

“They told me there’s water in the kidney!”
Follow-up of the abnormal prenatal ultrasound

Patty Seo-Mayer, MD, FAAP

Pediatric Specialists of Virginia / Inova Children’s Hospital / Georgetown MedStar
UVA – Inova Campus / Georgetown School of Medicine



@PattySeoMayerMD



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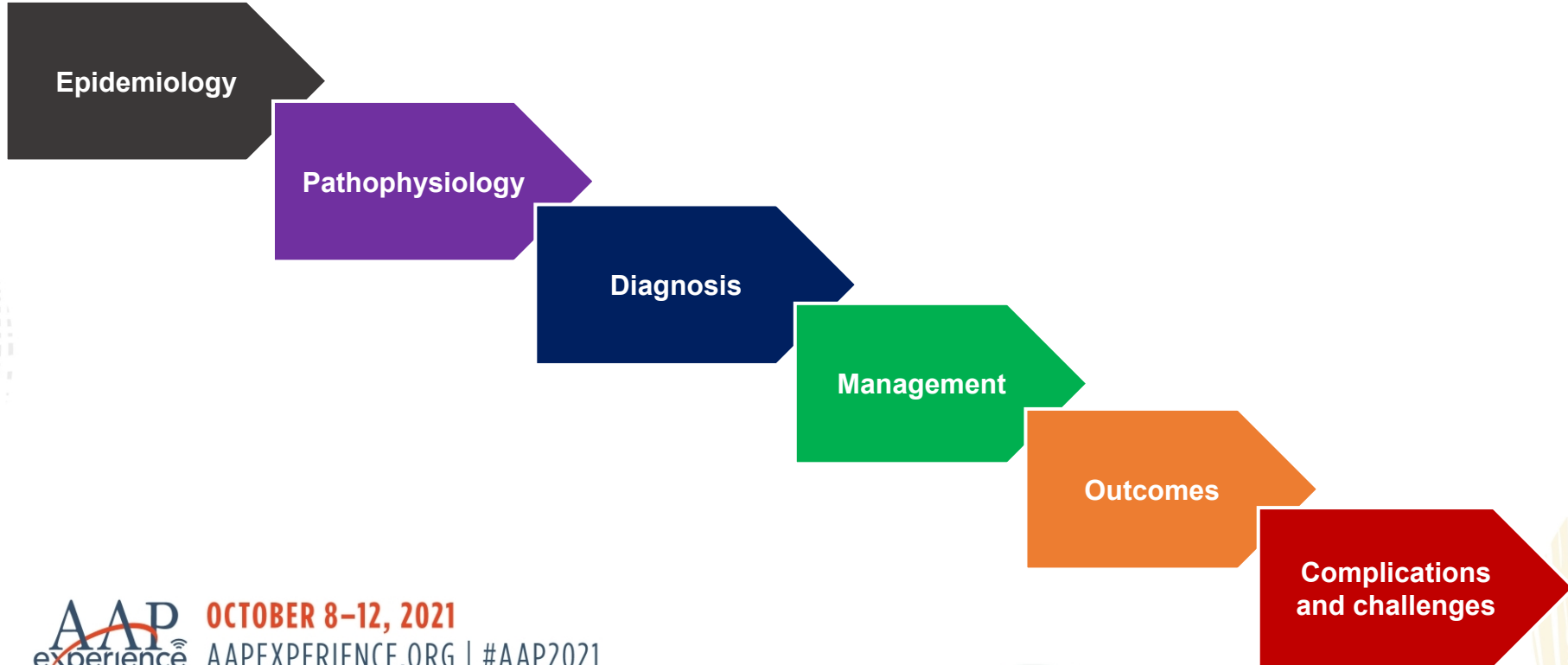
Learning Objectives

- Recognize common anomalies of the kidneys and urinary tract (CAKUT) and the factors that influence renal development
- Understand the imaging utilized to evaluate CAKUT
- Understand the implications of CAKUT and the role of the pediatrician in the long term management of these patients

Learning Objectives

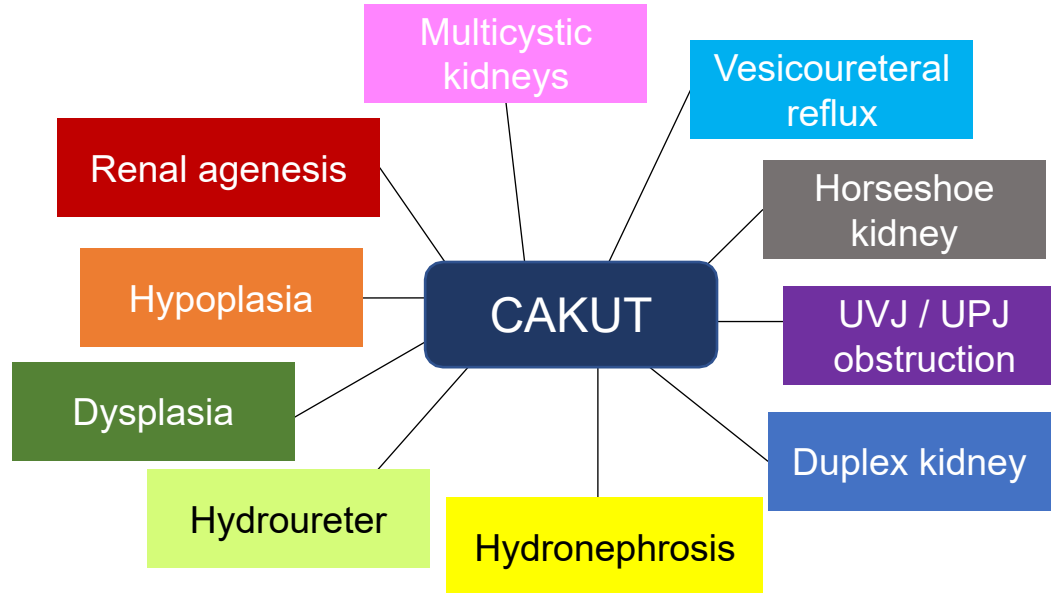
- Discuss renal findings on prenatal ultrasound and how renal imaging can be used to make a diagnosis
- Review practices for follow-up and treatment as well as outcomes

Roadmap



- Detected in ~1:500 (2%) of all fetal ultrasounds
 - Higher % reported in tertiary care systems
- Male > female
- Represent 20-30% of all prenatally diagnosed anomalies
- Account for 30-50% of all cases of pediatric ESRD
 - 60-70% of CKD in children <1 year
- Family history found in 10-15% of affected children

What is “CAKUT”?



Pathophysiology

Hypoplastic
kidney



Duplex kidney



UPJ obstruction



Multicystic
dysplastic kidney



Vesicoureteral reflux



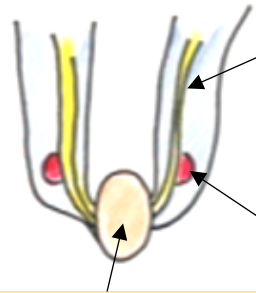
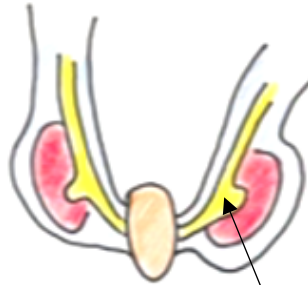
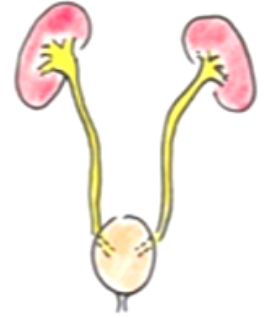
Posterior urethral
valves



Kidney development

First trimester	Second trimester	Third trimester
• Pronephros forms (simple tubules) at 3 weeks • Mesonephros (filtering units) forms at 4 weeks, generating mesonephric (Wolffian) duct • Ureteric bud outpouches and undergoes branching to develop collecting system • Metanephric mesenchyme converts to renal epithelia • Ureteric tree becomes collecting ducts, pelvis, ureters • Glomeruli form at 9-10 weeks	• Number of glomeruli increase • At 16-20 weeks, fetal urine is major contributor of amniotic fluid	• At 32-36 weeks nephron development complete

Kidney development



Mesonephric duct

Metanephric mesenchyme

Urogenital sinus

Ureteric bud

- Pronephros forms (simple tubules) at 3 weeks
- Mesonephros (filtering units) forms at 4 weeks, generating mesonephric (Wolffian) duct
- Ureteric bud outpouches and undergoes branching to develop collecting system
- Metanephric mesenchyme converts to renal epithelia
- Ureteric tree becomes collecting ducts, pelvis, ureters
- Glomeruli form at 9-10 weeks

Kidney agenesis

Kidney hypoplasia

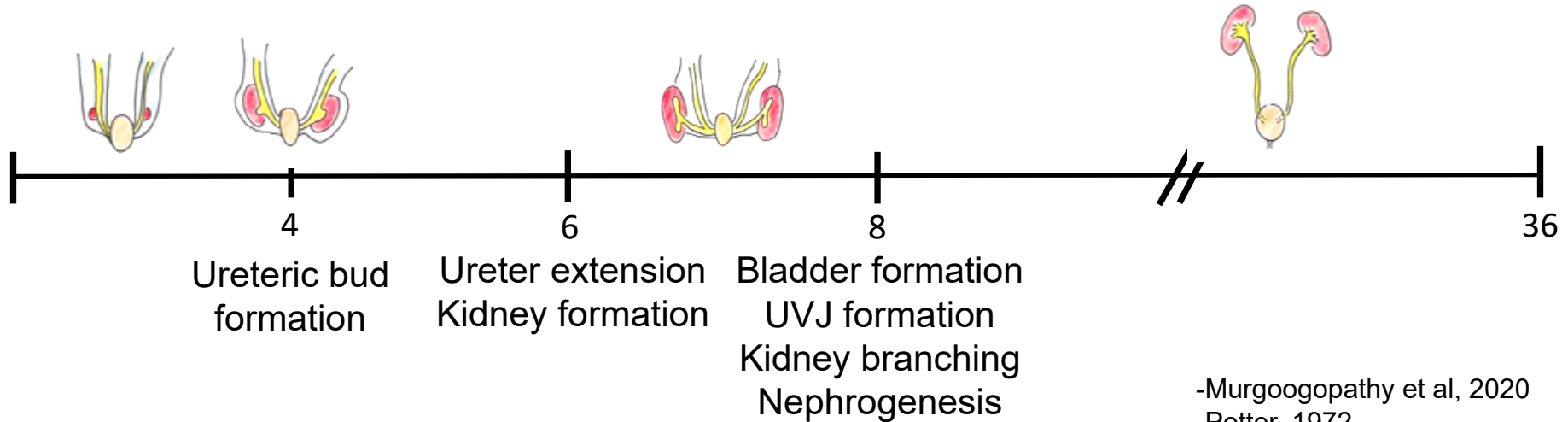
Ectopic kidney / Horseshoe kidney

Vesicoureteral reflux

Diminished nephron number

Kidney dysplasia

PUV



-Murgogopathy et al, 2020
-Potter, 1972
-Vize, 2003

Multiple signaling pathways and genes are involved in kidney development

ALDH1A2
BMP4/BMP7
CD2AP
CITED1
EMX2
EYA1
FAT1/FAT2
FGF2/FGF7
FOXD1
FRAS1
FREM2
FRS2alpha
GDNF
GFRA1
GLI3
GREM1
IRX3
KDR
KIRREL

LHX1
LIF
MET
NOTCH2
NPHP1-NPHP9
NPHS1
NPHS2
PSR1
PAX2/PAXB
PKD1-PKD2
PKHD1
POU3F3
RET
SALL1
SIX2
TFFB2
TP53
VEGFA
WNT4/WNT9B/WNT11
WT1

Environmental risk factors for CAKUT

Factors	Phenotype
Maternal diet Folic acid use Vit A deficiency	Duplex collecting system, VUR, PUV VUR, renal hypoplasia, renal dysplasia
Maternal conditions Obesity Diabetes Malnutrition	Duplex collecting system, VUR Wide range of CAKUT phenotypes Low nephron number, low birth weight
Maternal substance use Cocaine Alcohol ACE-I or ARB	Horseshoe, renal hypoplasia, dysplasia Renal hypoplasia AKI, renal hypoplasia
In vitro fertilization	UPJ, duplex collecting system, PUV, VUR

Genetic syndromes associated with CAKUT

Syndrome	Kidney finding	Extrarenal features
Turner	Agenesis, hypoplasia, horseshoe	Short stature, amenorrhea, webbed neck, cubitus valgus, hypogonadism
Down	Multiple	Intellectual disability, hypotonia, congenital heart disease, clinodactyly
Patau	Agenesis	Holoprosencephaly, midline anomalies, cleft lip/palate
CHARGE	Multiple	Cardiac defects, cleft palate, hearing loss, coloboma, choanal atresia, genital anomalies
DiGeorge	Agenesis, dysplasia, VUR	Optic disc/nerve anomalies, hearing loss, CNS and genital anomalies, skin and ligamentous laxity
Orofaciodigital	Cysts	Lobed tongue, cleft palate, hypodontia, micrognathia, clinodactyly
Branchio-oto-renal	Agenesis, dysplasia	Lat cervical fistulas or cysts, ear pits, hearing loss
Frasier	Agenesis, dysplasia	Cryptophthalmos, syndactyly, tracheal stenosis/atresia, ambiguous genitalia, craniofacial anomalies
Alagille	MCDK, dysplasia, mesangiolipidosis	Chronic cholestasis, cirrhosis, cardiac, butterfly vertebrae, dysmorphic facies
Bardet-Biedl	Dysplasia, calyceal malformations, cysts	Obesity, intellectual disability, retinal dystrophy, polydactyly
Beckwith-Wiedemann	Nephromegaly, nephrocalcinosis, medullary sponge, renal tumors	Macrosomia, hemihyperplasia, macroglossia, omphalocele
Simpson-Golabi-Behmel	Multiple	Craniofacial anomalies, organomegaly, intellectual deficits
Smith-Lemli-Opitz	Hypoplasia	Syndactyly, microcephaly, intellectual disability, heart, lung and GI abnormalities
Rubinstein-Taybi	Multiple	High arched eyebrows, high arched palate, micrognathia, internally deviated toes and thumbs, hirsutism, heart and eye abnormalities

It's complicated...

“Development of the urinary system is a highly complex process that depends on precise spatiotemporally regulated events and requires the integration of a variety of progenitor cell populations of different embryonic origins. These events culminate in precise anatomical connections between the proximal and distal nephrons in the kidney (upper tract) and the upper and lower urinary tract.”

Hypoplastic
kidney



Duplex kidney



UPJ obstruction



Common kidney anomalies

Multicystic
dysplastic kidney



Vesicoureteral reflux

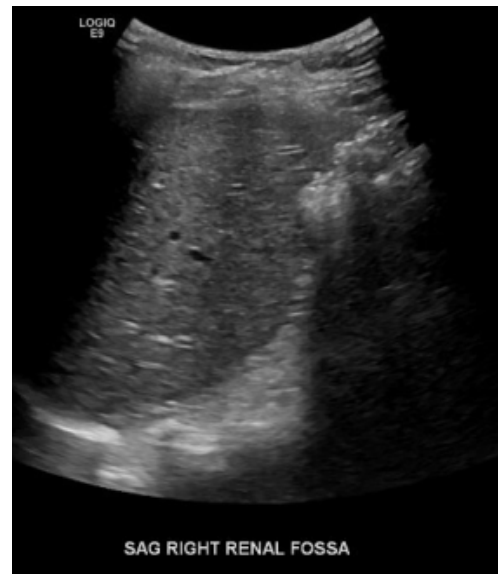


Posterior urethral
valves



Renal agenesis

- 1:3000 unilateral
- 1:7,000-10,000 bilateral
- Male > female
- L > R
- Ureteric bud does not form
- Abnormal signaling proteins allowing differentiation of metanephric blastema



Ectopic (pelvic) kidney

- Failure to ascent during week 6-8
- High risk of ureteral obstruction and stones
- May be associated with GU anomalies:
 - Vaginal atresia
 - Imperforate hymen
 - Hypoplastic uteri
 - Rudimentary fallopian tube/ovary



“United kidneys at birth” (horseshoe kidney, cross fused renal ectopia)

- 1:500
- Male 2:1
- 70% are left-dominant
- Mostly benign, but are associated with urological sequelae including stones
- Susceptibility to midline trauma and vascular anomalies
- Higher frequency of rare renal cancers



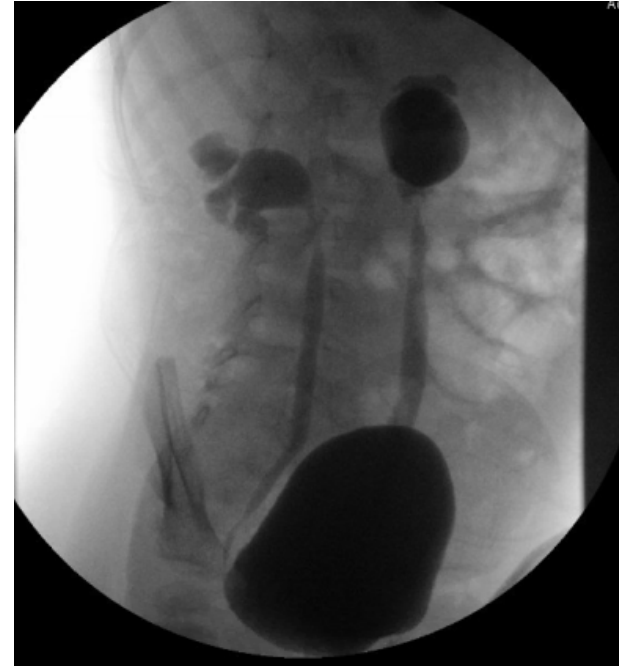
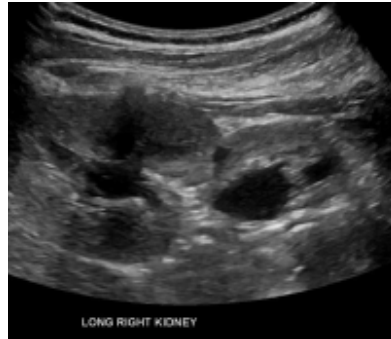
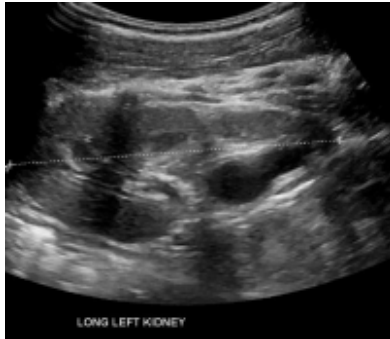
MCDK

- 1:2000-4000 live births
- Males > females
- L > R
- Multiple cysts of various sizes
- Usually non-functional w/ atretic ureter
- 60% involute by age 10 years



“I have four kidneys”: Duplex kidney

- 1:100
- More susceptible to reflux and obstruction



“Water in the kidney”

Hydronephrosis/pylectasis/pelviectasis

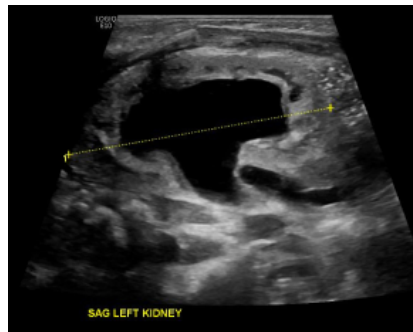
Normal



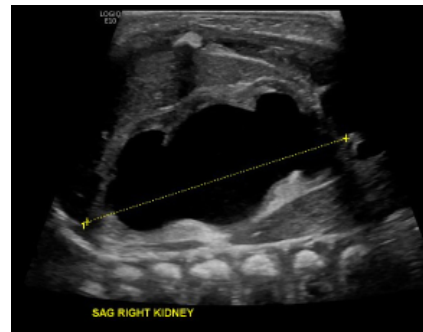
Mild



Moderate



Severe



3 possible causes:

1. VUR
2. Obstruction (UVJ, UPJ, PUV)
3. Non-refluxing, non-obstructed dilation (megaureter or physiologic)

50-75% transient or physiologic

Grading is key

Hydronephrosis grading systems

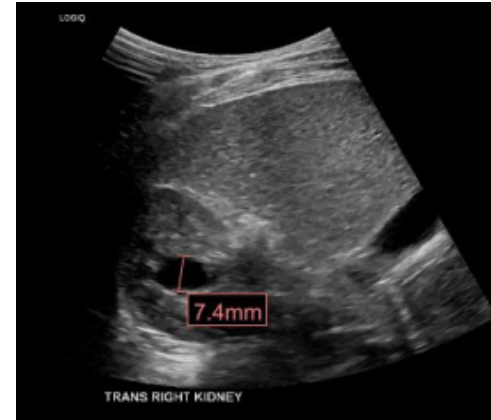
System	Publication	Stakeholders
AP diameter		Utilized widely by OB/gyn and fetal medicine teams
Urinary Tract Dilation (UTD)	Nguyen et al, Journal of Pediatric Urology, 2014	American College of Radiology American Institute of Ultrasound in Medicine American Society of Pediatric Nephrology The Society for Fetal Urology The Society for Maternal-Fetal Medicine The Society for Pediatric Urology The Society for Pediatric Radiology The Society of Radiologists in Ultrasounds
Society of Fetal Urology (SFU)	Fernbach SK, Maizels M, Conway JJ. Pediatric Radiology, 1993	
Onen	Onen A. Journal of Pediatric Urology, 2007	

Hydronephrosis grading systems

- Factors:

- Anterior-posterior renal pelvic diameter (APRPD):
 - Dependent on position, hydration, phase of voiding, respiration
- Calyceal dilation
- Renal parenchymal thickness
- Renal parenchymal appearance
- Bladder abnormalities
- Ureteral abnormalities
- Based on gestational age and whether the UT dilation is detected prenatally or postnatally

AP diameter





Classification for antenatal hydronephrosis and risk of postnatal uropathy

Grade	APD		Risk of uropathy (95% CI)
	2 nd trimester	3 rd trimester	
Mild	4 to <7 mm	7 to <9 mm	11.9 (4.5 – 28)
Moderate	7 to 10 mm	9 to 15 mm	45.1 (25.3 – 66.6)
Severe	>10 mm	>15 mm	88.3 (53.7 – 98)

Prenatal imaging

- **Equity of maternal care**
 - Race-based
 - Severe maternal morbidity is 2.1x higher in Black women and 1.4x higher in Hispanic women compared to White women, regardless of insurance type
 - PA Medicaid: White and Asian women more likely to receive prenatal and postnatal care
 - Black and Latinx women report 2x more barriers to prenatal care than White women
 - Rural – urban inequality

Postnatal ultrasound?



- Non-invasive
- No sedation
- Cost: \$400-500
- ***Timing matters***
 - DOL 1-2: low UOP, physiologically vol depleted
 - Can underestimate dilation
 - If unilateral and low risk: wait until feeding/voiding established (1-2 weeks)



Postnatal ultrasound?

- **Urgent** if high risk for significant kidney anomaly or there are concerns for follow-up
 - Oligohydramnios:
 - <500 mL of amniotic fluid
 - AFI <5-6
 - Suspected CAKUT and no void > 24 hours
 - Severe (>10mm 2nd trimester, >15mm 3rd trimester) hydro, especially if bilateral
 - Concern for PUV in a male:
 - Bilateral moderate to severe hydronephrosis
 - Unilateral moderate to severe hydroureteronephrosis
 - Distended bladder
 - Dilated posterior urethra

Postnatal counseling

- More severe dilation -> greater the likelihood of a condition requiring surgical intervention, either UPJ obstruction or VUR
- Antibiotic prophylaxis and voiding cystourethrogram (VCUG) indicated for infants with persistent moderate or severe hydronephrosis after birth
- Severity of dilation **does not correlate** well with severity of VUR; those with resolved hydronephrosis may have VUR
- Consensus guidelines for fetal hydronephrosis recommend **discussion with families about risk and benefits of antibiotics and the VCUG in these cases**

Hydration matters

DOL1



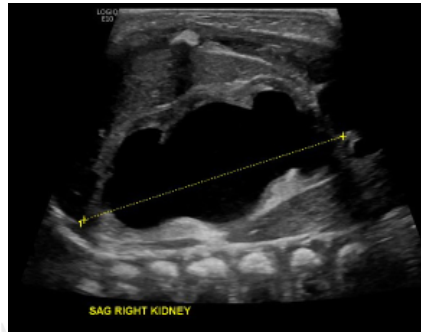
DOL40



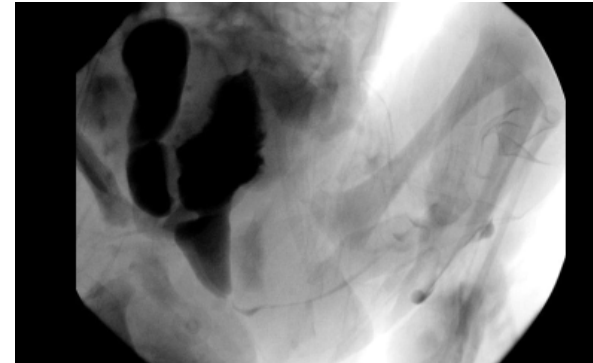
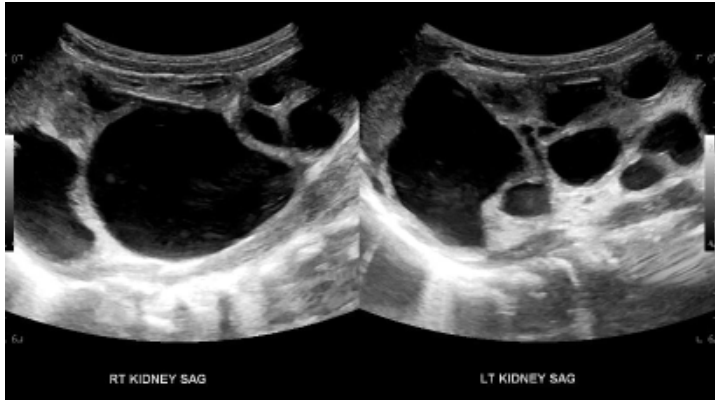
Repeating US at DOL 7-14 may be indicated

“Water in the kidney”

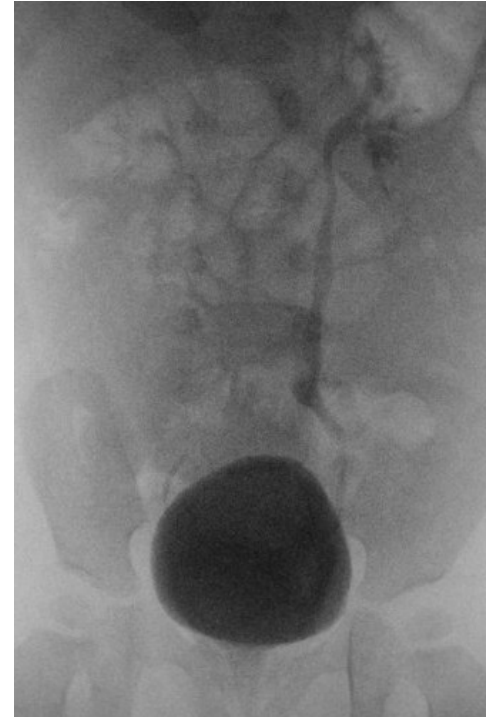
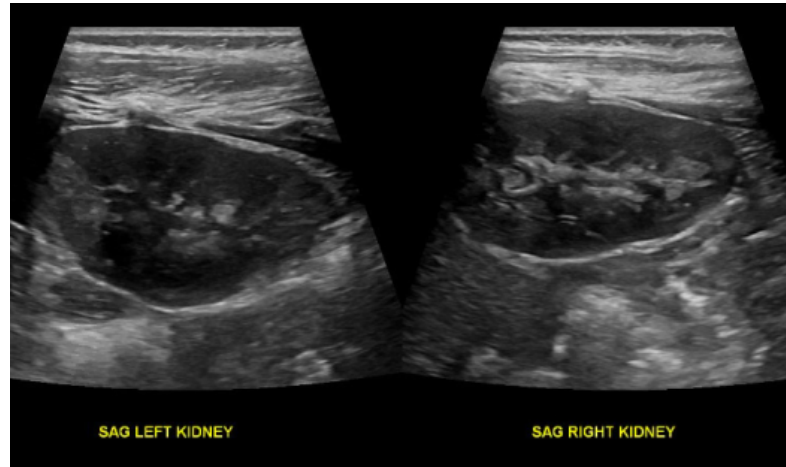
Hydronephrosis/pylectasis/pelviectasis



Posterior urethral valves



Vesicoureteral reflux



Postnatal ultrasound ASAP?

YES if high risk



- Oligohydramnios with any suspected CAKUT
- Suspected CAKUT and no void > 24 hours
- Severe (>10mm 2nd trimester, >15mm 3rd trimester) hydronephrosis, especially if bilateral
- Concern for PUV in a male:
 - Bilateral moderate to severe hydronephrosis OR
 - Unilateral moderate to severe hydroureteronephrosis OR Distended bladder OR
 - Dilated posterior urethra



Urgency of referral

EMERGENT (urology +/- nephrology)

- Evidence of PUV
- Moderate to severe CAKUT in a solitary kidney
- Ureterocele or urethral atresia
- Abnormal abdominal wall musculature consistent with Prune Belly Syndrome
- Other GU anomalies (imperforate anus, ambiguous genitalia, bladder exstrophy, cloacal exstrophy, spinal cord abnormality)

Check renal function, US and BP



Urgency of referral

URGENT (2-10 days)

- Mild prenatal hydronephrosis in solitary kidney
- Moderate to severe unilateral prenatal hydronephrosis

ROUTINE (within 4 weeks)

- Unilateral ectopic kidney
- Cystic kidney(s) with normal function
- Solitary kidney without hydronephrosis



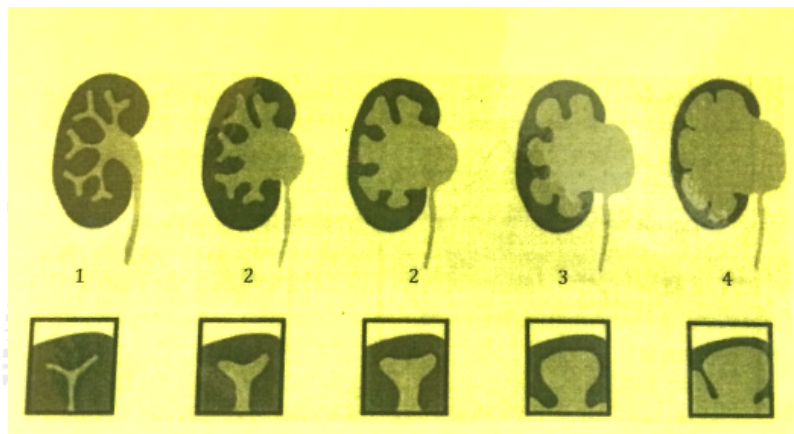
Uncomplicated unilateral hydronephrosis:

- Repeat renal / bladder ultrasound 7-14 days after birth
- Counsel on UTI prevention, symptoms, testing, antibiotics
- Follow US every 6 months for 2 years, then annually until 6 years old
- Refer to Urology AND Nephrology if:
 - Increasing hydronephrosis (moderate or severe)
 - Urinary tract infection
 - Flank pain
 - Gross hematuria
 - Poor growth, HTN or any other concerns

When to pursue imaging?

Grade	Renal pelvis	Renal cortex
0	No splitting	Normal
1	Urine in pelvis barely splits sinus	Normal
2	Urine fills intrarenal pelvis	Normal
2+	Urine fills extrarenal pelvis, major calyces dilated	Normal
3	SFU grade 2 and minor calyces dilated and parenchyma preserved	Normal
4	SFU grade 3 and parenchyma thin	Diminished

VCUG and/or MAG3



Standard Diagnostic Algorithm for Congenital Hydronephrosis

Grade	Study	Initial Visit	6 mos	12 mos	18 mos	24 mos	36 mos
1							
	US	X					
	VCUG	Optional*					
2							
	US	X	X	Optional	Optional		
	VCUG	X					
3							
	US	X	X	X	X	X	X
	VCUG	X					
4							
	Mag-3	X	X	Possible*	Possible	Possible	Possible
4							
	US	X	X	X	X	X	X
	VCUG	X					
4							
	Mag-3	X	X	X	Possible	Possible	Possible

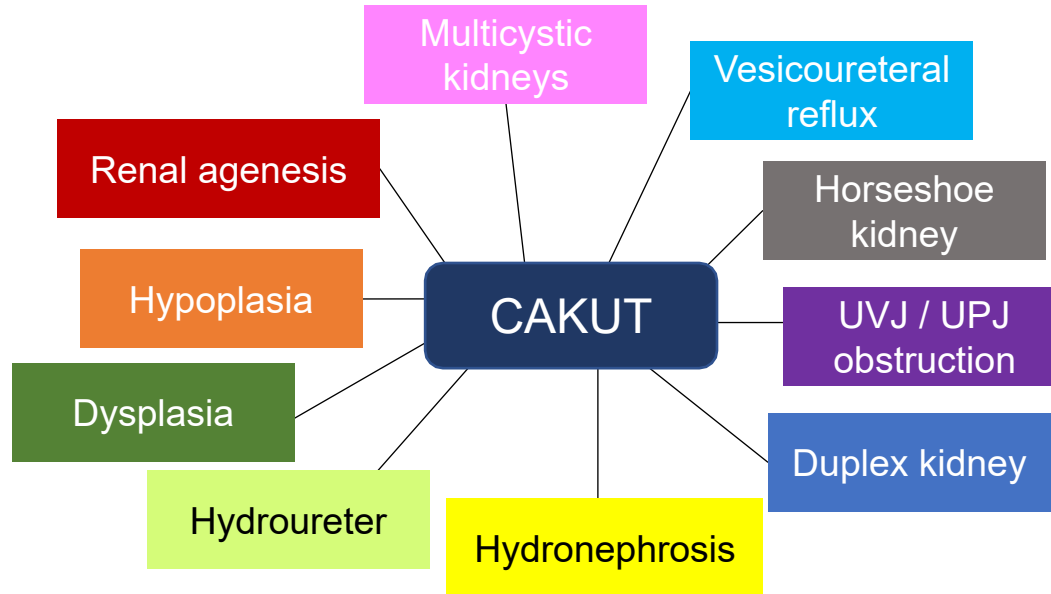
For patients with reduced DRF <35-40 % and obstructive drainage curve, recommend pyeloplasty.

For patients with good DRF ≥40% DRF and either a flat ($T-1/2 \geq 100$ minutes) or rising curve, recommend 1 follow-up scan in 6 months.

*Optional: It is up to the treating physician's discretion whether this test is needed.

*Possible: Evaluate sonogram first and obtain MAG-3 lasix only if hydronephrosis is grade 3 or grade 4.

CAKUT



Case: Baby L

Labor & Delivery Data:

Maternal Antibiotics in Labor: None

Delivery type: Cesarean

Time of ROM: 6/29/2020 4:14 PM

Time of Delivery: 6/29/2020 9:37 PM

ROM duration: 5h 23m

APGARS: 9 at 1 minute, 9 at 5 minutes

Resuscitation: Tactile Stimulation,

Maternal Temperatures: Temp (72hr):
Avg:98.3 °F (36.8 °C), Min:97.8 °F (36.0 °C), Max:98.6 °F (37 °C)

Presentation: Vertex

Fluid color: Clear

Cord: 3 vessels

Cord complications: None

Anesthesia: Epidural

Case: Baby L

Pediatrician: “Anything concerning on your prenatal ultrasound?”

Mom: “They said there was water in the kidneys!”

Maternal problem list: “Abnormal prenatal ultrasound”

 ☒ Prenatal pelviectasis - Monitor UOP. Per prenatal ultrasound 5/2020 - "KNOWN BILATERAL HYDRONEPHROSIS AND HYDROURETERS ARE VISUALIZED. LT RENAL PELVIS AP DIAMETER MEASURES 1.5 CM; RT RENAL PELVIS DIAMETER MEASURES 1.4 CM"

Renal ultrasound

Radiology:

Us Renal Kidney Bladder Complete

Result Date: DOL 1

1. Severe right greater than left hydronephrosis with debris. Question left-sided cysts versus dilated calyces as well. 2. Bilateral cortical thinning, also right greater than left. 3. Posterior bladder wall thickening. Recommend VCUG for further evaluation. Please also note that the degree of renal dilatation may still be underestimated if the patient is dehydrated and less than birth weight.

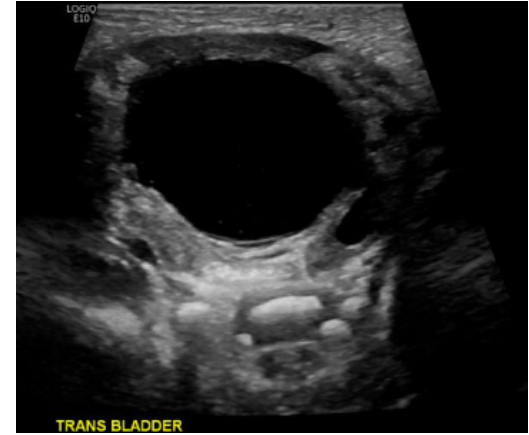
Management

- Severity? (>15 mm APD)
- Bilateral versus unilateral?
- Gestational age?
- Urologic lower tract or upper tract?
- Isolated or syndrome-related?
- If prenatally detected: risk assessment of fetal outcome?

Management

- Obtain RBUS

“Water in the kidney”/hydronephrosis



- Counseled parents
- Prophylactic antibiotics
- VCUG -> PUV
- Consulted urology and nephrology



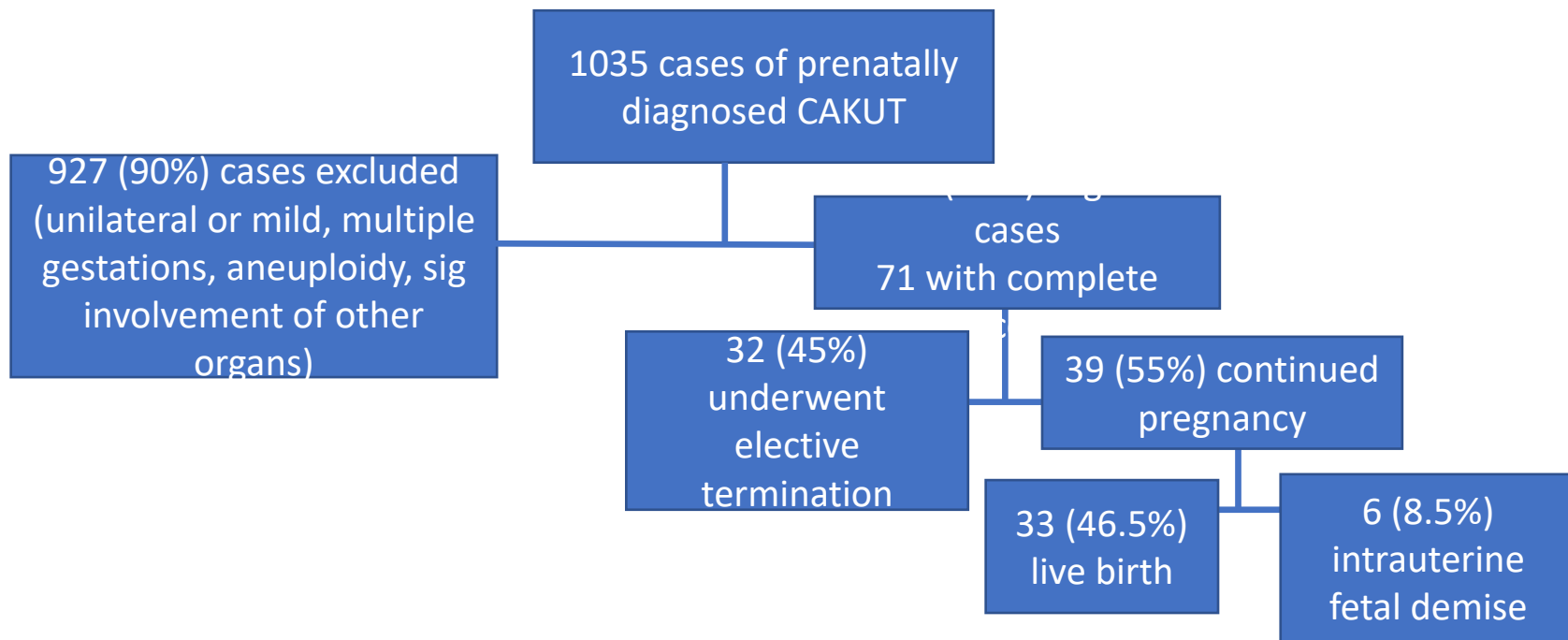
Management

- Begins with prenatal counseling
 - Maternal fetal medicine multidisciplinary team
- Thorough physical exam
- Renal ultrasound postnatally
 - If high risk -> in neonatal period
 - If low risk -> after feeding established
- Consider renal function panel, BP measurement
- Consider genetics

How should we counsel families?

- “Severe” defined as:
 - Bilateral
 - Documented concern for significant renal insufficiency
- Danziger et al: Severe congenital anomalies of the kidney and urinary tract: epidemiology can inform ethical decision-making. *J Perinatology* 2016
- Retrospective cohort study to “improve perinatal counseling and decision-making for families facing such diagnoses”

Study patients and outcomes



Predictors of poor postnatal renal function

- Oligohydramnios
- Renal cortical appearance
- Gestational age <24 weeks

Predictors of survival

- Survivors had better Apgar scores and presence of spontaneous respirations at birth ($p=0.02$)
- Survivors tended to be older and bigger (NS)
- Cause of death in non-survivors predominantly respiratory failure

Outcomes

Outlook

“If your child has kidney dysplasia in one kidney, their outlook is typically good. The child may have a few health problems, such as increased risk of UTIs, but will mostly likely live a normal life.

“If your child has kidney dysplasia in both kidneys, they may need dialysis and a kidney transplant as well as close monitoring.”

CAKUT patient follow-up

- More UTIs
- Require more antibiotics
- Had more surgeries
- More subspecialty follow-up
- More imaging
- Often needed more educational support (29 vs 11%) but did not require more neurodevelopmental follow-up
- Risk of progression to ESKD
 - Anemia, growth delay, metabolic bone disease, acidosis, hypertension

Changes you may wish to make in practice

1. Advocate for accurate communication of prenatal imaging and maternal risk factors
2. Consider timing of first antenatal imaging based upon risk factors
3. Communicate with your local pediatric nephrologist or urologist

In a perfect world...



- Comprehensive, accurate, succinct integrated EMR for mother-fetus-baby
- Thorough and accurate prenatal counseling given and absorbed
- Optimal and timely imaging available for newborn
- Perfect flow of accurate information from nursery to pediatrician's office
- Easy access to nephrology/urology if there is a problem

Resources for parents



- Healthychildren.org website
- Partnership between AAP, National Kidney Foundation and American Society of Pediatric Nephrology
- Relevant topics:
 - Posterior urethral valves
 - Children with a single kidney
 - Chronic kidney disease in children
 - Detecting urinary tract infections
 - Genitourinary reconstruction
 - Kidney cysts in infants and children



Summary

- CAKUT represent a common and heterogeneous spectrum of disease
- CAKUT is responsible for a sig proportion of ESRD in children
- Antenatal testing is important in counseling patients but is not perfect in predicting renal outcome
- Pulmonary outcomes at birth remain the most important predictor of survival
- Low risk: Antenatal ultrasound at 7-14 days of life
- High risk: Antenatal ultrasound before discharge +/- antibiotics, consult

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