>
</tr>
</tbody>
</table>
How confident are you at antenatal counselling for CAKUT?

- Unsure, would always ask others.
- Depends on the case; OK in some.
- Can generally give an informed view.
- Fairly confident in most cases.

Percent
Question 2

What is the most important prognostic counselling of CAKUT antenatally?

- Gestation at presentation: 5%
- Size of the kidneys: 20%
- Amniotic fluid – deepest pool: 65%
- Family history: 10%
Overdiagnosed antenatally?

- 0.8% to 3.0% of antenatal scans pick up a renal or urinary tract abnormality
- The vast majority are of no clinical significance, but they still have a major impact on the families involved
Response to unexpected finding

- Hope and acceptance
- Distancing and denial
- Grief and guilt
- Desperate for (proper) medical guidance
Quotations

• I knew it as soon as he looked at me, really
• It took 3 times as long as before and they called someone else in
• We cried all the time and had a tiny hope that everything would work out all right
• I simply gave up that Friday. What can I do either way, I thought. Then the weekend started, and I thought this is my last day as a happy pregnant woman
• Even though I thought a lot about what was going to happen, it was just as if it kind of concerned someone else. It wasn’t about me anymore
• The toughest part is that you lose something which you really want if she is healthy, but which you have decided that you don’t want
Abortion Legislation in Europe

This report summarizing laws on abortion in selected European countries shows diverse approaches to the regulation of abortion in Europe. A majority of the surveyed countries allow abortion upon the woman’s request in the early weeks of pregnancy, and allow abortion under specified circumstances in later periods. A comparative summary with maps is included.

January 2015 Report, (PDF, 399KB)
Large bright kidneys: what does it mean?
Echogenic kidneys: differential diagnosis

- Aneuploidy
- Normal variant
- Autosomal recessive polycystic kidney disease
- Autosomal dominant polycystic kidney disease
- Renal cysts and diabetes syndrome
- Beckwith Wiedemann syndrome
- Other genetic syndromes
Most likely one of three common things

- Normal variant
- Dysplastic kidneys
- Polycystic kidneys
How does ultrasound help?

1) Kidney size
2) Kidney structure
3) Amniotic fluid

We want to estimate:
- number of nephrons
- functional renal mass
Case 1

Referral at 21 weeks gestation because of potentially abnormal kidneys

Both parents alive and well

Previous obstetric history of:
- Severe renal dysplasia/agenesis
- Twin to twin transfusion syndrome
Initial scans

1) Kidney size
   - normal

2) Kidney structure
   - normal - bright

3) Amniotic fluid
   - normal

Main care between local and tertiary
Amniotic fluid index

Summary
Huge kidneys
Structurally abnormal kidneys
No amniotic fluid

But
Fetal kidneys not needed for survival
Postnatal renal replacement possible
Normal amniotic fluid up to 28 weeks
Transferred obstetric care to UCLH

Premature labour, 2.1Kg, ventilated

Great Ormond Street
- poor urine output
- rising creatinine
- peritoneal dialysis from 1 week of age
- big echogenic kidneys, no cysts

What is the diagnosis?
6 months
5 months in hospital, slow weight gain

1 year
Ng tube; peritonitis, occasional
60-70% at home

18 months
Transplant with father’s kidney
Eating at last

Diagnosis – Dysplasia, unknown cause;
100k genome
Parent’s and her patient journey

- Anxiety
- Uncertainty
- Time commitment
- Family disruption
- A life time of medicalisation
Prenatally Diagnosed Echogenic Kidneys: Postnatal Outcome

Yulia A¹, Aref A¹, Napolitano R¹, Pandya P¹, Winyard PJD¹,²

¹Fetal Medicine Unit, University College Hospital London.
²Nephrology Unit, UCL GOS Institute of Child Health

A 15-year retrospective review of all fetuses identified with echogenic kidneys seen in a London tertiary fetal medicine unit.

316 cases of increased renal echogenicity, gestation 21wks (13-37)
139 (44%) did not survive beyond birth
    105 termination; 5 intrauterine and 29 early neonatal death
134/139 bilateral
    36 further renal tract and 94 g extra renal abnormalities

177 (56%) survived beyond birth
ISUOG’s World Congress is the main annual scientific meeting for clinicians who use or research ultrasound in obstetrics and gynecology.

28th World Congress on Ultrasound in Obstetrics and Gynecology
20 – 24 October 2018, Singapore
Incorporating ASUM 2018
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Isolated echogenic Kidneys</th>
<th>Other renal anomaly</th>
<th>Extra-renal anomaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidy</td>
<td>41</td>
<td>3</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>Bladder obstruction</td>
<td>36</td>
<td>14</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>ARPKD</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ADPKD</td>
<td>12</td>
<td>9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bilateral cystic Dysplasia</td>
<td>15</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Unilateral cystic Dysplasia</td>
<td>22</td>
<td>9</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>MCDK</td>
<td>18</td>
<td>7</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Duplex kidneys</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven genetic syndromes</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>18</td>
<td></td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>
Case 2

Referral at 21 weeks gestation because of potentially abnormal kidneys

Both parents alive and well

No significant previous obstetric history
26, 31, 35 weeks

- Kidneys growing to 95\textsuperscript{th} centile
- Bright with loss of corticomedullary differentiation
- Falling amniotic fluid <5\textsuperscript{th} centile
- Transferred care to UCLH
Summary
Big kidneys
Structurally abnormal kidneys
Reduced amniotic fluid

But
Fetal kidneys not needed for survival
Postnatal renal replacement possible
Normal amniotic fluid up to 31 weeks
Progress

Induced post term
Priest in the delivery room; Apgars 9 and 10
Normal urine output, normal creatinine

NORMAL scan (albeit with ‘perhaps’ reporting)
Apparent normalisation of fetal renal size in autosomal dominant polycystic kidney disease (PKD1)

Steve Jeffery, Anand K Saggar-Malik, Demetrios L Economides, Sally E Blackmore, Kay D MacDermot

First published: April 1998  Full publication history
DOI: 10.1111/j.1399-0004.1998.tb02701.x  View/save citation
Cited by: 4 articles  Citation tools

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Abstract

We present a family with adult onset autosomal dominant polycystic kidney disease (ADPKD) in two generations, linked to the PKD1 locus and with paternal transmission to the fetus. The fetus carried the PKD1 haplotype and was, therefore, a gene carrier. Progressive hyperechogenic renal enlargement, but no cysts, was documented by serial fetal ultrasounds at 21, 23 and 34 weeks of gestation. Surprisingly, the newborn renal scan showed normal sized kidneys with apparently normal corticomedullary differentiation. However, at 11 months of age, the evolution of cysts in one kidney, and then in the other kidney at 20 months, was documented by ultrasound in the absence of clinical symptoms or signs. The observed normalisation of fetal renal ultrasound appearances at birth has not previously been described in fetuses presenting with PKD1.
Follow up

• Upper normal limit creatinine
• GFR – 83, 75, 73
• Ultrasound – few small cysts, questionable cortico-medullary differentiation

And the diagnosis could be …. ?
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardet–Biedl syndrome</td>
<td>Multiple genes/loci implicated, several associated with centrosomes/cell cycle gene</td>
</tr>
<tr>
<td>Beckwith–Wiedemann syndrome</td>
<td>p57Kip2 mutation in a minority of patients, cell cycle gene</td>
</tr>
<tr>
<td>Branchio-oto-renal syndrome</td>
<td>EYA1 mutation, transcription factor-like protein</td>
</tr>
<tr>
<td>Campomelic dysplasia</td>
<td>SOX9 mutation, transcription factor</td>
</tr>
<tr>
<td>Carnitine palmitoyltransferase II deficiency</td>
<td>Gene for this enzyme is mutated</td>
</tr>
<tr>
<td>CHARGE association</td>
<td>Genetic basis unknown</td>
</tr>
<tr>
<td>Di George syndrome</td>
<td>Microdeletion at 22q11, probably several genes involved</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>Six mutant genes reported, DNA repair pathways</td>
</tr>
<tr>
<td>Frasier syndrome</td>
<td>FRAS1 and FREM mutations, cell adhesion molecules</td>
</tr>
<tr>
<td>Glutaric aciduria type II</td>
<td>Glutaryl-CoA dehydrogenase mutation</td>
</tr>
<tr>
<td>Hypoparathyroidism, sensorineural deafness and renal anomalies (HDR) syndrome</td>
<td>GATA3 mutation, transcription factor</td>
</tr>
<tr>
<td>Kallmann's syndrome</td>
<td>X-linked form: KAL1 mutation, cell adhesion molecule</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
<td>Three loci mapped with two major genes, MKS1 (17q23) and MKS3 (16p13)</td>
</tr>
<tr>
<td>Nail-patella syndrome</td>
<td>LMX1B mutation, transcription factor</td>
</tr>
<tr>
<td>Renal dysplasia</td>
<td>Some cases have de novo heterozygous mutations in uropathtin 11a</td>
</tr>
<tr>
<td>Renal-coloboma syndrome</td>
<td>PAX2 mutation, transcription factor</td>
</tr>
<tr>
<td>Renal cysts and diabetes syndrome</td>
<td>TCF2HNF1β mutation, transcription factor</td>
</tr>
<tr>
<td>Simpson–Coulby–Behmel syndrome</td>
<td>GPC3 mutation, proteoglycan</td>
</tr>
<tr>
<td>Situs inversus and nephronphthisis type 2</td>
<td>Inversion mutations, primary cilia and plane of cell polarity</td>
</tr>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>Dehydrocholesterol reductase mutation, cholesterol biosynthesis</td>
</tr>
<tr>
<td>Townes–Brocks syndrome</td>
<td>SALL1 mutation, transcription factor</td>
</tr>
<tr>
<td>Urofacial (Ochoa) syndrome</td>
<td>Locus on 10q, gene undefined</td>
</tr>
<tr>
<td>Urogenital adysplasia syndrome</td>
<td>Some cases have HNF1β mutation</td>
</tr>
<tr>
<td>VACTERL association</td>
<td>Basis unknown, apart from one report of a mitochondrial gene mutation</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>Peroxisomal protein mutation</td>
</tr>
</tbody>
</table>
Abnormal kidneys
- occasional genetic causes

- TCF2/HNF1β
- PAX2
- GDNF/RET
- DSTYK
Renal cysts and diabetes syndrome

The commonest cause of renal malformations in antenatal clinic

**Decramer et al.** Anomalies of the TCF2 gene are the main cause of fetal bilateral hyperechogenic kidneys.

**************************

Early GOS experience: about a quarter
- Gout, Post-transplant
- Diabetes onset after child diagnosed
- Low magnesium

And, ……new mutations in up to 50%
Follow up

• Upper normal limit creatinine

• GFR – 83, 75, 73

• Ultrasound – few small cysts, questionable cortico-
  medullary differentiation

Diagnosis – Renal cysts and diabetes syndrome
Case 3

Referred after local 20 week scan
  • normal scan at 12 weeks
  • bright kidneys at 20 weeks
  • ‘perhaps’ low amniotic fluid volume

Miscarriage 8 weeks first pregnancy
Mother and father well
Ultrasound scans

23 weeks: large bright kidneys, no cysts, normal amniotic fluid
Progress

Repeated antenatal scans:
Large and bright kidneys, but no cysts
Amniotic fluid always in the low normal range

Postnatal:
• 3 months – kidneys large and bright but no cysts
• 12 months – normal size, but 2 cysts in L, 1 R
• 3 years – big kidneys again, multiple small cysts, maximum 1.5 cm

Diagnosis – ADPKD !
Case 4

Referred in third pregnancy:
• massive kidneys occupying whole abdomen
• oligohydramnios

Past history:
Terminations at 24 weeks with similar history

Family:
Mum 32, 1 cyst upper pole
Dad 35, normal kidneys

Diagnosis – ARPKD!
Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases
A Clinical Practice Recommendation
With Systematic Literature Reviews

Charlotte Gimpel, MB, BChir, MA; Fred E. Avni, MD, PhD; Carsten Bergmann, MD, PhD; Metin Cetiner, MD;
Sandra Habbig, MD; Dieter Haffner, MD, PhD; Jens König, MD; Martin Konrad, MD, PhD; Max C. Liebau, MD;
Lars Pape, MD, PhD; Georg Rellensmann, MD; Andrea Titieni, MD; Constantin von Kaisenberg, MD, PhD;
Stefanie Weber, MD, PhD; Paul J. D. Winyard, BM, BCh, MA, PhD; Franz Schaefer, MD, PhD

Published online November 27, 2017.
Time course of cysts in PKD

ARPKD – cysts are always present in fetal kidneys but too small to see by ultrasound

ADPKD – cysts visible from third trimester

i.e. cysts at 20 weeks, or unilateral

- THINK DYSPLASIA!
# Fetal echogenic kidneys

<table>
<thead>
<tr>
<th>Condition</th>
<th>General population</th>
<th>Antenatal presentation</th>
<th>Antenatal clinic frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD</td>
<td>1 in 1,000</td>
<td>1%</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>ARPKD</td>
<td>1 in 20,000</td>
<td>75%</td>
<td>1 in 25,000</td>
</tr>
<tr>
<td>Dysplastic kidneys</td>
<td>1 in 1,000 to 1 in 5,000</td>
<td>90%</td>
<td>1 in 2,000</td>
</tr>
</tbody>
</table>
Key factors on antenatal renal scan

1) Kidney size
2) Kidney structure
3) Amniotic fluid
How much normal tissue is there?

- Multicystic dysplastic kidney
- Cystic dysplastic kidney
- Bardet-Biedl
- Renal cysts and diabetes
- Nephronopthisis
- ARPKD
- ADPKD

Almost none

Nearly 100%
Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases: A Clinical Practice Recommendation With Systematic Literature Reviews.


eFigure. Visual analog scale for counselling about prognosis of perinatal renal cystic disease

CKD: chronic kidney disease
courtesy of P. Winyard, graphics C. Gimpel
Management of antenatally detected kidney malformations

Angela Yulia, Paul Winyard

Fetal Medicine Unit, Elizabeth Garrett Anderson Hospital, University College Hospitals London, Huntley Street, London WC1N 6AU, UK
Nephro-Urology Group, Developmental Biology and Cancer programme, University College London Great Ormond Street Institute of Child Health, 30 Guildford Street, London WC1N 1EH, UK

Abstract

Congenital anomalies of the kidneys and the urinary tract (CAKUT) are one of the most common sonographically identified antenatal malformations. Dilatation of the renal pelvis accounts for the majority of cases, but this is usually mild rather than an indicator of obstructive uropathy. Other conditions such as small through large hyperechogenic and/or cystic kidneys present a significant diagnostic dilemma on routine scanning. Accurate diagnosis and prediction of prognosis is often not possible without a positive family history, although maintenance of adequate amniotic fluid is usually a good sign.

Both pre- and postnatal genetic screening is possible for multiple known CAKUT genes but less than a fifth of non-syndromic sporadic cases have detectable monogenic mutations with current technology. In utero management options are limited, with little evidence of benefit from shunting of obstructed systems or installation of artificial amniotic fluid. Often outcome hinges on associated cardiac, neurological or other abnormalities, particularly in syndromic cases. Hence, management centres on a careful assessment of all anomalies and planning for postnatal care.

Early delivery is rarely indicated since this exposes the baby to the risks of prematurity in addition to their underlying CAKUT. Parents value discussions with a multidisciplinary team including fetal medicine and paediatric nephrology or urology, with neonatologists to plan perinatal care and clinical geneticists for future risks of CAKUT.

Keywords:
Prenatal ultrasound
CAKUT
LUTO
Dysplastic
Multicystic
Polycystic
Hyperechogenic
Bright
Hydronephrosis
Renal dysplasia
# Random Fetal CAKUT Case Generator

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney size (centile)</td>
<td>5th</td>
<td>25th</td>
<td>N</td>
<td>75th</td>
<td>95th</td>
</tr>
<tr>
<td>Kidney structure</td>
<td>Very bright</td>
<td>Possibly bright</td>
<td>N</td>
<td>One cyst</td>
<td>Many cysts</td>
</tr>
<tr>
<td>Amniotic fluid (centile)</td>
<td>5th</td>
<td>25th</td>
<td>N</td>
<td>75th</td>
<td>95th</td>
</tr>
</tbody>
</table>
Conclusions

- Echogenic kidneys are common
- Many ‘normal’ kidneys now being picked up
- Normal versus dysplastic versus polycystic
- Size, structure, amniotic fluid
- Pathology and radiology develops over time
The importance of antenatal diagnosis … summary

- Experienced team
  - known unknowns

- Severe parental distress

- Opportunity to be better prepared

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Question 1
poll evaluation

How confident are you at antenatal counselling for CAKUT?

before the presentation

after the presentation
Question 2
poll evaluation

Before the presentation

Amniotic fluid - deepest pool.

Size of the kidneys.

Gestation at presentation.

Family history.

After the presentation

Amniotic fluid - deepest pool.

Size of the kidneys.

Gestation at presentation.

Family history.
The next webinar

Nov 06, 2018:
Rachel Lennon (Manchester) & Jaap Groothoff (Amsterdam)
‘Microscopic Haematuria’