Antenatal aspects of CAKUT / Ciliopathies

Paul Winyard

UCL

Great Ormond Street Hospital for Children NHS Foundation Trust

uclh NHS

ERKNet
The European Rare Kidney Disease Reference Network

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

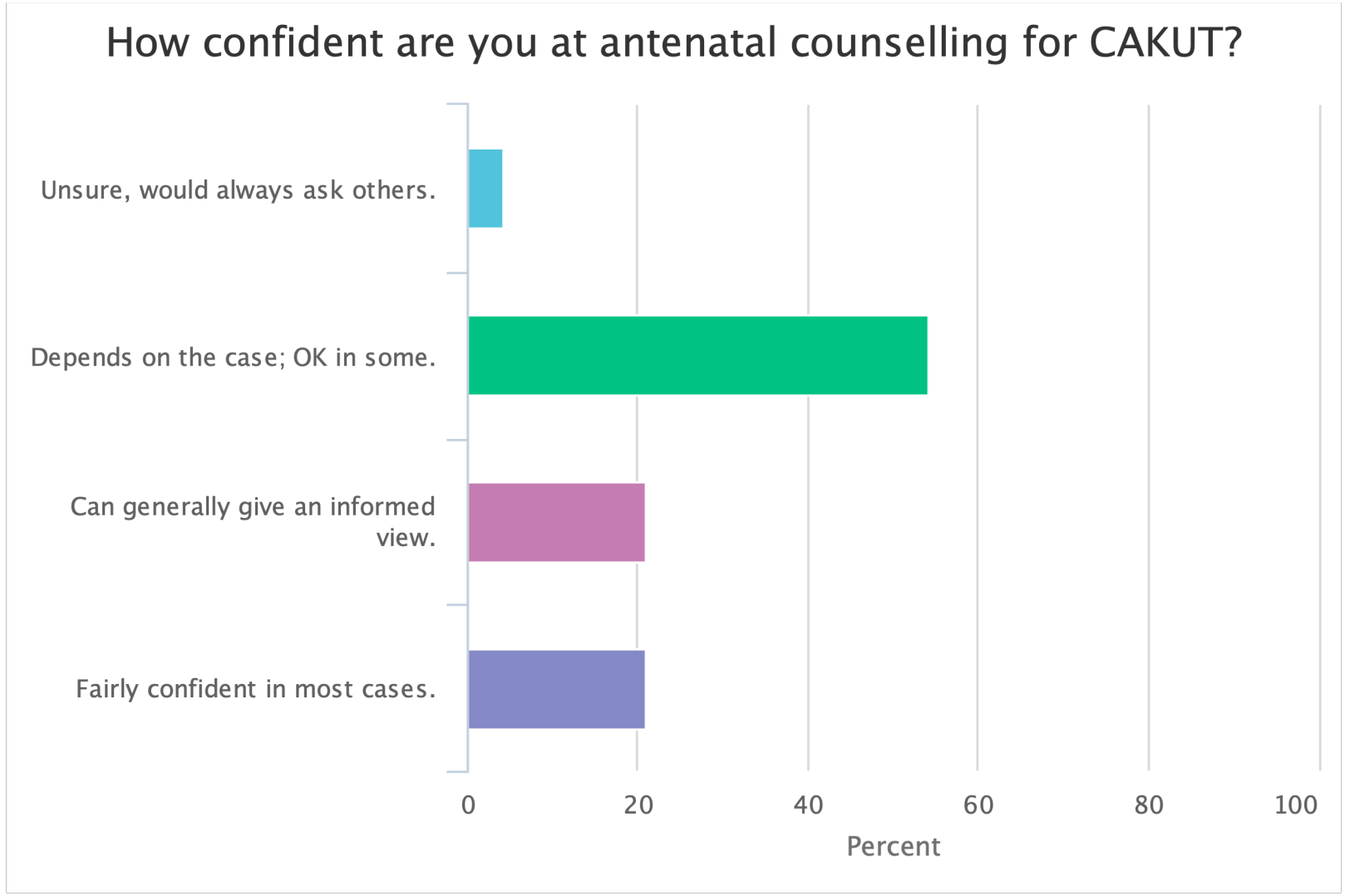
CAKUT

- 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

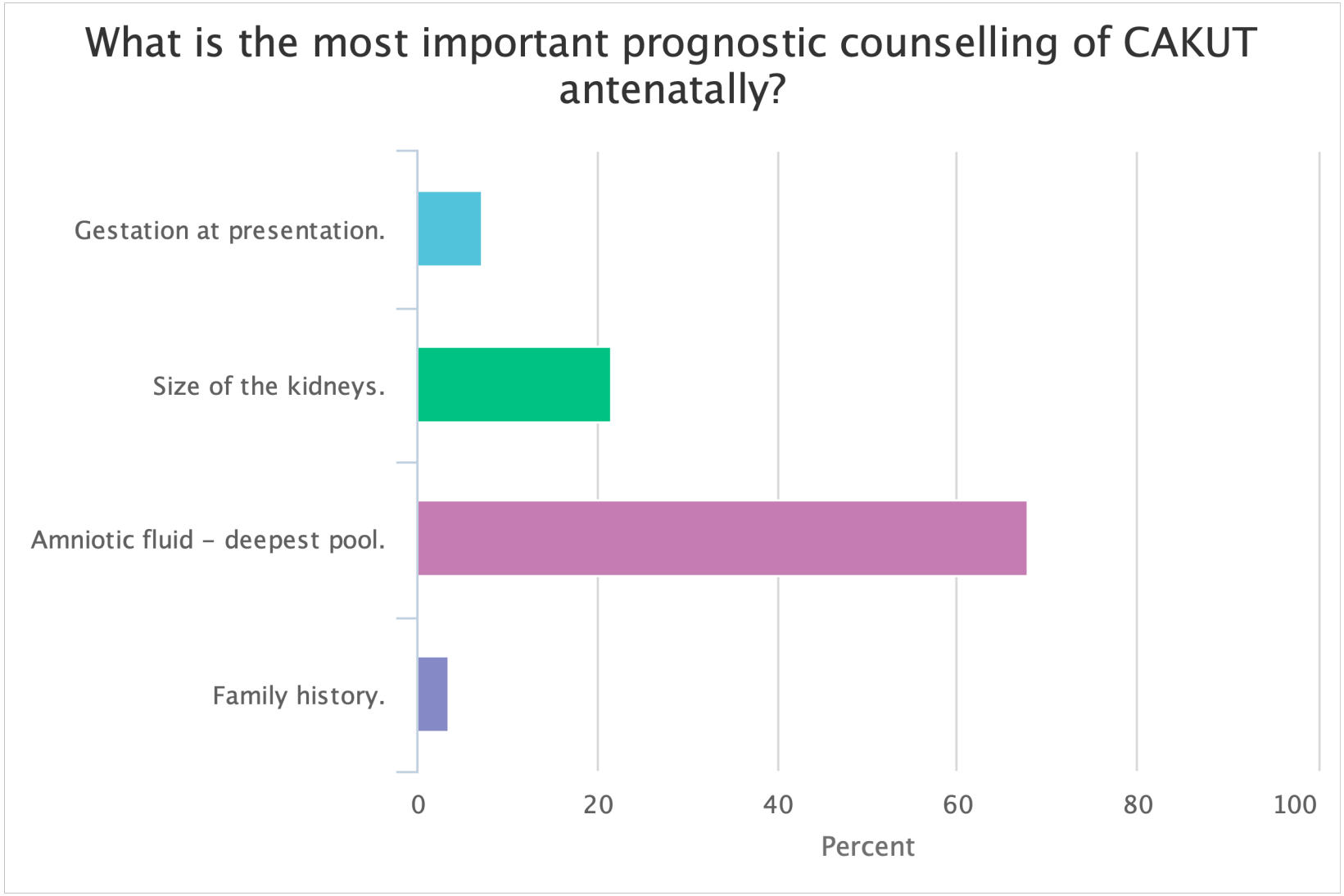
Causes of end-stage renal failure in UK children

Diagnostic group	*N*	%	Male
Renal dysplasia ± reflux	240	34.2	147
Obstructive uropathy	128	18.2	121
Glomerular disease	74	10.5	32
Congenital nephrotic syndrome	68	9.7	37
Tubulo-interstitial diseases	46	6.6	19
Renovascular disease	32	4.6	19
Polycystic kidney disease	31	4.4	11
Metabolic	27	3.8	14
Uncertain aetiology	25	3.6	11
Malignancy & associated disease	16	2.3	5
Missing	15	2.1	9
Total	**702**	**100**	**425**

Question 1


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.
0
20
40
60
80
100
Percent

Question 2


What is the most important prognostic counselling of CAKUT antenatally?
Gestation at presentation.
Size of the kidneys.
Amniotic fluid - deepest pool.
Family history.
0
20
40
60
80
100
Percent

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*

/law/help/abortion-legislation/europe.php#germany

abortion regulations across eu

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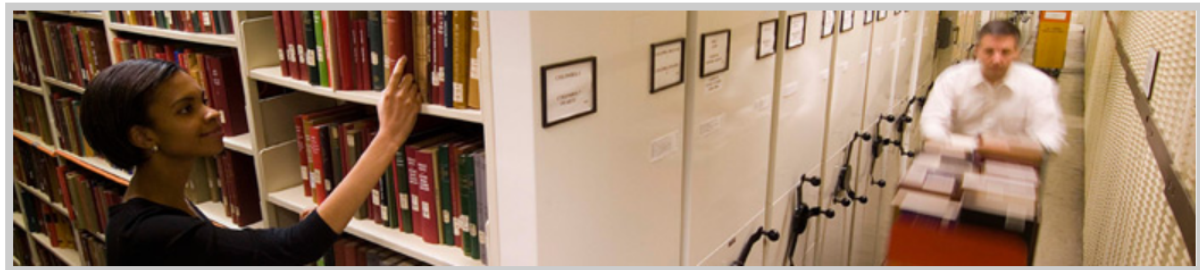
Abortion Legislation in Europe



« Back to Index of Legal Reports

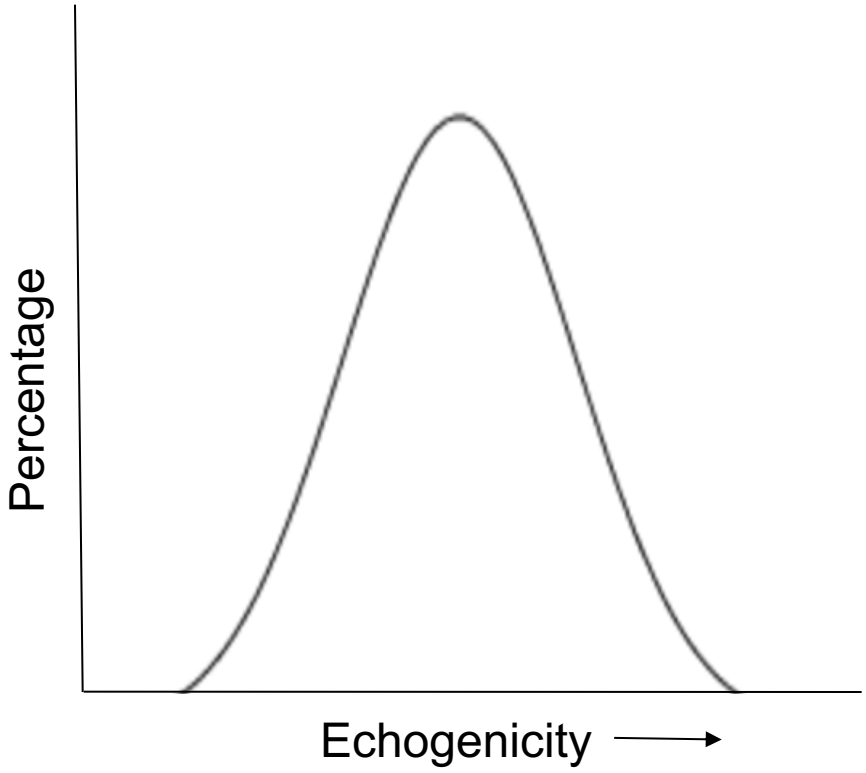
This report summarizing laws on abortion in selected European countries shows diverse approaches to the regulation of abortion in Europe. A majority of the surveyed countries allow abortion upon the woman's request in the early weeks of pregnancy, and allow abortion under specified circumstances in later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

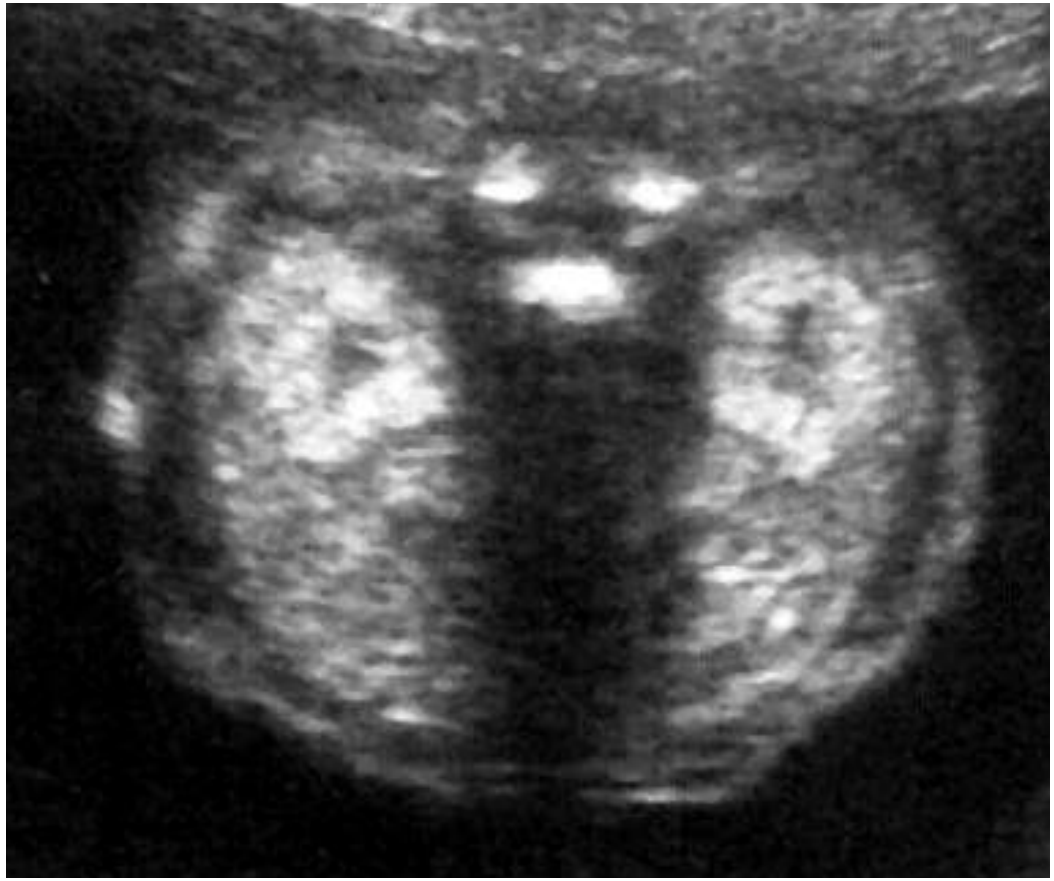
January 2015 Report, (PDF, 399KB)

https://www.loc.gov/law/help/abortion-legislation/europe.php

Large bright kidneys:

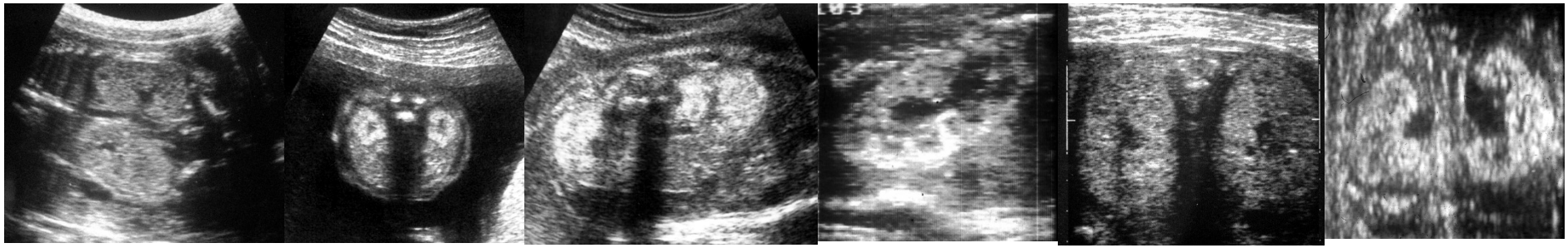
what does it mean?



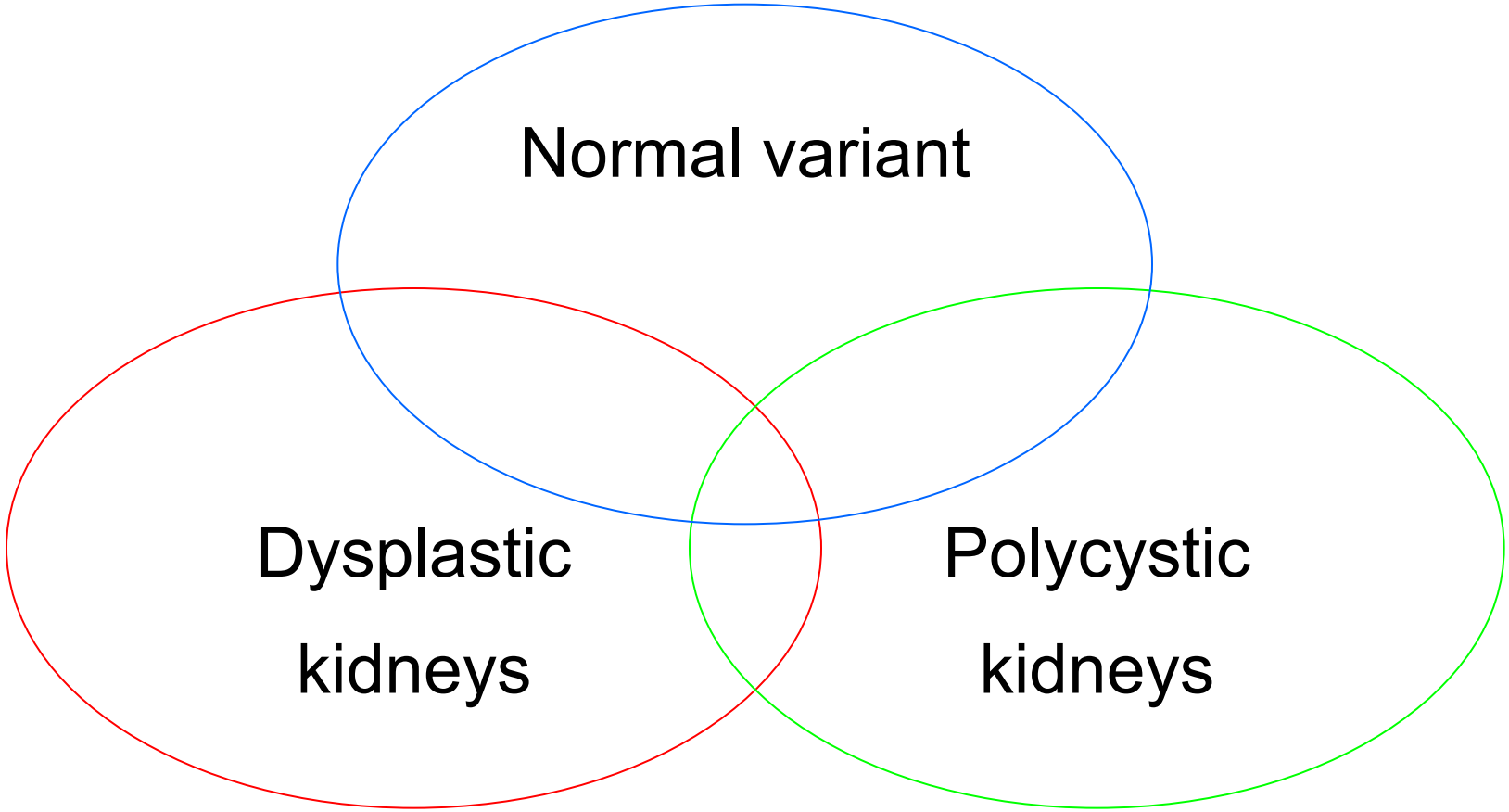


Echogenic kidneys: differential diagnosis

- Aneuploidy
- Normal variant
- Autosomal recessive polycystic kidney disease
- Autosomal dominant polycystic kidney disease
- Renal cysts and diabetes syndrome
- Beckwith Wiedemann syndrome
- Other genetic syndromes

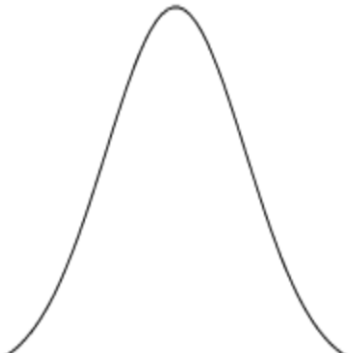


Most likely one of three common things



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:

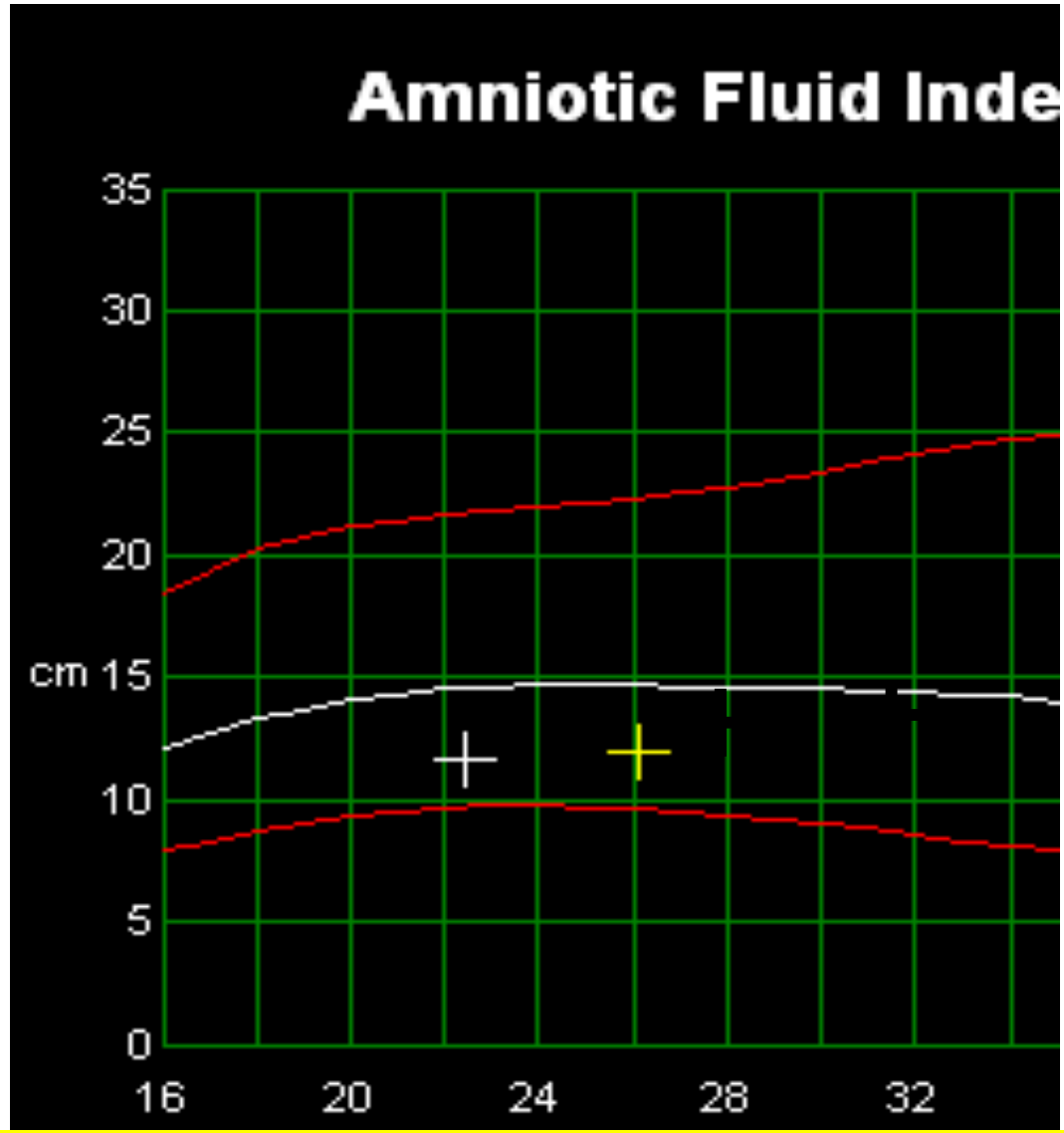
- Severe renal dysplasia/agenesis
- Twin to twin transfusion syndrome

Initial scans

1) Kidney size
   - normal

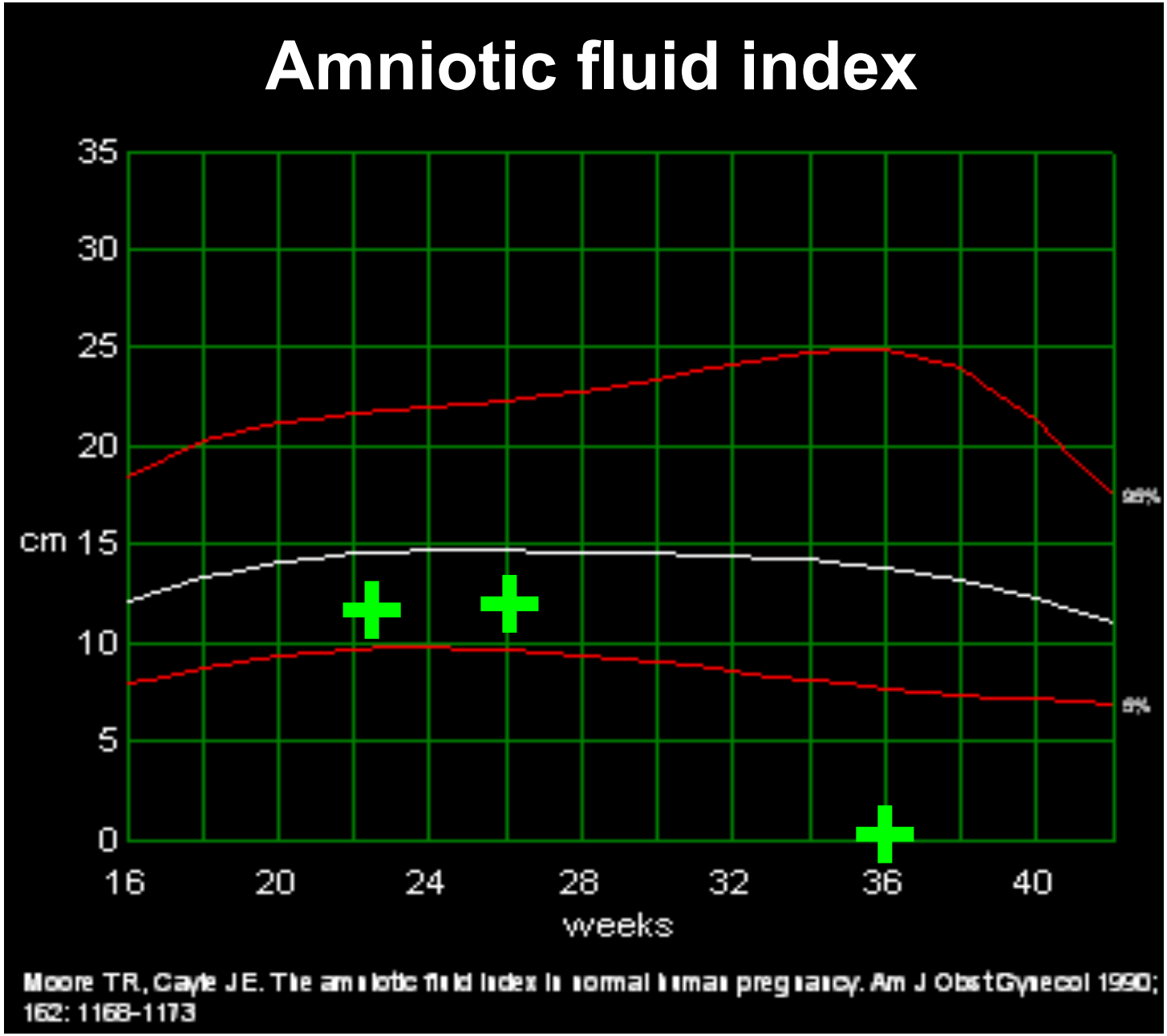
2) Kidney structure
   - normal - bright

3) Amniotic fluid
   - normal



Main care between local and tertiary

Amniotic fluid index



Moore TR, Cayle JE. The amniotic fluid index in normal human pregnancy. Am J ObstGynecol 1990; 162: 1168-1173

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, occ… …ysis

60…

…months

…plant 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 A[1], Aref A[1], Napolitano R[1], Pandya P[1], Winyard PJD[1,2].

[1]Fetal Medicine Unit, University College Hospital London.
[2]Nephrology 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

World Congress

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

- World Congress
  - Organising committee 2018
  - Registration
  - Scientific Program
  - Accommodation
  - Call for Papers

Diagnosis	Number	Isolated echogenic Kidneys	Other renal anomaly	Extra-renal anomaly
Aneuploidy	41	3	1	37
Bladder obstruction	36	14	22	
ARPKD	10	7	3	
ADPKD	12	9	2	1
Bilateral cystic Dysplasia	15	7	6	
Unilateral cystic Dysplasia	22	9	11	2
MCDK	18	7	10	1
Duplex kidneys	8		8	
Proven genetic syndromes	7	1	2	4
Others	18		3	15

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 95th centile
- Bright with loss of corticomedullary differentiation
- Falling amniotic fluid <5th 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)

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Explore this journal >

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

View issue TOC
Volume 53, Issue 4
April 1998
Pages 303–307

1 Department of Clinical Genetics, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF, UK. Fax: + 44 0171 8302834.

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 …. ?

Syndrome	Gene defects
Bardet–Biedl syndrome	Multiple genes/loci implicated, several associated with centrosomes/c
Beckwith–Wiedemann syndrome	*p57KIP2* mutation in a minority of patients, cell cycle gene
Branchio-oto-renal syndrome	*EYA1* mutation, transcription factor-like protein
Campomelic dysplasia	*SOX9* mutation, transcription factor
Carnitine palmitoyltransferase II deficiency	Gene for this enzyme is mutated
CHARGE association	Genetic basis unknown
Di George syndrome	Microdeletion at 22q11, probably several genes involved
Fanconi anaemia	Six mutant genes reported, DNA repair pathways
Fraser syndrome	*FRAS1* and *FREM* mutations, cell adhesion molecules
Glutaric aciduria type II	Glutaryl-CoA dehydrogenase mutation
Hypoparathyroidism, sensorineural deafness and renal anomalies (HDR) syndrome	*GATA3* mutation, transcription factor
Kallmann's syndrome	X-linked form: *KAL1* mutation, cell adhesion molecule
Meckel–Gruber syndrome	Three loci mapped with two major genes, *MKS1* (17q23) and *MKS3* (
Nail-patella syndrome	*LMX1B* mutation, transcription factor
Renal adysplasia	Some cases have de novo heterozygous mutations in *uroplakin IIIa*
Renal-coloboma syndrome	*PAX2* mutation, transcription factor
Renal cysts and diabetes syndrome	*TCF2*/HNF1β mutation, transcription factor
Simpson–Golabi–Behmel syndrome	*GPC3* mutation, proteoglycan
Situs inversus and nephronophthisis type 2	*Inversin* mutations, primary cilia and plane of cell polarity
Smith–Lemli–Opitz syndrome	Dehydrocholesterol reductase mutation, cholesterol biosynthesis
Townes–Brockes syndrome	*SALL1* mutation, transcription factor
Urofacial (Ochoa) syndrome	Locus on 10q, gene undefined
Urogenital adysplasia syndrome	Some cases have HNF1β mutation
VACTERL association	Basis unknown, apart from one report of a mitochondrial gene mutatic
Zellweger syndrome	Peroxisomal protein mutation

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.
J Am Soc Nephrol (2007) 18:923–933

****

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

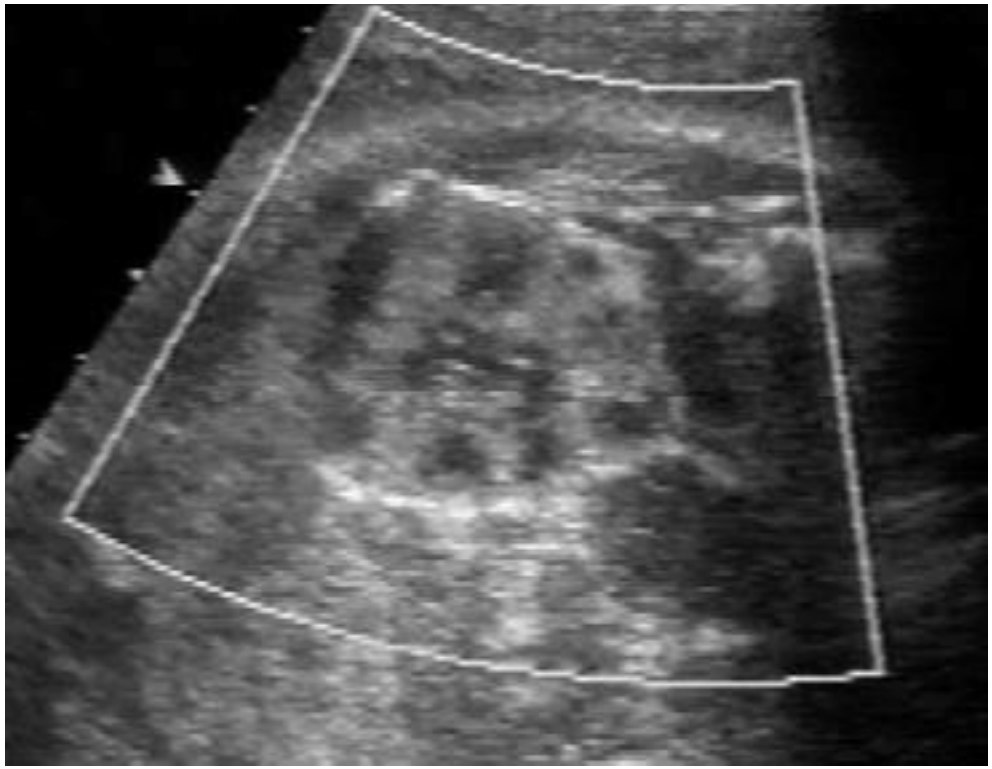
Referred after local 20 week scan

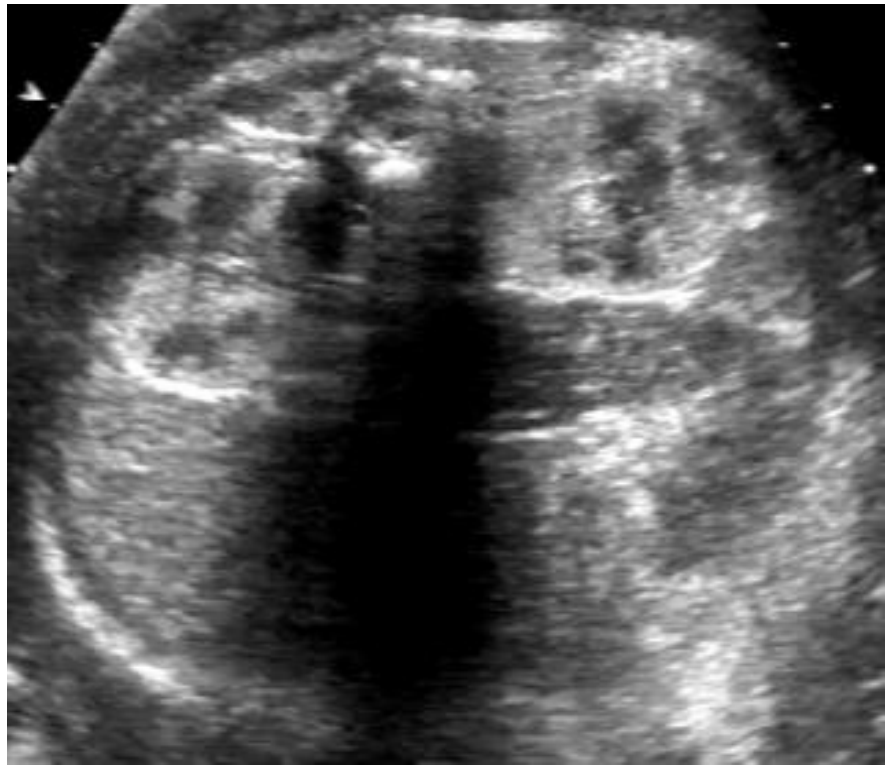
- normal scan at 12 weeks
- bright kidneys at 20 weeks
- ‘perhaps’ low amniotic fluid volume

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 n[illegible] range

Postnatal:
• 3 months – k[illegible]arge and bright but no cysts
• 12 months – [illegible]ormal size, but 2 cysts in L, 1 R
• 3 years – big kidneys again, multiple small cysts, maximum 1.5 cm

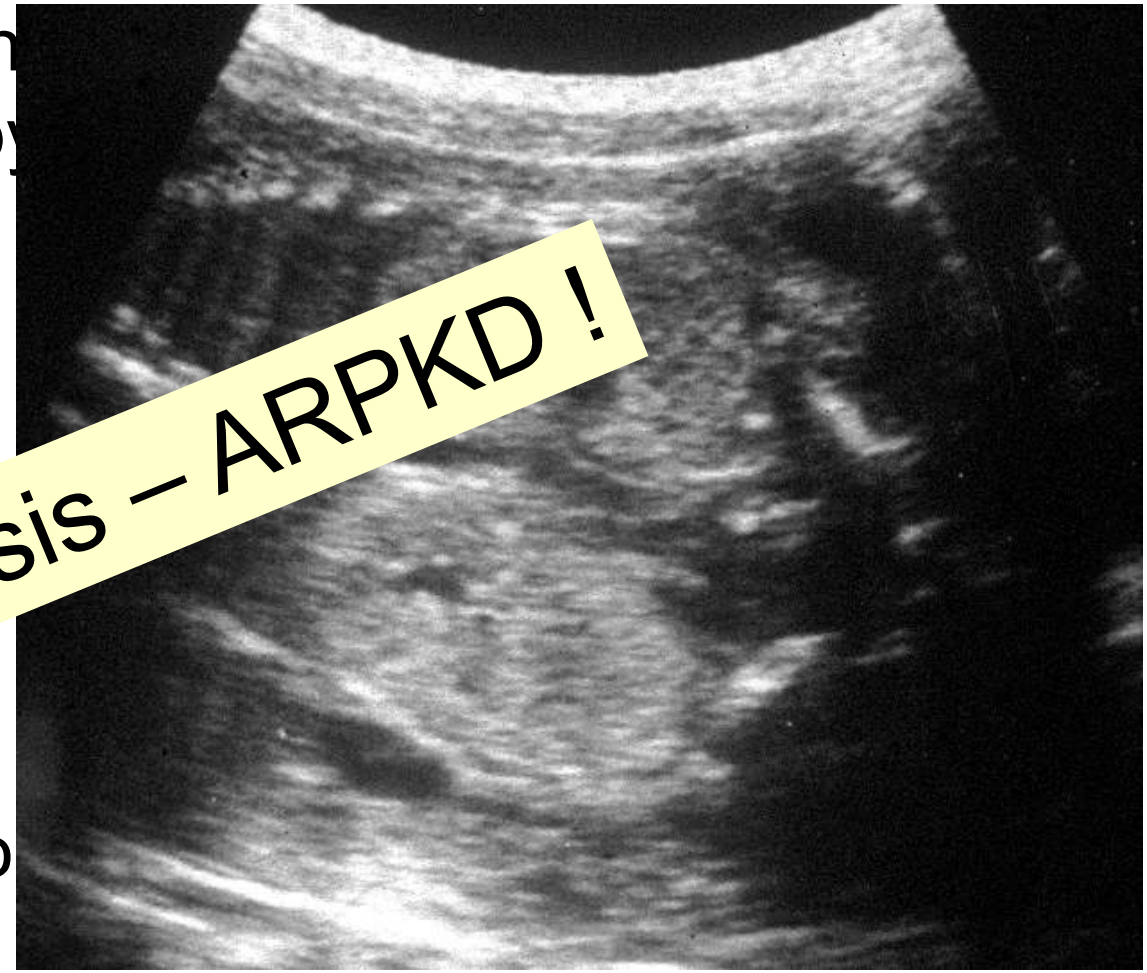
Diagnosis – ADPKD !

Case 4

Referred in third pregnan
• massive kidneys occup
• oligohydramnios

Past history:
Terminations at 24 we
similar history

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



Clinical Review & Education

JAMA Pediatrics | Special Communication

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

JAMA Pediatr. 2018;172(1):74-86. doi:10.1001/jamapediatrics.2017.3938
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

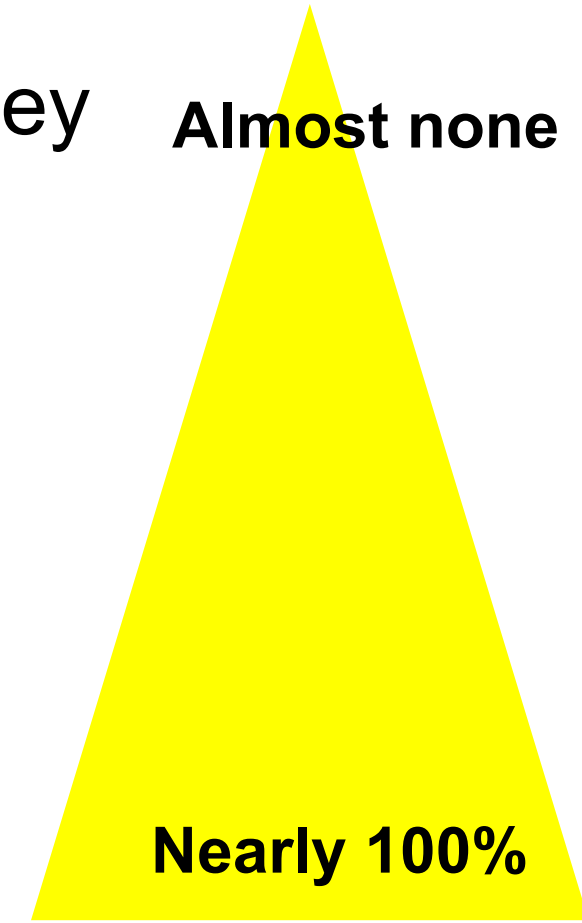
	General population	Antenatal presentation	Antenatal clinic frequency
ADPKD	1 in 1,000	1%	1 in 100,0000
ARPKD	1 in 20,000	75%	1 in 25,000
Dysplastic kidneys	1 in 1,000 to 1 in 5,000	90%	1 in 2,000

Key factors on antenatal renal scan

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

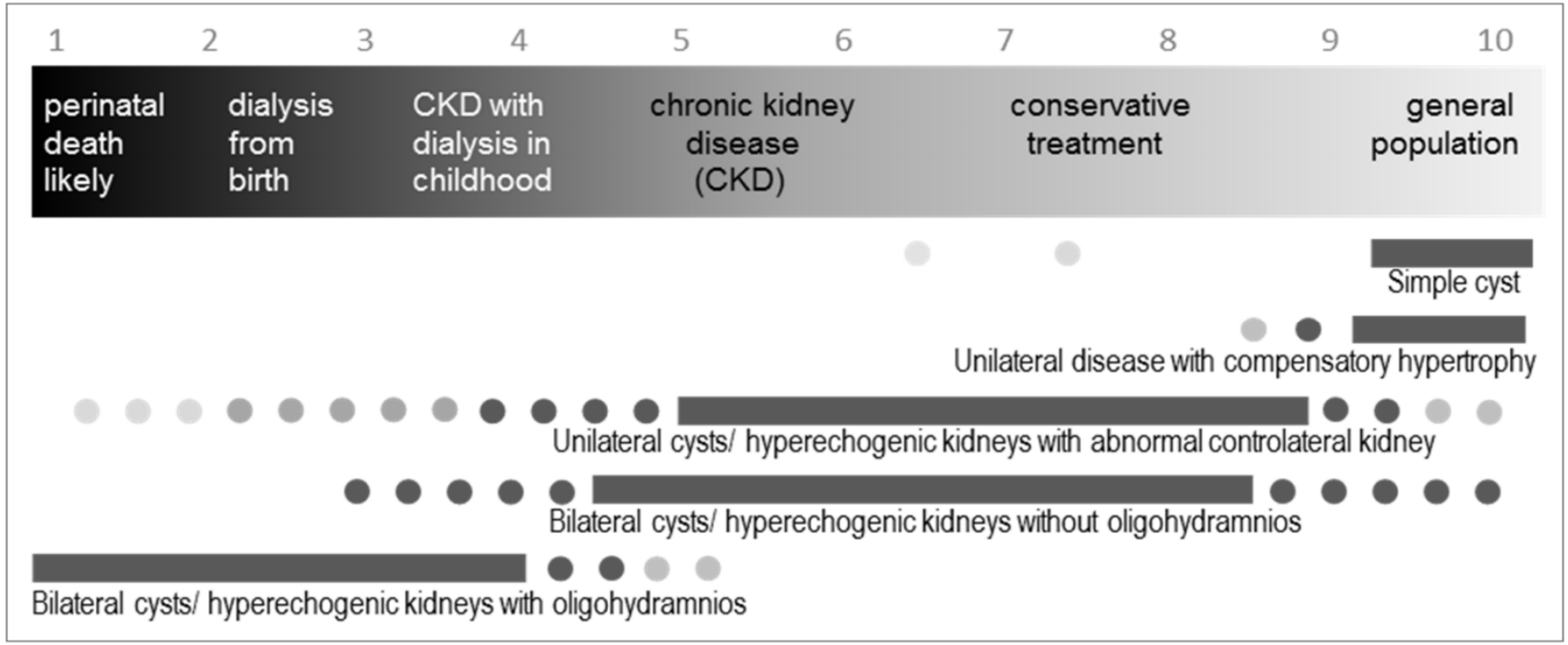
How much normal tissue is there?

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



Gimpel C, Avni FE, Bergmann C, Cetiner M, Habbig S, Haffner D, König J, KonradM, Liebau MC, Pape L, Rellensmann G, Titieni A, von Kaisenberg C, Weber S, Winyard PJD, Schaefer F.
Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases: A Clinical Practice Recommendation With Systematic Literature Reviews.
JAMA Pediatr. 2017 Nov 27. doi: 10.1001/jamapediatrics.2017.3938. PubMed PMID: 29181500.

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



CKD: chronic kidney disease

courtesy of P. Winyard, graphics C. Gimpel

Early Human Development xxx (xxxx) xxx–xxx

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Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Management of antenatally detected kidney malformations

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ARTICLE INFO

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LUTO
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Polycystic
Hyperechogenic
Bright
Hydronephrosis
Renal dysplasia

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.

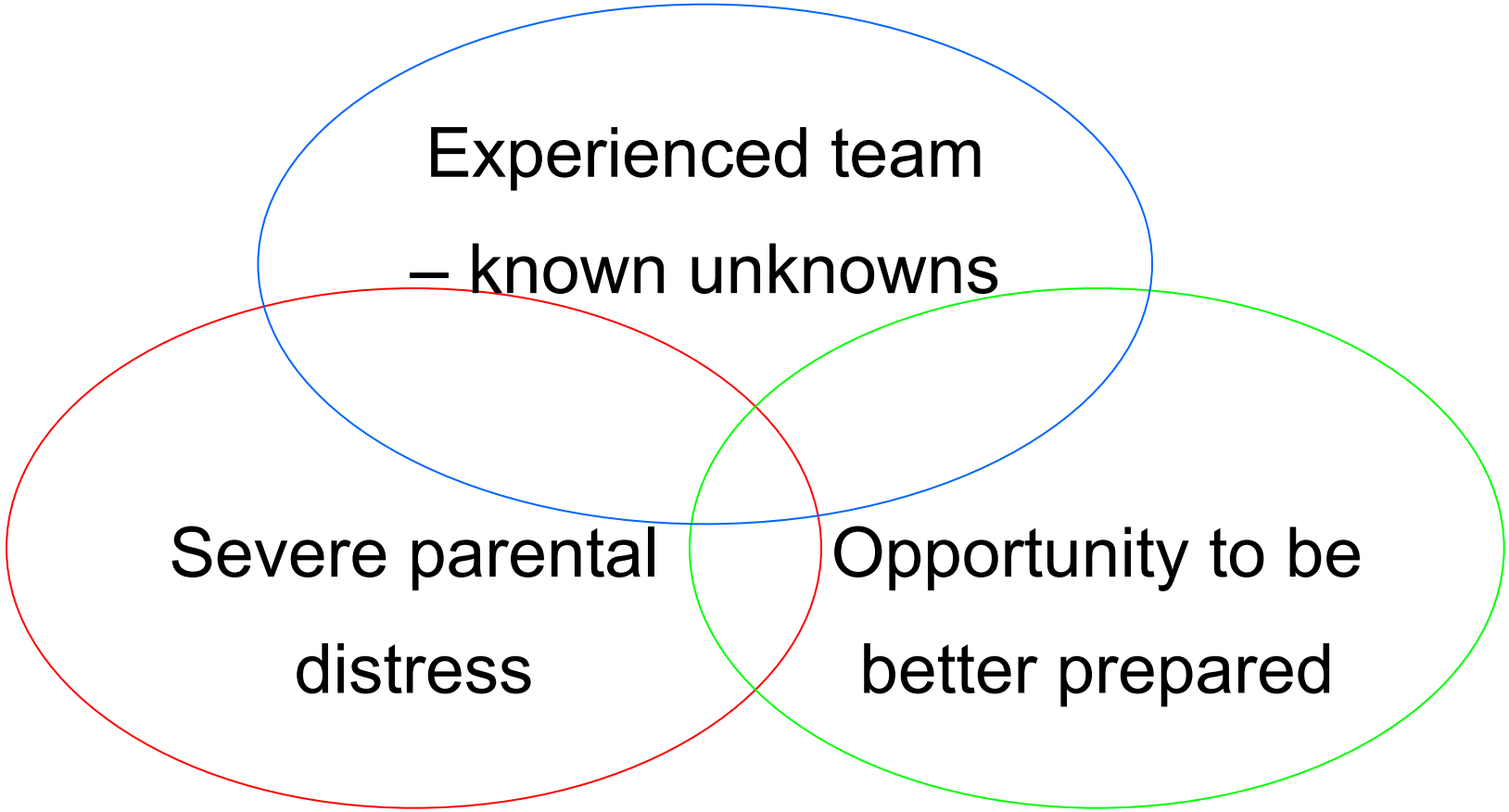
Random Fetal CAKUT case generator

Gestation (weeks)	20	24	28	32	36
Kidney size (centile)	5th	25th	N	75th	95th
Kidney structure	Very bright	Possibly bright	N	One cyst	Many cysts
Amniotic fluid (centile)	5th	25th	N	75th	95th

Conclusions

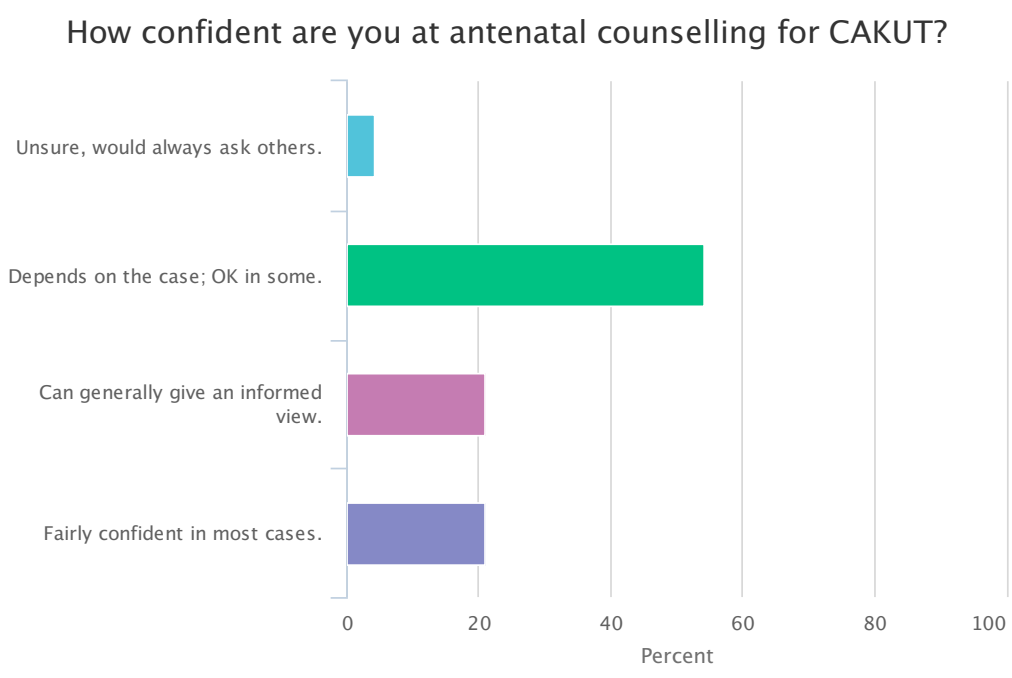
- Echogenic kidneys are common
- Many ‘normal’ kidneys now being picked up
- Normal versus dysplastic versus polycystic
- Size, structure, amniotic fluid
- Pathology and radiology develops over time

The importance of antenatal diagnosis … summary

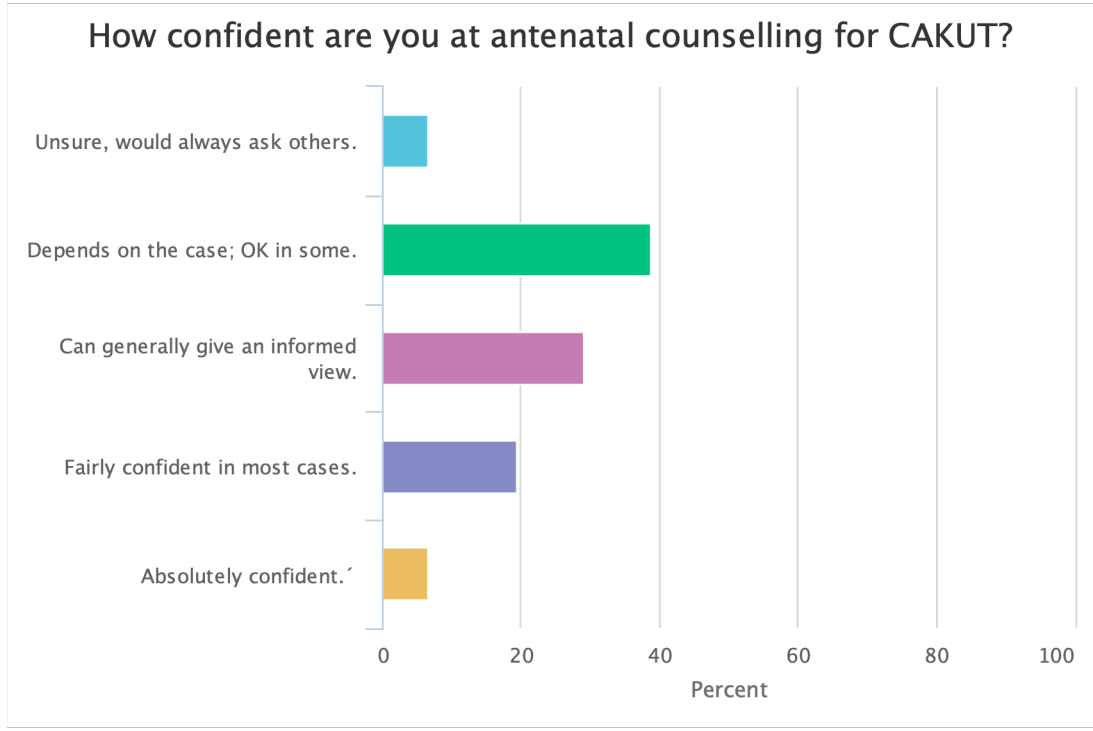


p.winyard@ucl.ac.uk

Question 1
poll evaluation

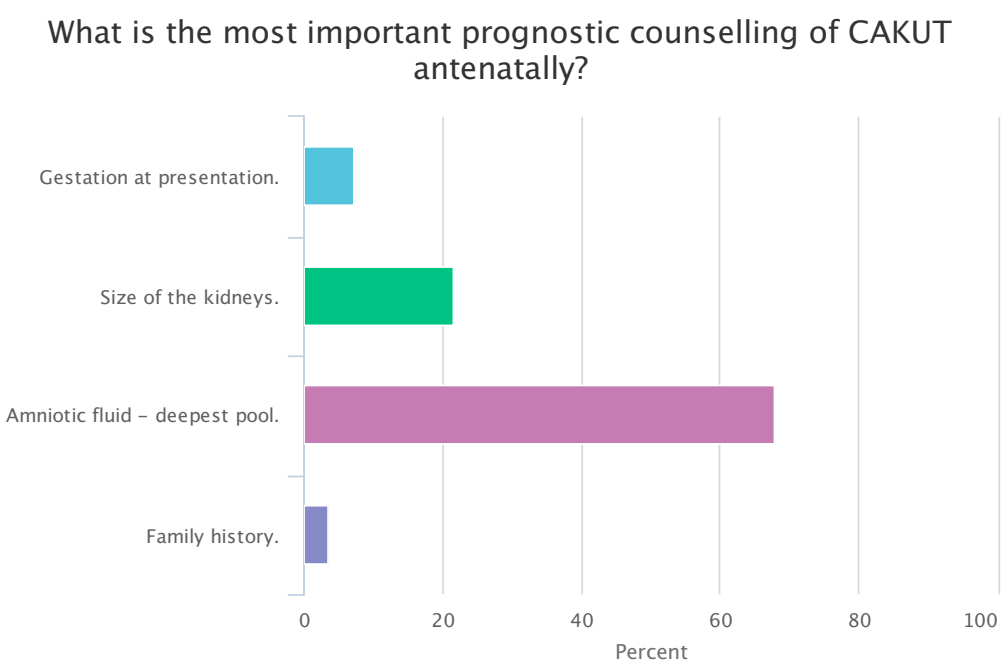


before the presentation

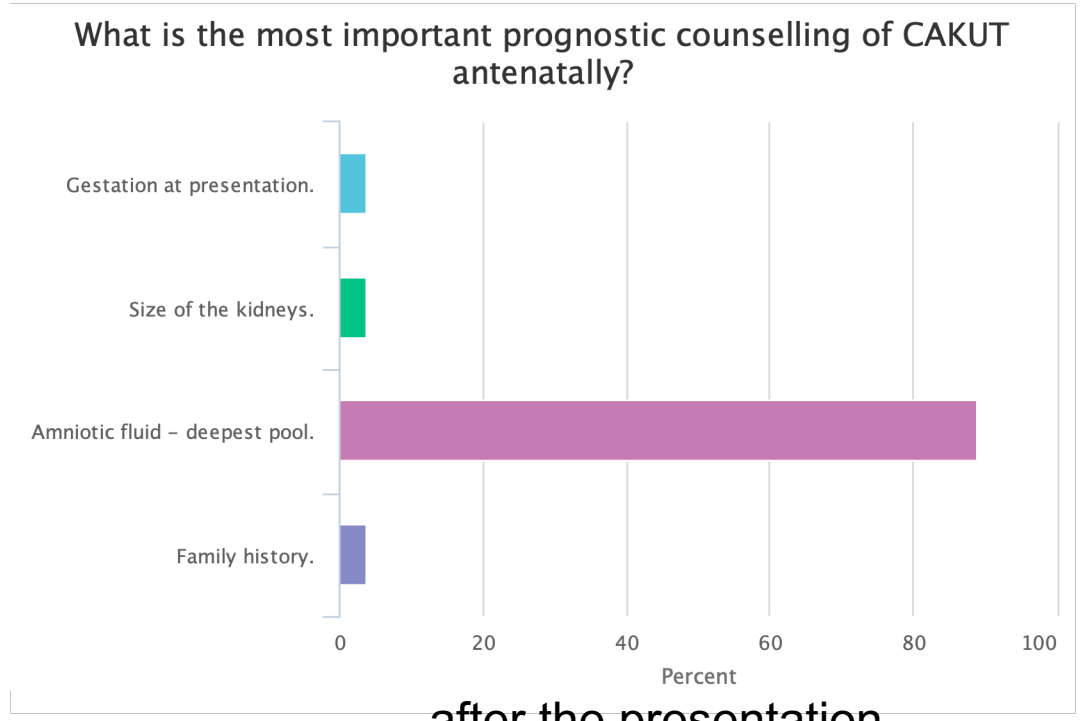


after the presentation

Question 2
poll evaluation



before the presentation



after the presentation

The next webinar

Nov 06, 2018:

Rachel Lennon (Manchester)

& Jaap Groothoff (Amsterdam)

‘Microscopic Haematuria’

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The European
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