CAKUT

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PEDIATRIC NEPHROLOGIST

Introduction –approximately 20 to 30 percent of all anomalies identified in the prenatal period

Pathogenesis –abnormal embryogenic kidney development

- **Renal parenchymal malformations** –
  renal dysplasia, renal agenesis (RA), renal tubular dysgenesis, and polycystic renal diseases

- **Renal ectopia and fusion** –
  migration of the kidneys results in renal ectopia (eg, pelvic kidney) fusion anomalies (eg, horseshoe kidney)

- **Collection system anomalies** –
  renal pelvis (ureteropelvic junction obstruction)
  ureter (megaureter, ectopic ureter, or vesicoureteral reflux)
  bladder (bladder exstrophy)
  urethra (posterior urethral valve)

Anomalies of the collecting system :

- Renal pelvis (eg, ureteropelvic junction obstruction)
- Ureter (eg, megaureter, ectopic ureter, ureterocele, or vesicoureteral reflux)
- Bladder (eg, bladder exstrophy)
- Urethra (eg, posterior urethral valve)

DIAGNOSIS

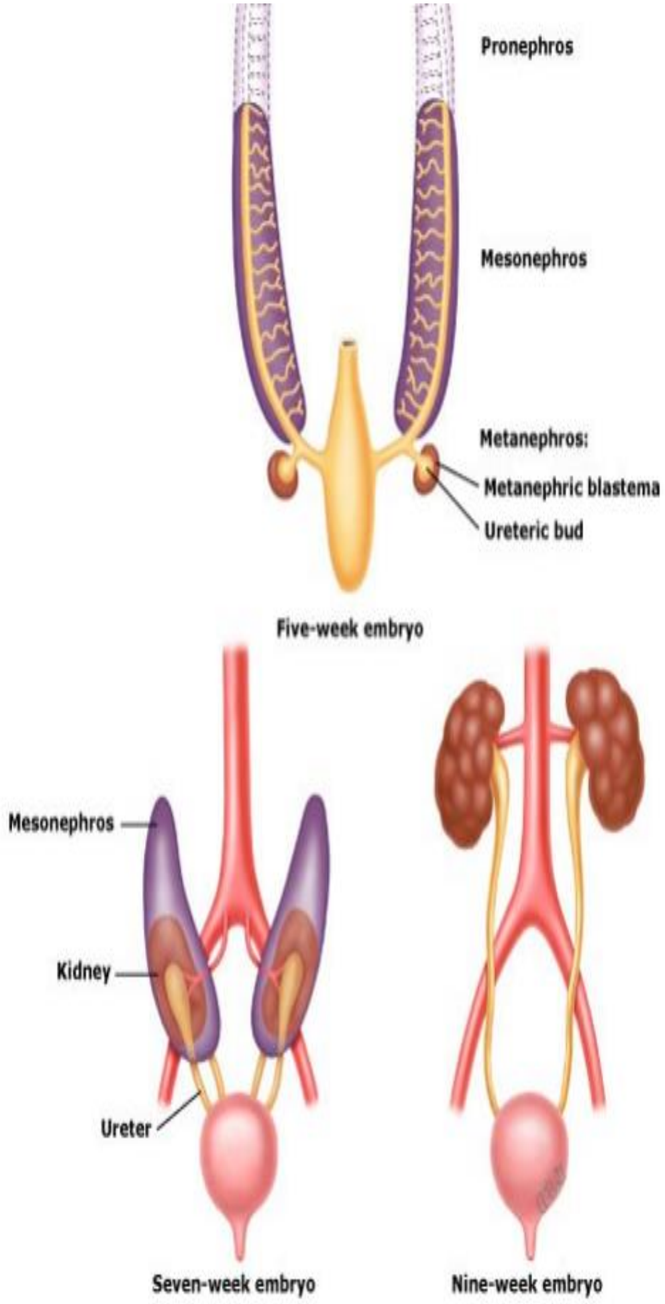
ultrasonography during pregnancy

INCIDANCE:unselected populations has been reported to be between 0.1 to 0.7 percent

optimal timing recommended for a screening antenatall :

between 16 to 20 weeks of gestation because of :

- good visualization of anatomy with a high sensitivity in detecting anomalies
- It is early enough in the pregnancy to allow completion of prenatal diagnostic procedures (eg, fetal karyotype, additional imaging studies) while legal termination of pregnancy is possible, if desired.



May lead to renal failure and the need for dialyses and/or renal transplantation

Abnormal interaction between the ureteral bud and metanephric blastema (hypodysplasia, vesicoureteral reflux, and ectopic ureters)

The genetic and biochemical modulation of urinary tract development

The animals show defective apoptosis of undifferentiated mesenchymal cells

This abnormal apoptosis may well interfere with the normal interaction between the ureteral metanephric blastema resulting in CAKUT

Diverse spectrum Including:

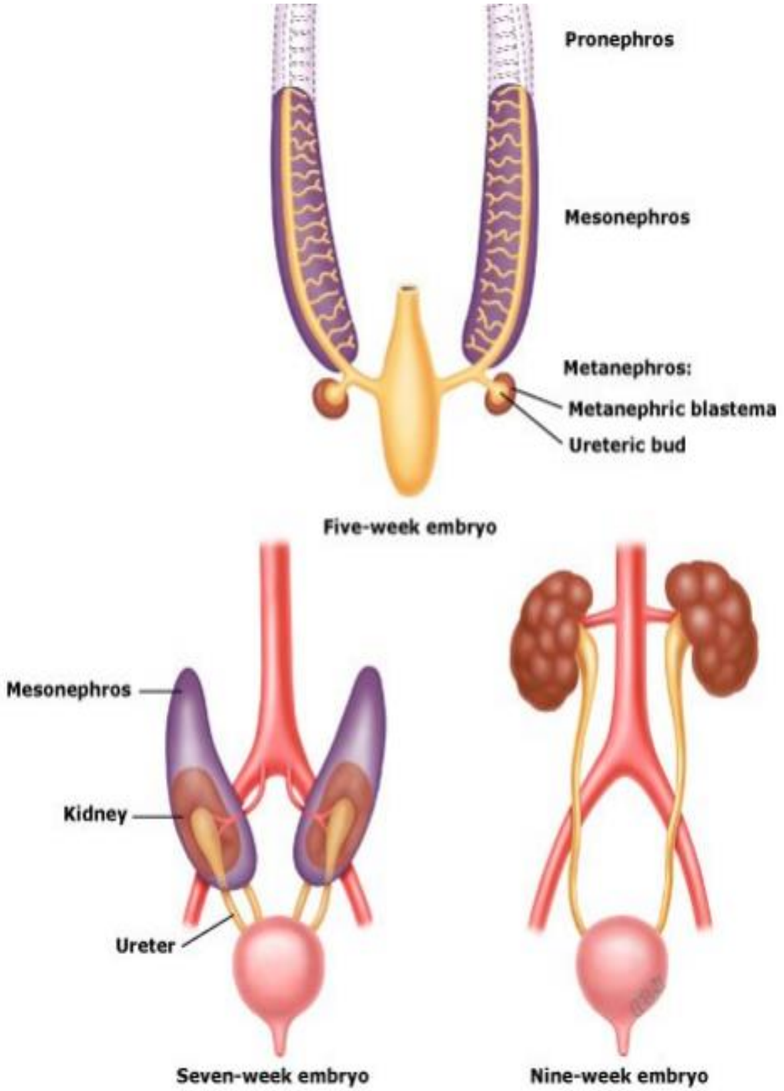
Cystic/Multicystic = containing cysts

Dysplastic Kidneys = abnormal structures

Hypoplastic Kidnyes = reduced normal structures

Lower urinary tract dysfunction such as
- pelvi-ureteric junction(UPJO)
- vesico-ureteric junction (UVJO)
- posterior urethral valves(PUV)
- reflux

Congenital anomalies of the kidney and urinary tract (CAKUT)



Gestational age (weeks)	*Kidney length (mm)*		*Kidney volume (ml)*	
	50th %	5th %	50th %	5th %
15	12.5	10	–	–
20	20	16	2	1.5
25	26	23	4	2.5
30	33	28	7	4
35	38	34	12	7.5
40	44	38	17	11

diagnostic tests

Serum creatinine
Voiding cystourethrography(VCUG)
Dynamic renal scan(MAG3)
Static renal scan(DMSA)
Genetic testing
Serial ultrasound

Serum creatinine

kidney kidney impairment and follow the infant's kidney function

when there is bilateral kidney disease or an affected solitary kidney

at birth is similar to that in the mother

It declines to normal values in approximately one week in term infants and two to three

weeks in preterm infants

should be measured after the first 24 hours to avoid overestimation of creatinine that may

be high and reflective of maternal creatinine value

Voiding cystourethrography

requires urethral catheterization and injection of a contrast agent

suspicion of a thick-walled bladder, ureteric dilatation, hydronephrosis, and in male infants, any urethral pathology (eg, posterior urethral valves)

VUR, which often accompanies other CAKUT (eg, multicystic dysplastic, hypoplastic, or ectopic kidney)

Dynamic renal scan — Dynamic radionuclide scans

kidney excretory function and utilize 99mTc-mercapto acetyl triglycine (MAG-3 or MAG3) MAG-3 is intravenously, absorbed from the blood by the proximal tubules, and secreted into the tubular lumen and then into the bladder

Dynamic renal scans are used to differentiate between obstructive versus nonobstructive

Static renal scan — Static radionuclide scan

focal renal parenchymal abnormalities

between the two kidneys

detection of kidney scarring

99mTc–dimercaptosuccinic acid (DMSA)

(IV) injection, DMSA is taken up by proximal tubular

no minimum age can be performed

Serial ultrasound

compensatory kidney growth of unaffected kidneys

growth is monitored six months in the first year of life

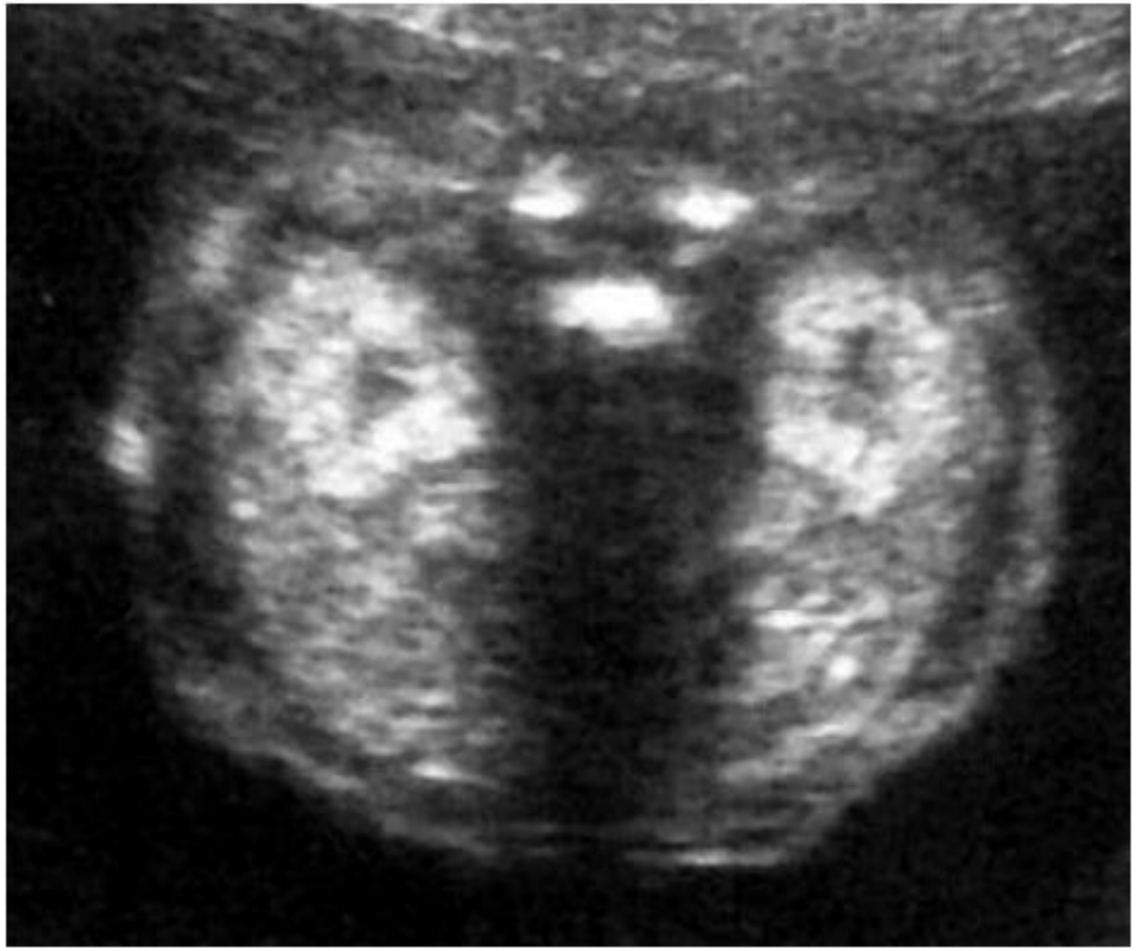
and then yearly or every second year until puberty

progressive hydronephrosis in patients with mild/modercompleted

obstructive uropathy or changes in the affected kidneys (eg, size of multicystic

dysplastic kidney)

Large Bright Kidneys: What does it mean?



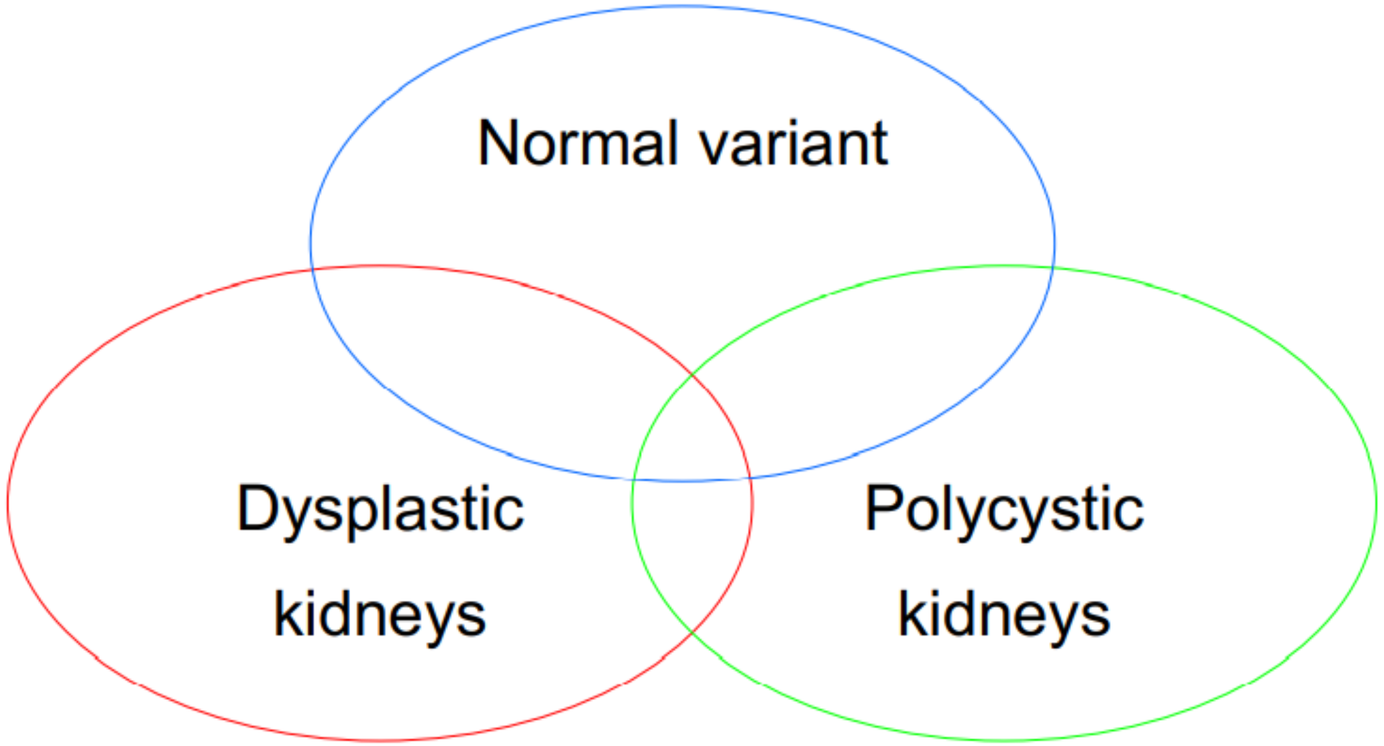
- Aneuploidy
- Normal variant
- Autosomal recessive polycystic kidney disease
- Autosomal dominant polycystic kidney disease
- Renal cysts and diabetes syndrome
- Beckwith Wiedemann syndrome
- Other genetic syndrome

How does ultrasound help?

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

We want to estimate: the number of nephrons / functional renal mass

Most likely one of three common things



[Ultrasound screening and follow-up study of congenital anomalies of the kidney and urinary tract in neonates]

Conclusion: The most common CAKUT in neonates is hydronephrosis and most cases with hydronephrosis had a good prognosis but they should be followed up regularly Urinary ultrasound screening for neonates, especially those high-risk neonates with abnormal fetal urinary ultrasound, has important clinical implications for the early detection of CAKUT

genetic testing

No role for routine genetic testing

in a retrospective study, genetic mutation was detected in

14 of 66 patients (approximately 20 percent)

No mutations were detected in the six patients with urinary tract obstruction

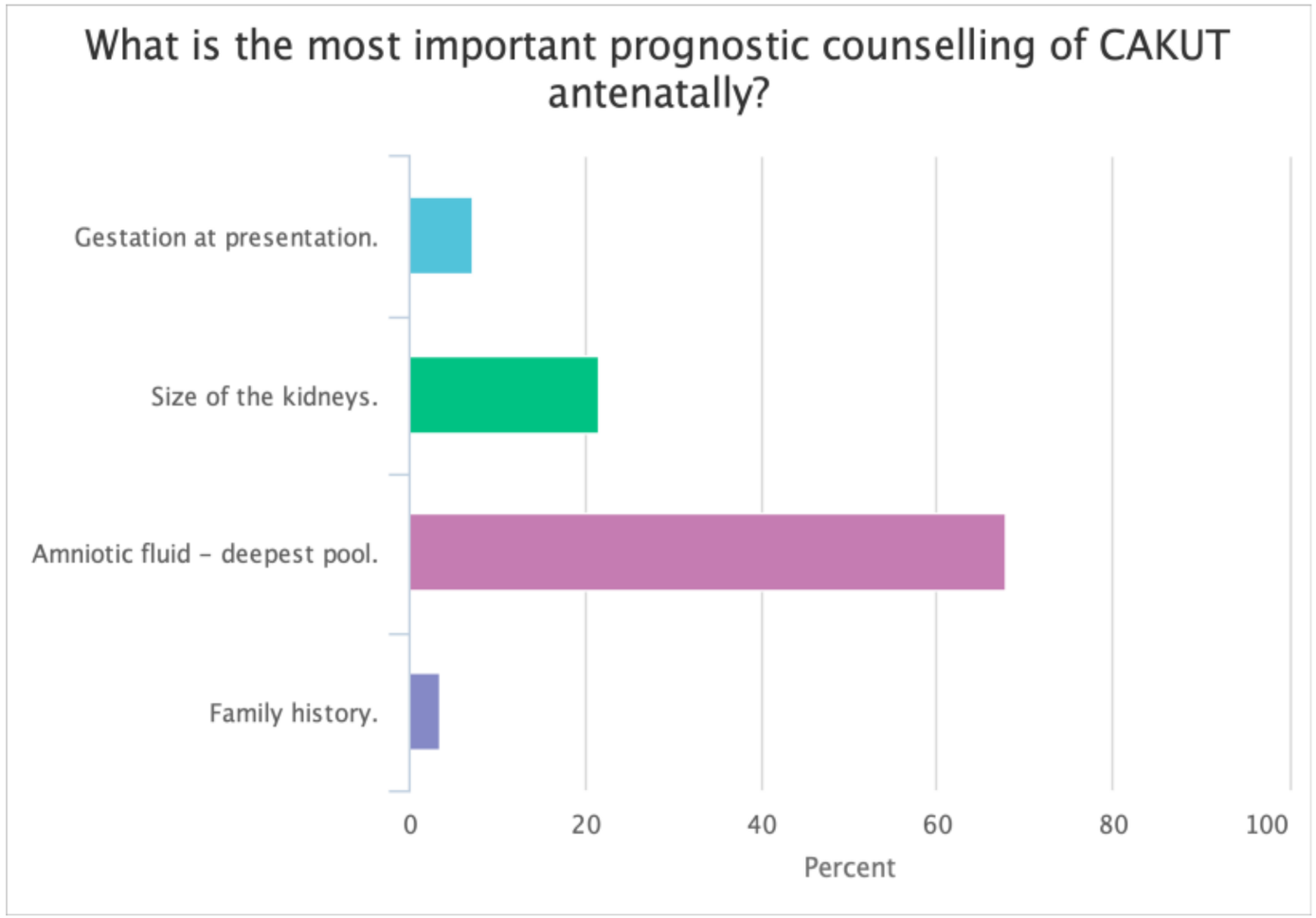
whereas patients with bilateral kidney lesions were more likely to have an underlying genetic mutation

diagnosing a genetic condition did not alter long-term kidney prognosis

genetic testing is not recommended for routine evaluation

genetic causes

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



AFI(cm)	*50th percentile*	*2.5th percentile*
16	12.1	7.3
20	14.1	8.6
25	14.7	8.9
30	14.5	8.2
35	14.0	7.0
40	12.3	6.3

(AFI) is calculated by antenatal ultrasonography as the sum of the largest vertical diameter (cm) of amniotic fluid in each of the four quadrants in the image. Mean (50th percentile) and lower limit (2.5th percentile) for various gestational ages

Amniotic fluid Analysis

high urinary electrolyte excretion

sodium and chloride concentration greater than 90 mEq/L (90 mmol/L)

urinary osmolality less than 210 mosmol/kg H2O (210 mmol/kg H2O)

use gestation specific cut-offs because with increasing gestational age, renal tubular resorptive function increases

Distribution of CAKUT type : 2012-2016

Type of CAKUT	Total patients	Percent incidence	Median age	Percent males
Obstructive Uropathy	665	9.3	10	83.2
Renal aplasia/hypoplasia/dysplasia, oligonephronia	744	10.4	9	59
Reflux nephropathy/chronic pyelonephritis	165	2.3	16	54.5

2018 USRDS ANNUAL DATA REPORT

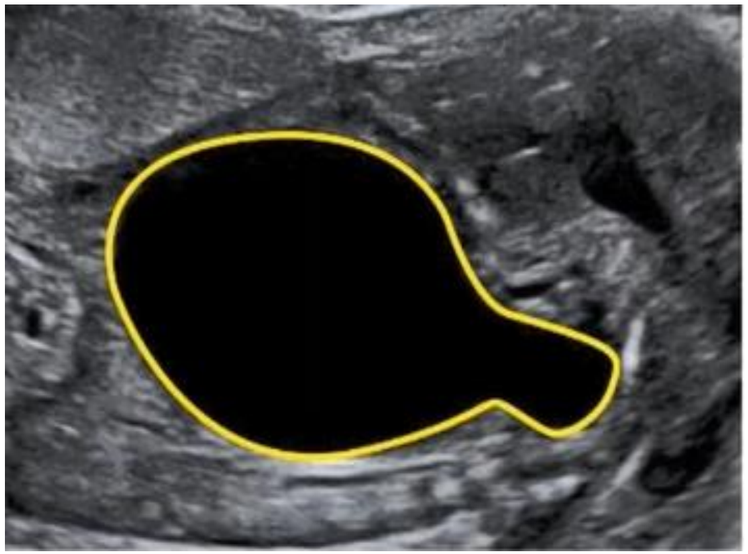
Congenital kidney/urinary tract diseases

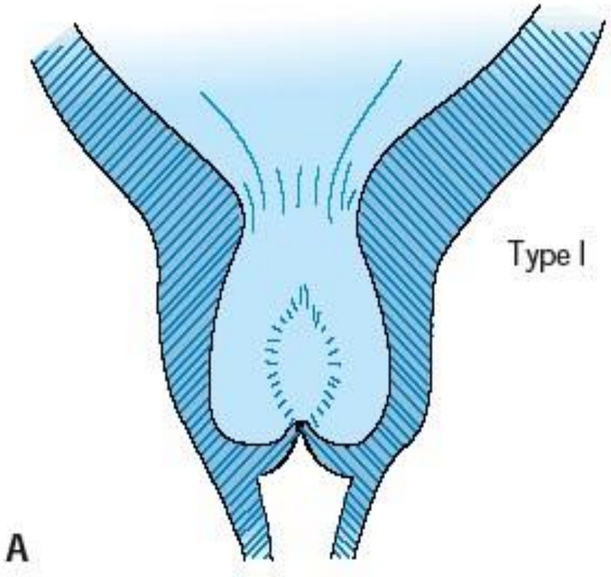
1. **Obstructive Uropathy**
2. **Aplasia/Dysplasia/Hypoplasia**
3. **Reflux nephropathy**

Major Causes of Pediatric Obstructive Uropathy:

- Posterior urethral valves
- Prune belly syndrome
- Myelomeningocele (with neurogenic bladder)
- due to disordered innervation of detrusor muscle and external sphincter
- Ureteropelvic junction (UPJ) obstruction
- Ureterovesical junction (UVJ)obstruction
- Ureterocele (intravesicle ureter)

Obstructive Uropathy-PUV





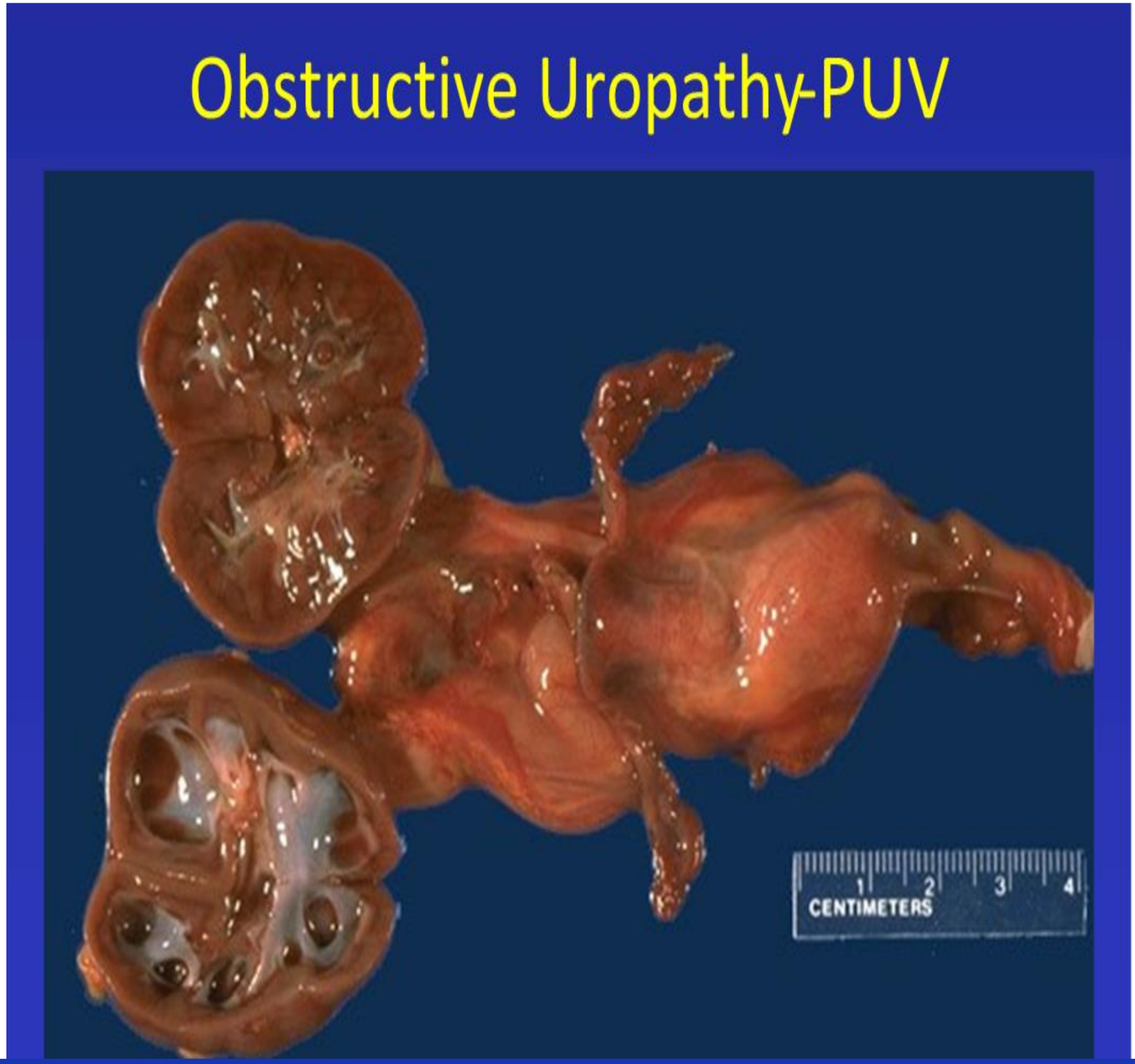
Postnatal evaluation the first 24 hours of life for

neonates bilateral involvement

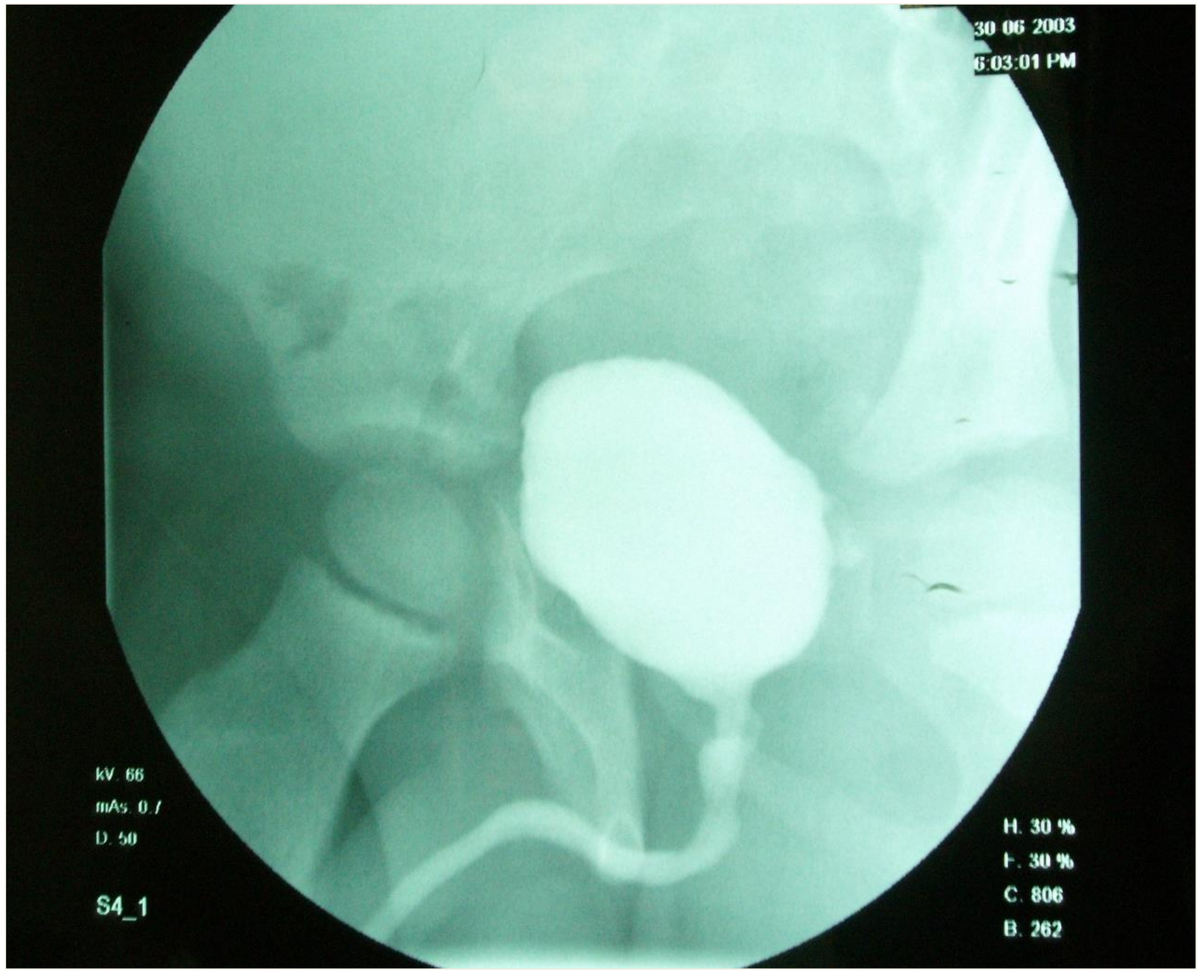
distended bladder with thickened bladder wall

bilateral hydronephrosis

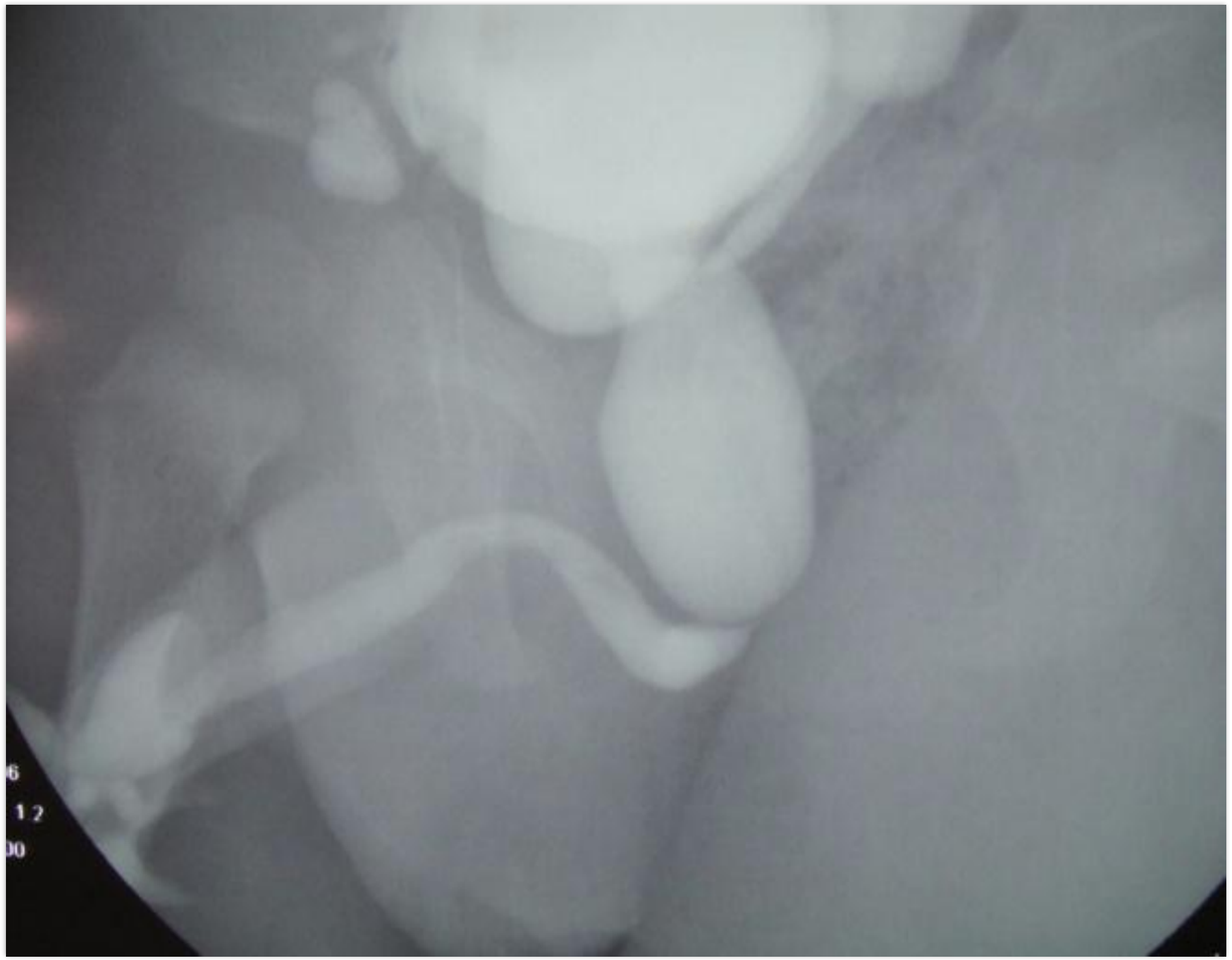
require surgical intervention



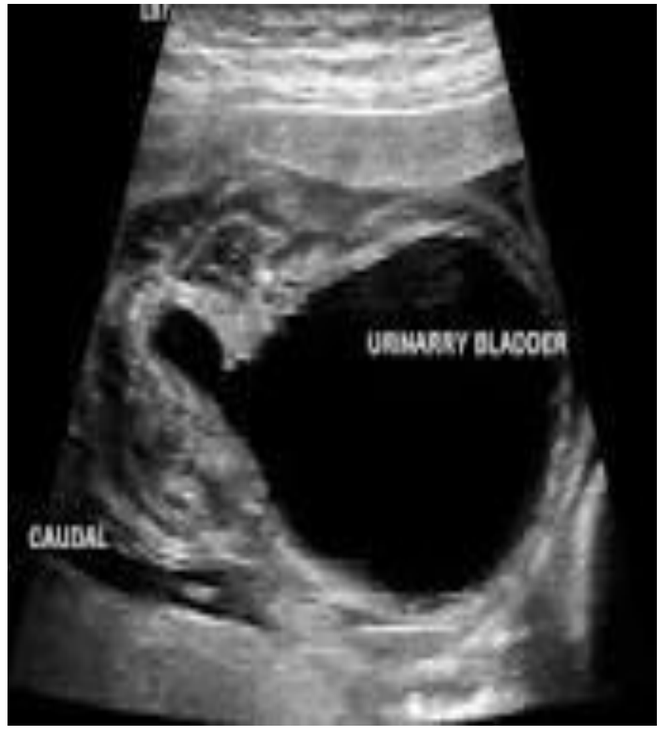
Normal

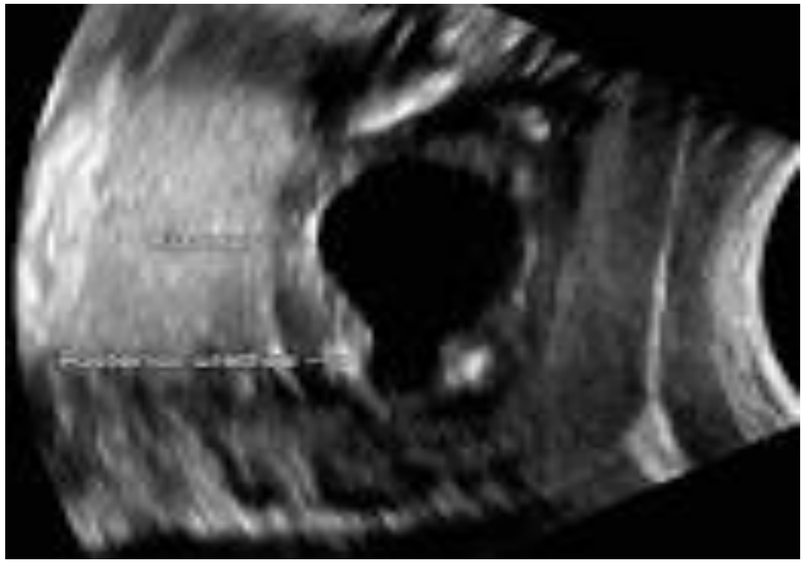


Posterior urethral valves



PUV:





UPJO:

Obstructive Uropathy UPJ obstruction

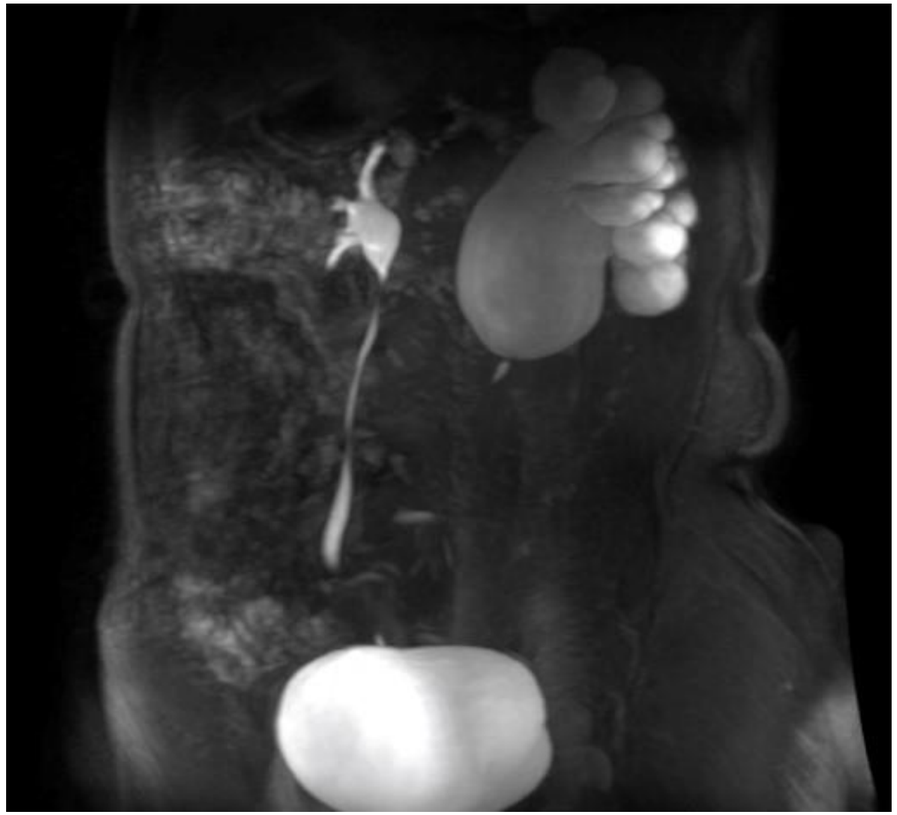
Major causes of pediatric obstructive Uropathy:

Ureteral Dysgenesis

-incidence 1:1500- 1:2000 births

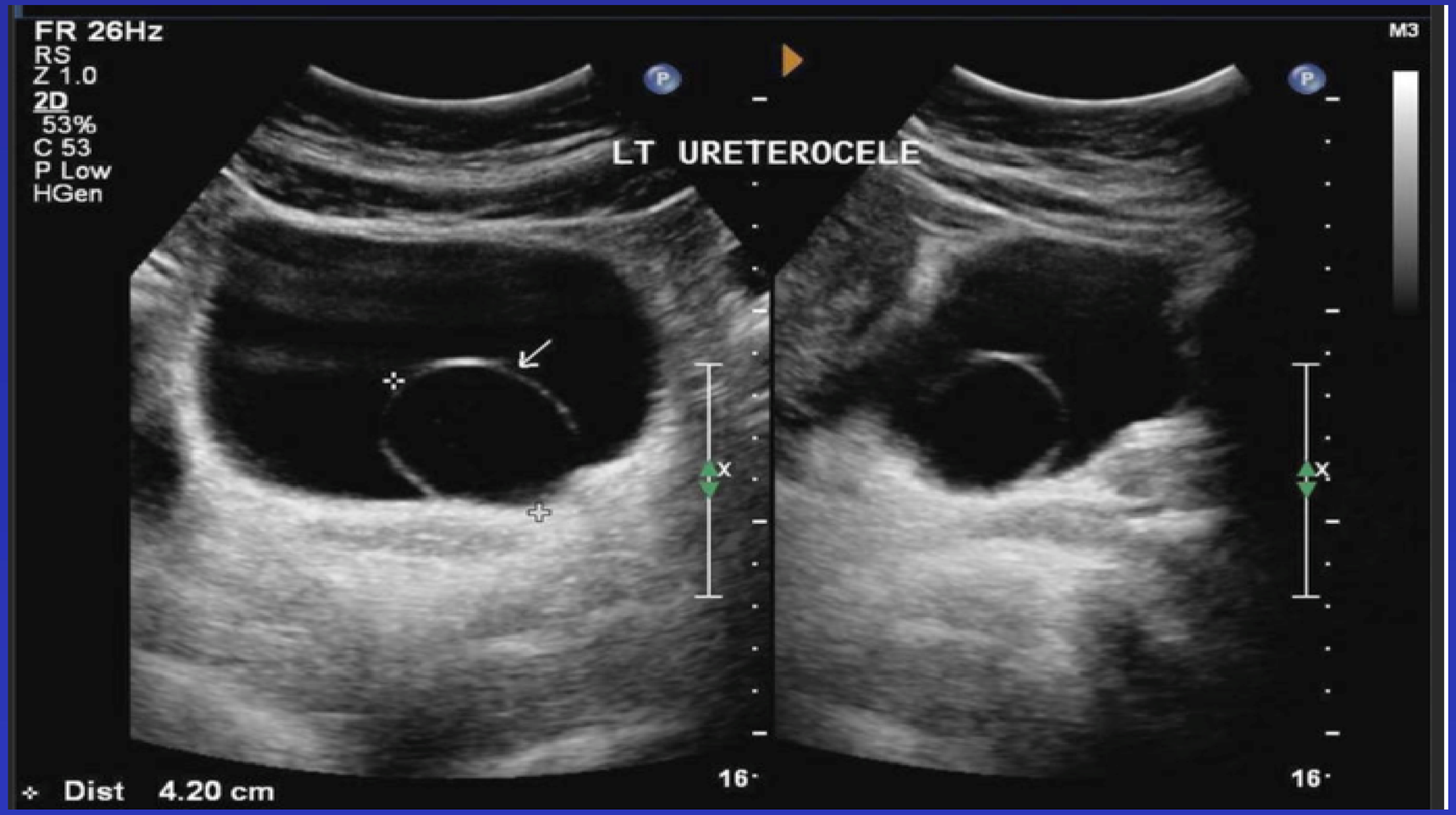
-75% are unilateral

-Male predominance



Obstructive Uropathy UVJ obstruction

Obstructive Uropathy - Ureterocele



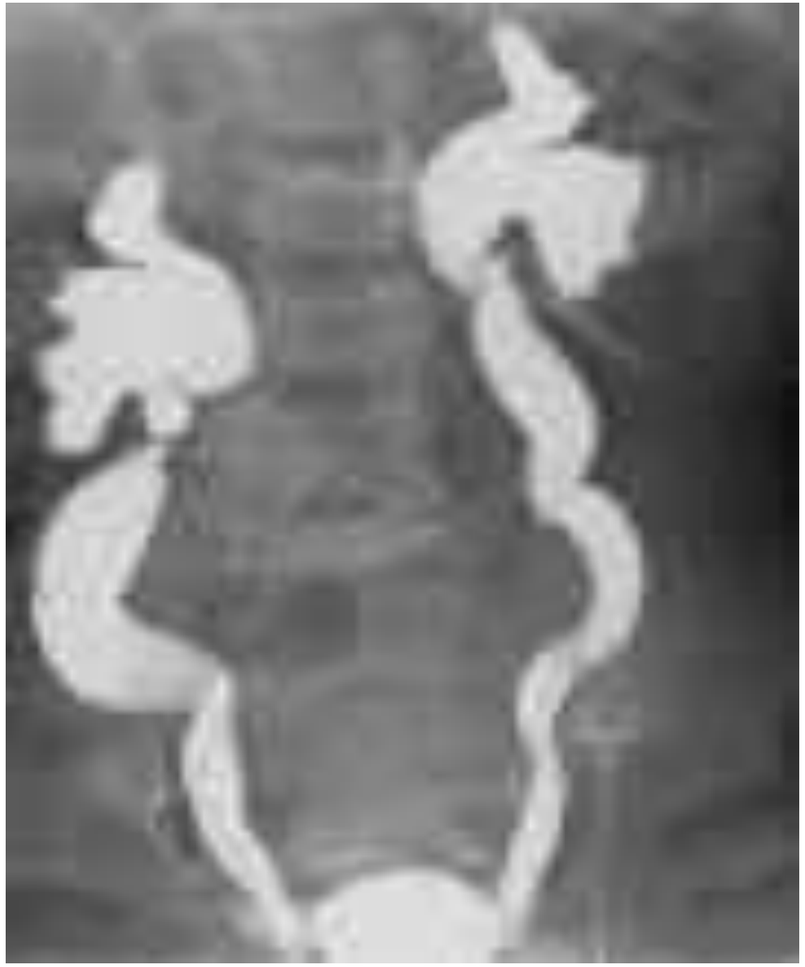
Bladder US

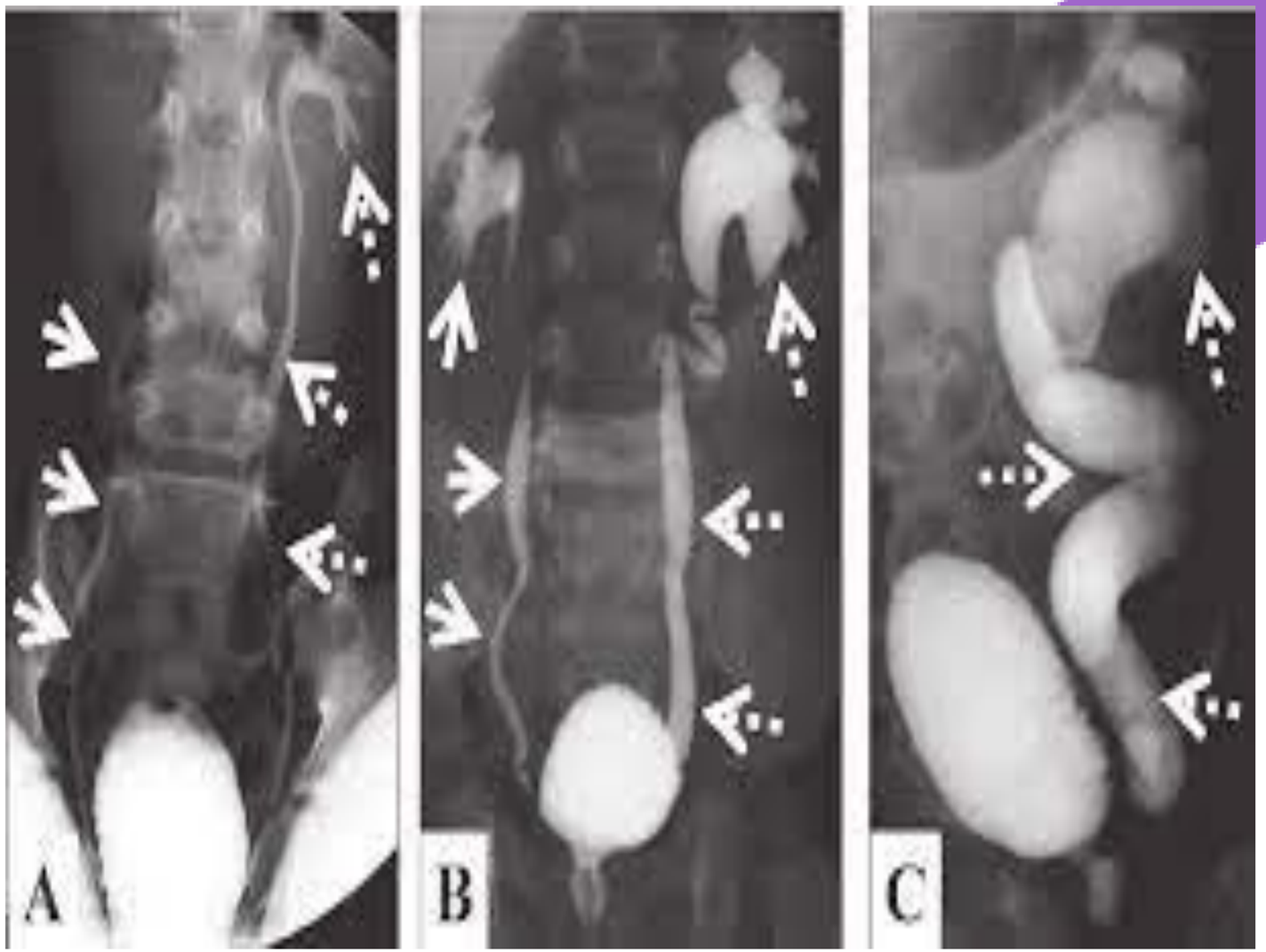
Ultrasound - images.com

Vesico-ureteric reflux (VUR)

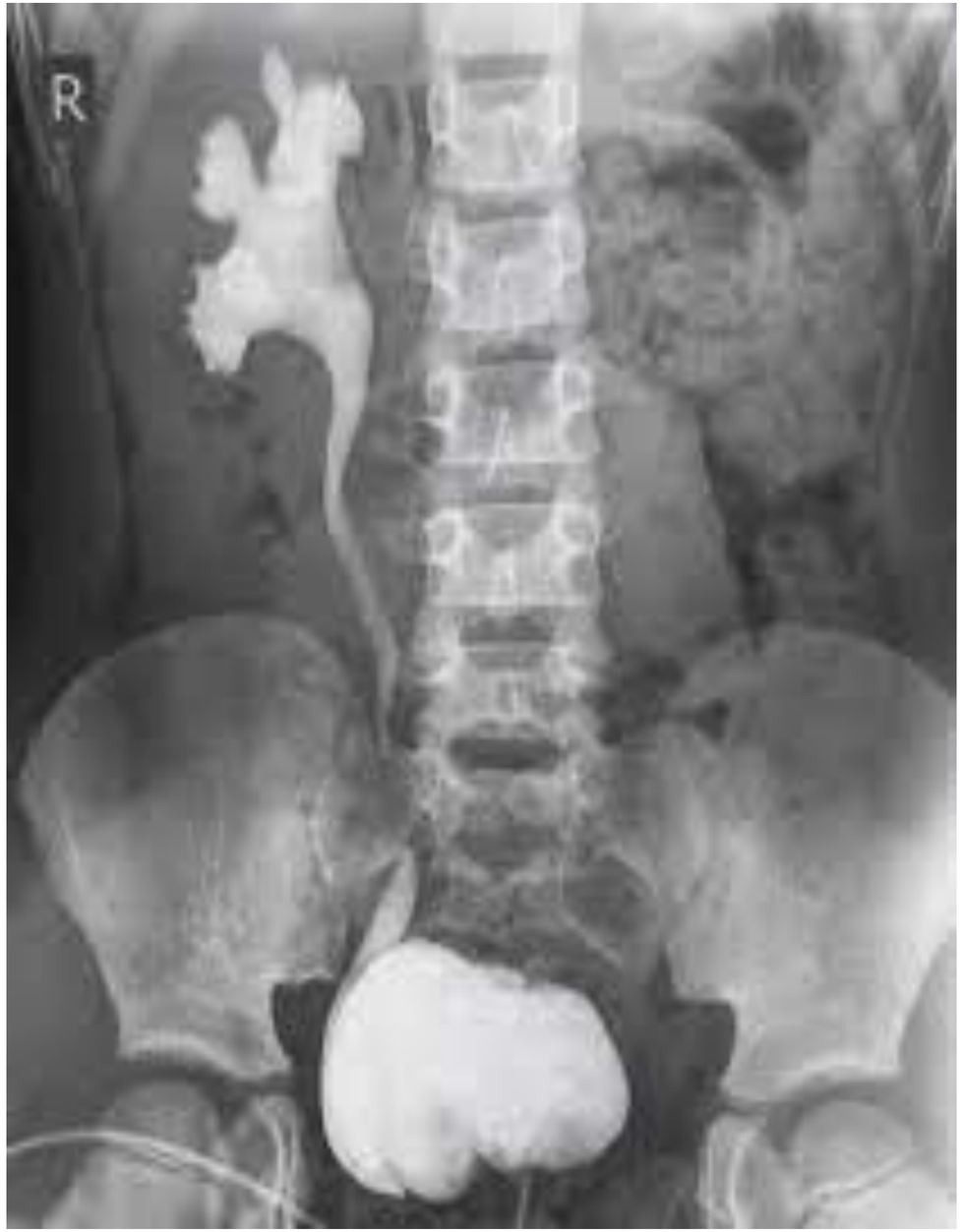
- Affects 1-2% of the population with a higher incidence in females versus males (most common congenital urological abnormality)
- Appears to be autosomal dominant (no major gene identified that causes most cases although genes within families have been identified)
- Peak incidence is in early childhood with gradual resolution
- Majority of patients do well
- Others develop Reflux nephropathy
  - Scarring, inflammation, fibrosis associated with VUR

VUR(VCUG)

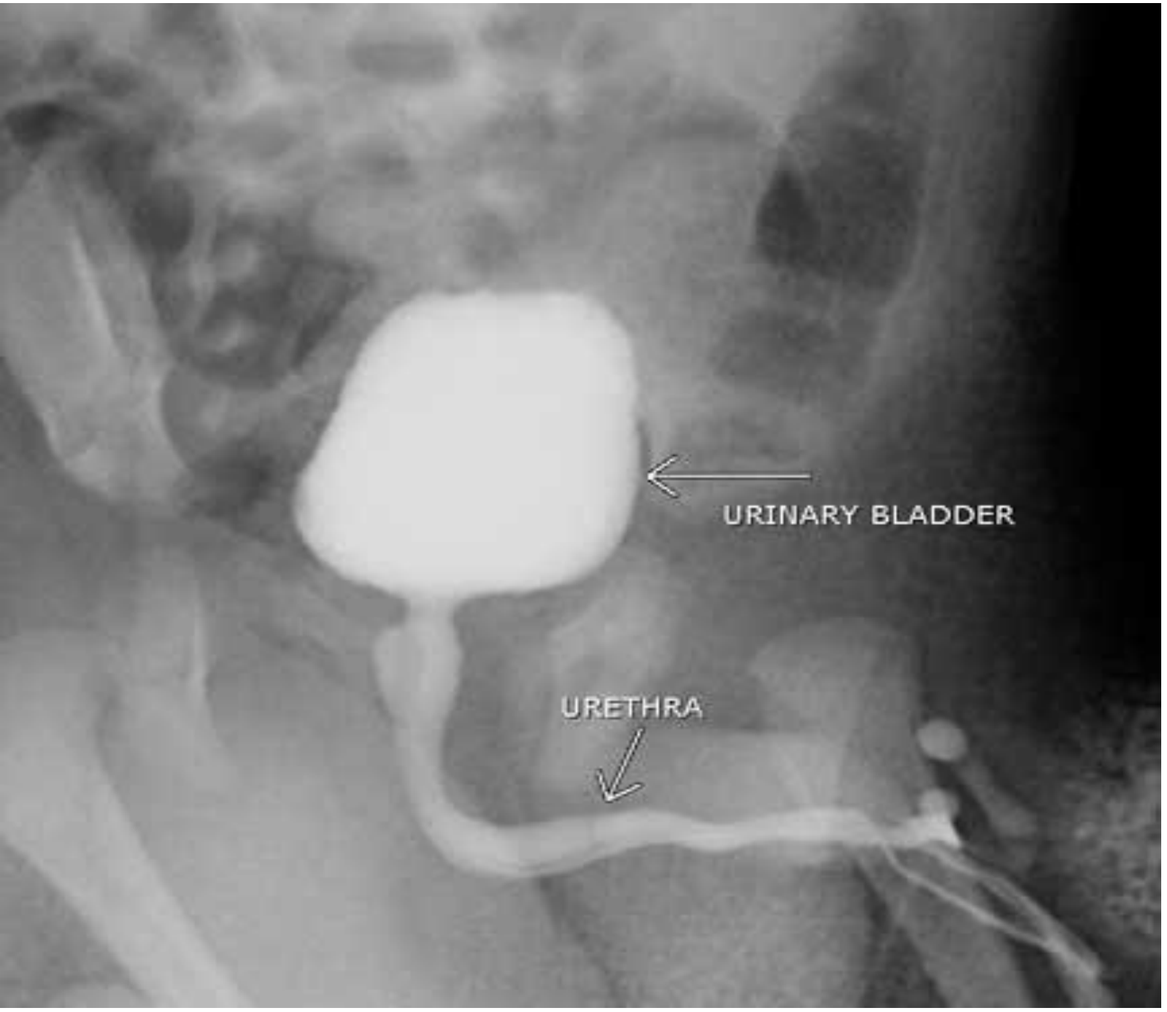




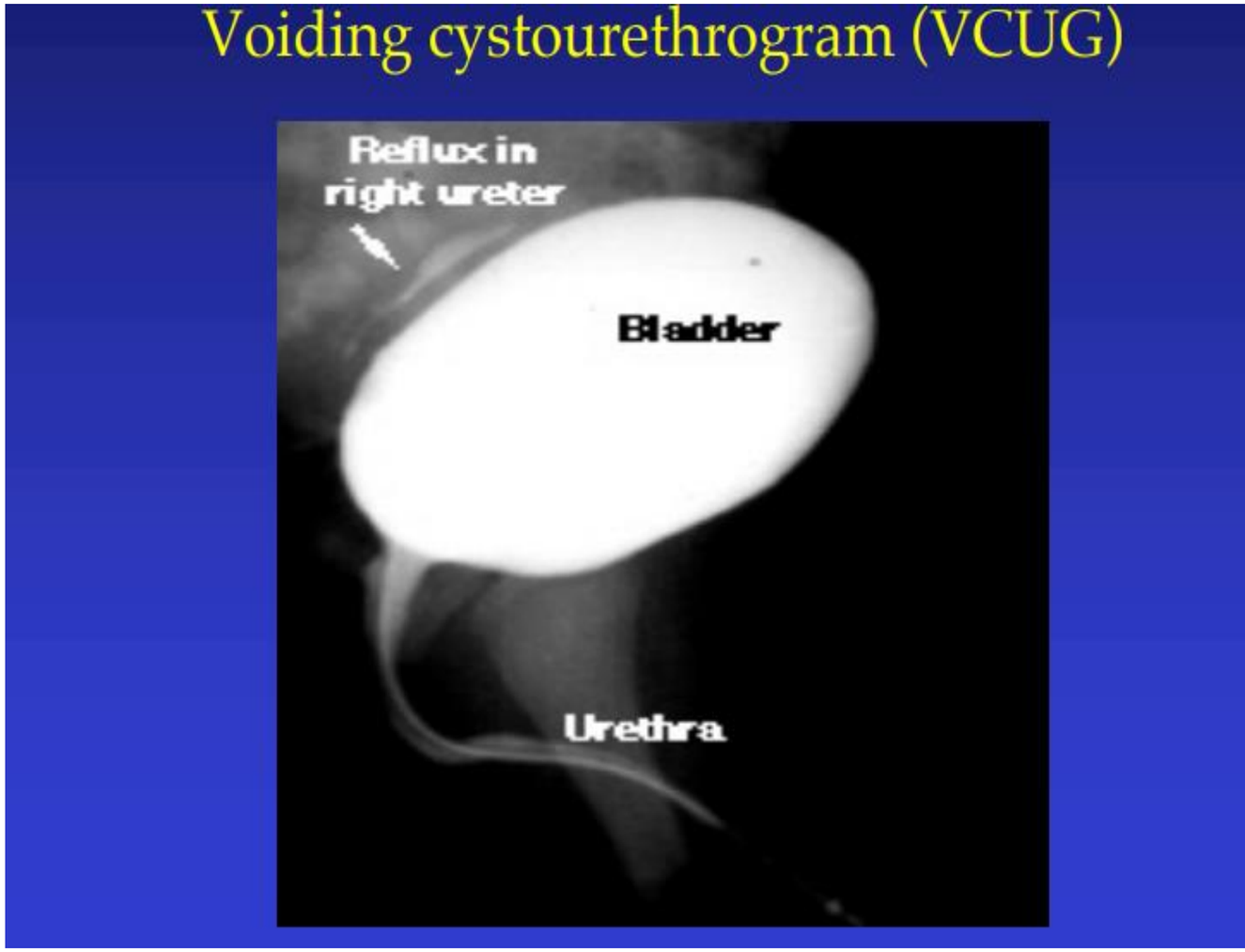
VUR



NORMAL VCUG



VUR



Relationship of VUR, UTI and renal scarring

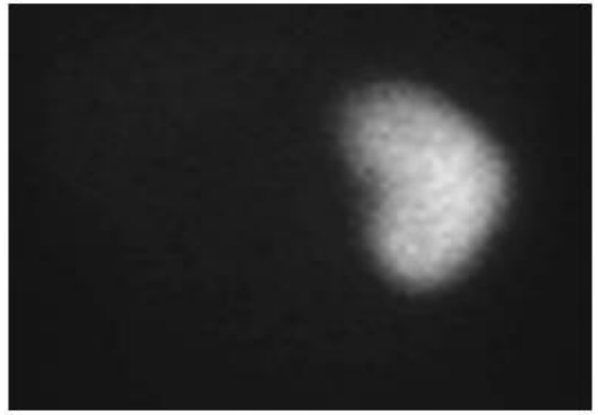
- 10-15% of patients with VUR and UTI develop scars

  Pediatrics. 2010; 126:1084-91; NEJM. 2014; 370 (25) 2367-2376

- Mechanisms underlying scar formation is unknown
  - ? Immune dysregulation, vascular defects, mesangial abnormalities
- Higher grades of VUR associated with increased scars
  - Unclear if this is a causal relationship an association only
- Scar risks increase with bowel and bladder dysfunction
- A delay in febrile UTI treatment increases risks of scarring
- Younger age with UTI confers a higher risk of scarring

  Pediatrics. 2010; 126:1084-91

Unitlateral renal agenesis



ultrasound measures:

size of the solitary kidney

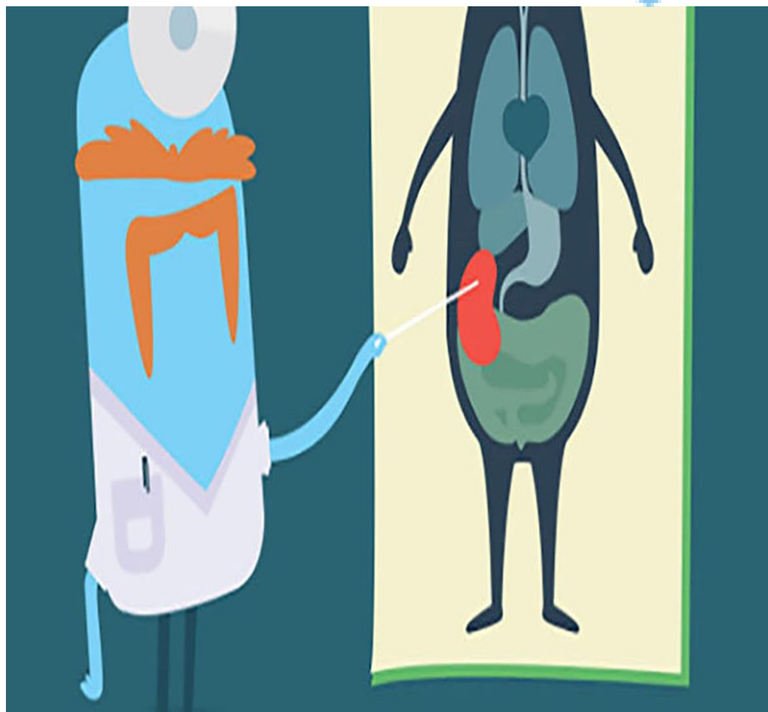
any other kidney abnormalities

compensatory renal hypertrophy

May in pelvic area ectopic kidney is present

magnetic resonance imaging or static renal scan with(DMSA)

a renal scan may miss nonfunctional kidney tissue



Unitlateral renal agenesis

1.Renal-coloboma syndrome: renal hypoplasia, vesicoureteral reflux, and optic nerve coloboma ,PAX2

2.BOR syndrome

3.Müllerian abnormalities – (eg, uterine didelphys and/or vaginal duplication) are common in girls because the Wolffian and müllerian ducts are contiguous part of the spectrum of Mayer-Rokitansky syndrome and typically present during the onset of puberty with menstrual obstruction symptoms such as cyclical pain, excessive discharge, and/or infection

Microphallus and cryptorchidism are findings noted in infants with congenital gonadotropin-releasing hormone deficiency Older affected children may present with anosmia (lack of sense of smell), cleft lip/palate, or syndactyly.

4.trisomies 13 and **18** and Turner syndrome

ANOMALIES OF RENAL EMBRYONIC MIGRATION

ectopy or fused kidneys

are at increased risk for other anomalies:

genitourinary abnormalities

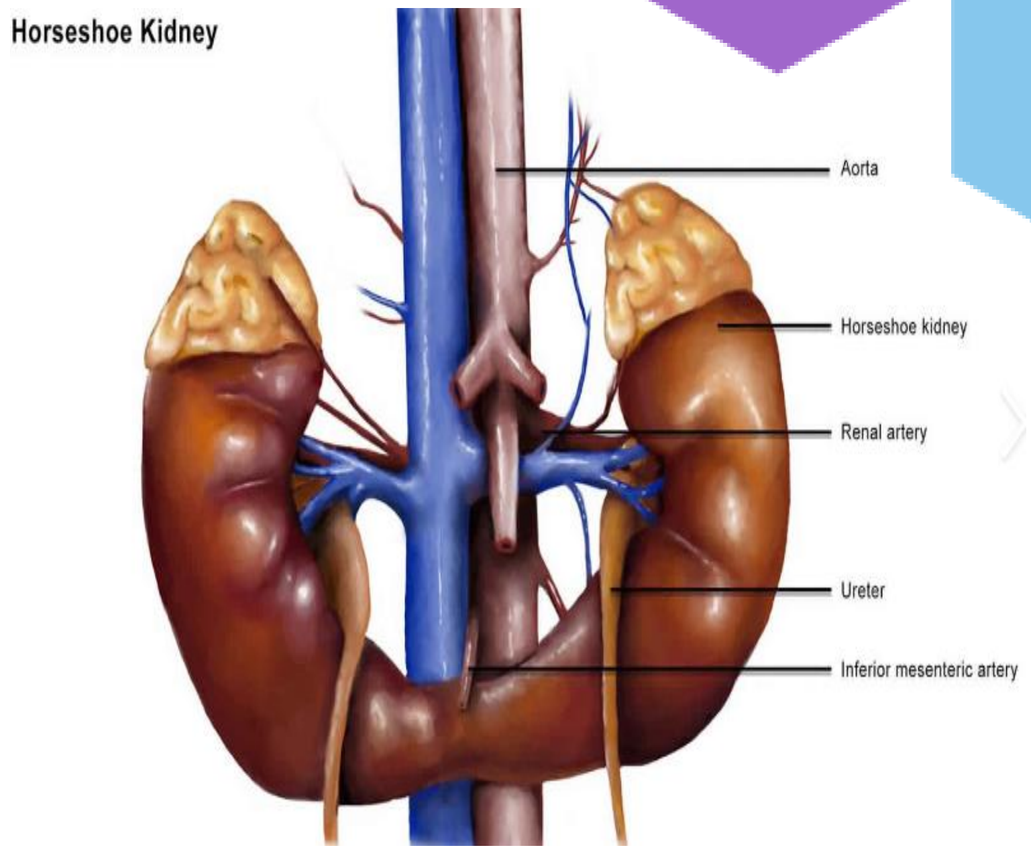
vesicoureteral reflux

COMPLICATION:

UTI

NEPHROLITHIASIS

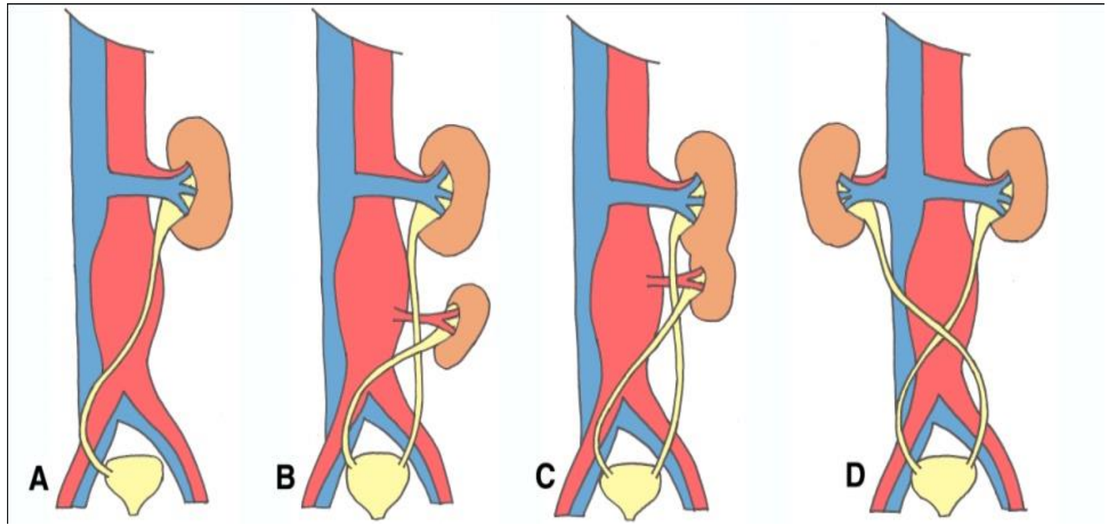
OBSTRUCTION



Renal ectopy

● Simple ectopy refers to a kidney that lies on the correct side of the body, but lies in an abnormal position.

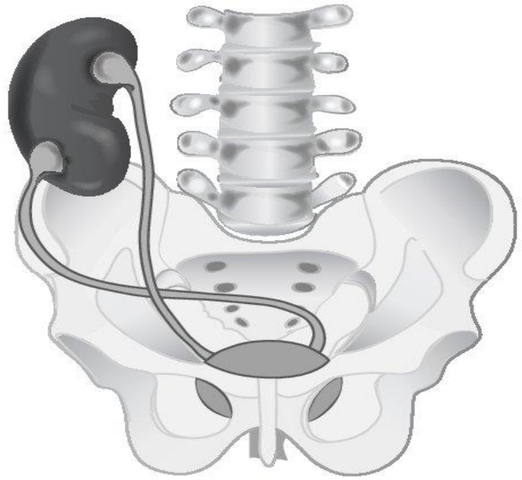
● Crossed renal ectopy refers to a kidney that crosses the midline



Crossed renal ectopy

with and without fusion

Crossed fused ectopy —the ectopic kidney and ureter crosses the midline to fuse with the contralateral kidney, but the ureter of the ectopic kidney maintains its normal insertion into the bladder the ectopic kidney is positioned inferiorly to the contralateral kidney The contralateral kidney can either retain its normal dorsolumbar position or is positioned lower in the pelvis or lower lumbar vertebral level (L4 or L5).



Duplication

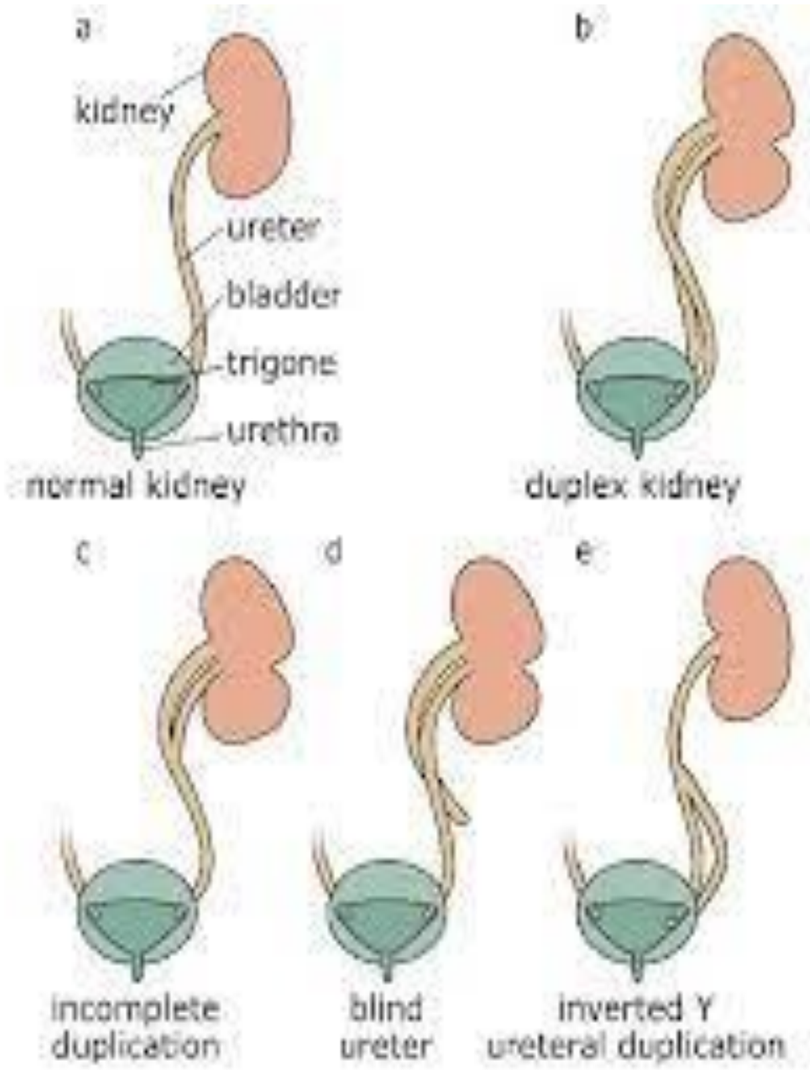
asymptomatic uncomplicated (no dilation)

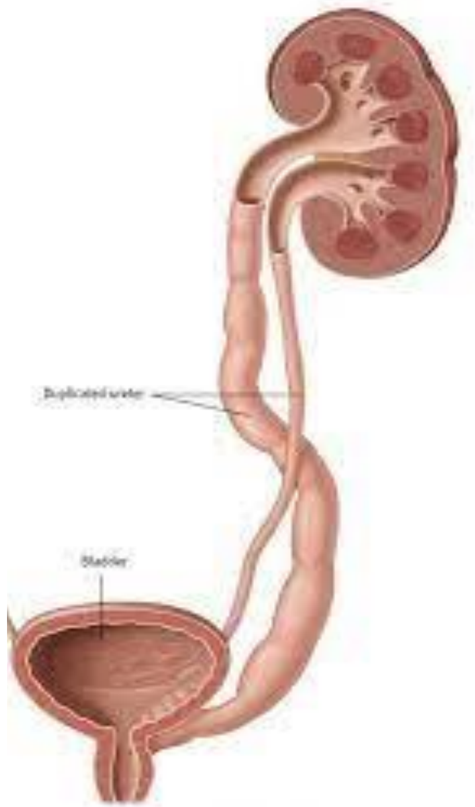
no further intervention or referral is needed

A history of urinary tract infection (UTI) or

dilatation (typically due to obstruction) surgica

repair

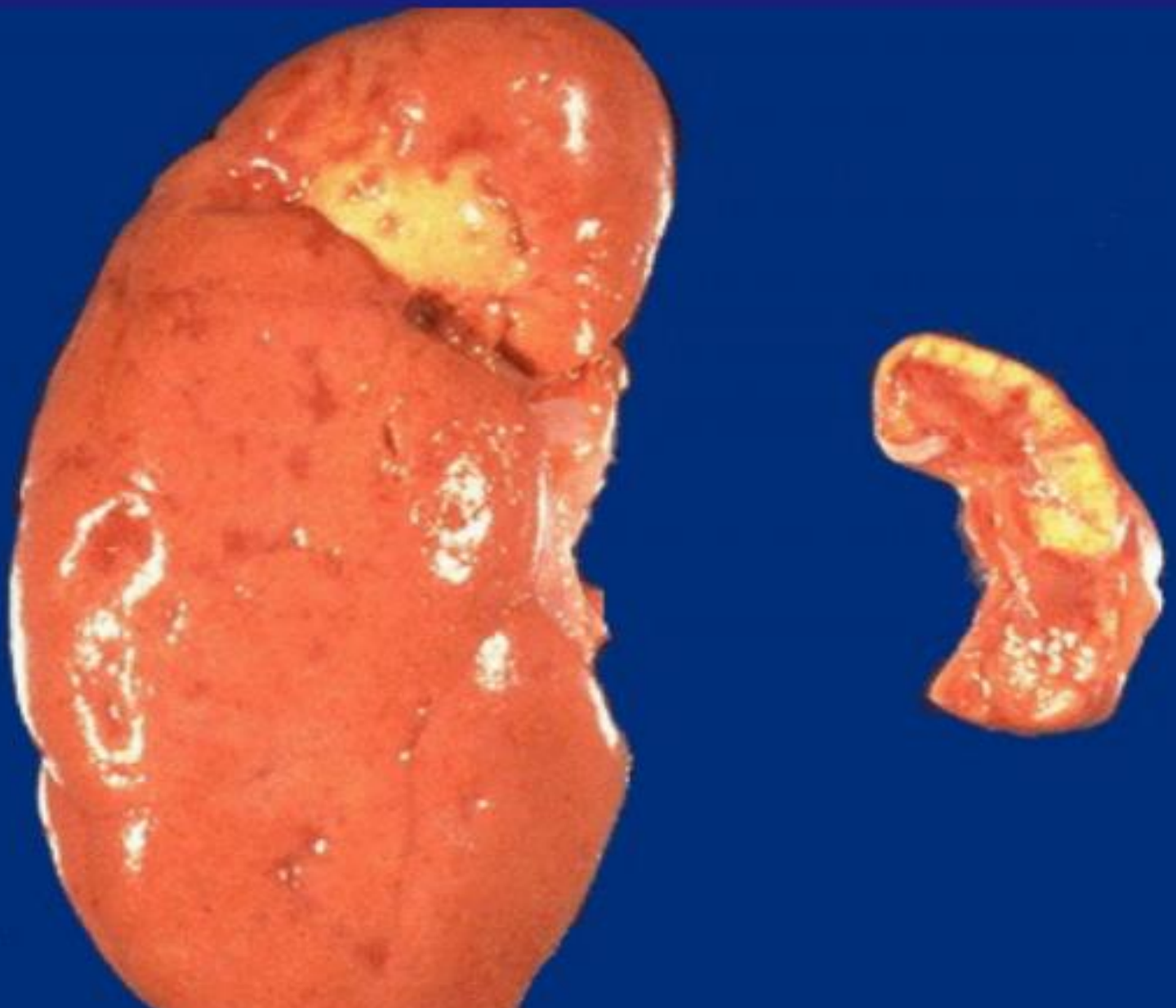




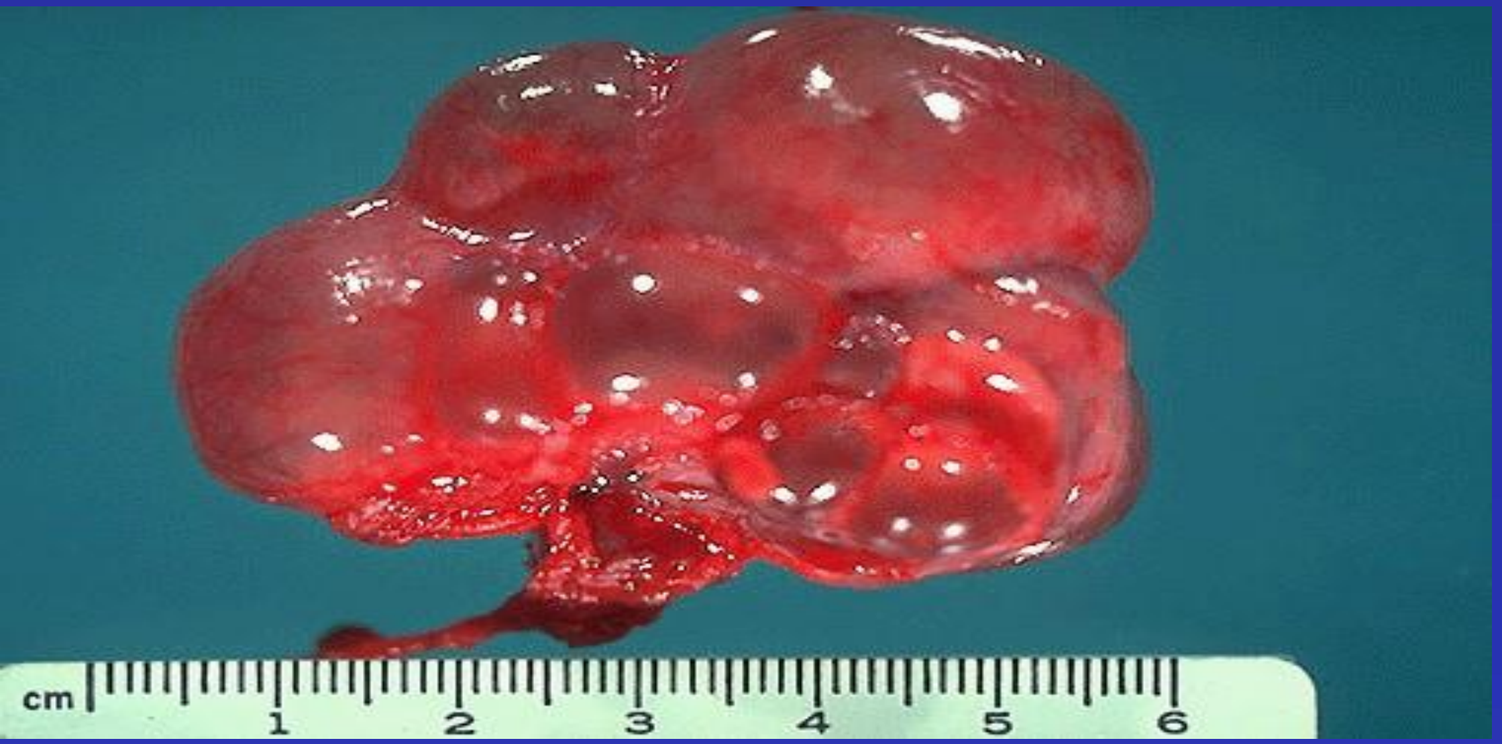
Aplasia / dysplasia / hypoplasia

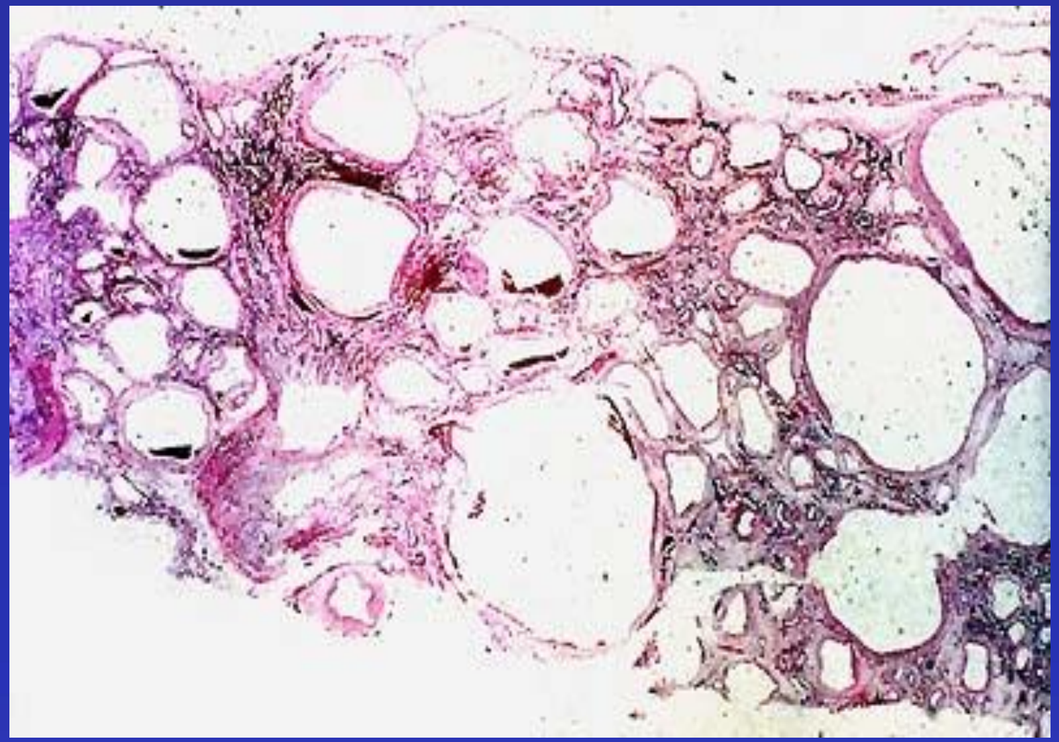
- Aplasia-absent kidney
  - Agenesis- never kidney tissue at all (probably very rare)
  - Involution of kidney from severe / early fetal hypo-dysplasia
- Dysplasia- abnormal kidney structures
  - aberrant ureteric bud / metanephric mesenchyme interaction
  - Complete (no kidney function), partial (some function)
  - Cystic (MCDK) and non-cystic
- Hypoplasia- normal kidney structures, just smaller / fewer
  - Often combined with dysplasia

Aplasia (hypoplasia)



Multicystic Dysplasia





Multicystic Dysplastic Kidney (MCDK) is a severe renal dysplasia the kidney is

tense noncommunicating macrocyst

there is no functional parenchyma

early progression to advanced CKD including

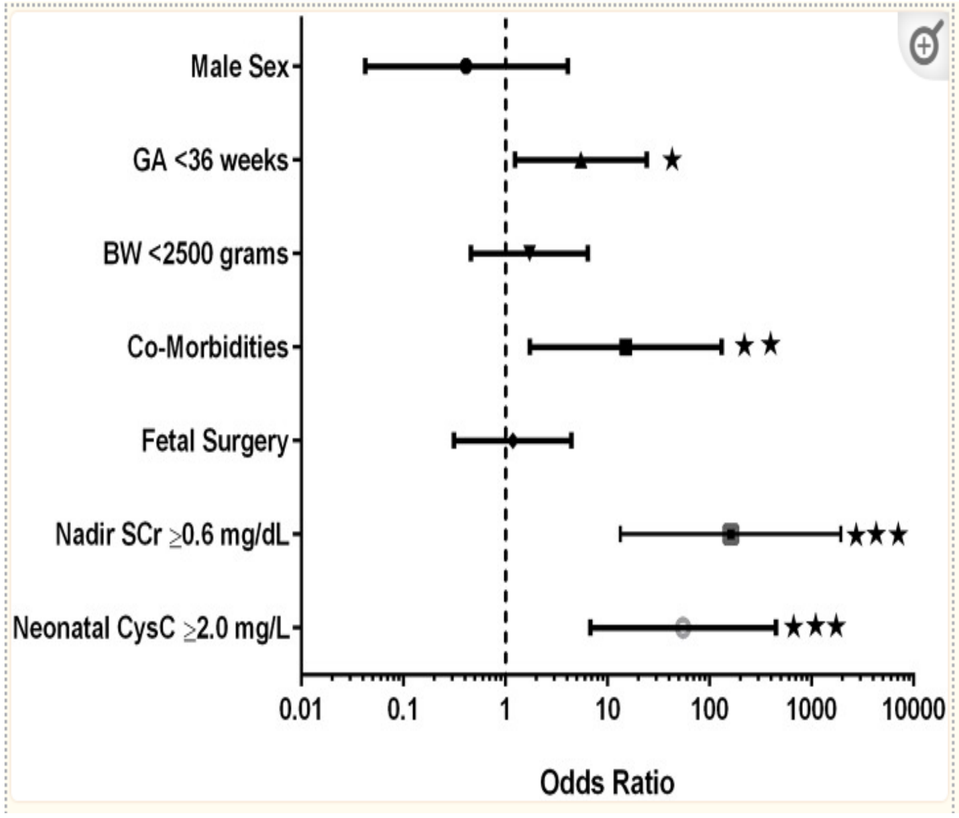
1.male gender and fetal surgery were not significant predictors of early progression

Preterm birth with GA <36 weeks was a predictor of early progression;

low birth weight <2,500 grams was not

Co-morbidities which included lung hypoplasia and congenital anomalies involving other organ systems were a significant predictor of progression

The lowest thresholds for SCr (≥0.6 mg/dL) and Cystatin C (≥2.0 mg/L) were included in the analysis and proved to be the most significant predictors of progression to early CKD



Front Pediatr. 2019; 7: 182.
Published online 2019 May 14. doi: 10.3389/fped.2019.00182

Risk Assessment of Severe Congenital Anomalies of the Kidney and Urinary Tract

Summary

- Congenital kidney diseases are leading causes of chronic kidney disease in children, especially in the very young
- Obstructive nephropathy is a leading cause of chronic kidney disease and can result from either lower urinary tract obstruction or bilateral ureteral dysgenesis
- Although aplasia/hypo/dysplasia is most often unilateral, bilateral disease is a leading cause of end stage renal failure
- VUR is the most common congenital urogenital anomaly and may lead to reflux nephropathy
- Animal models are valuable in elucidating molecular control of kidney development and in generating biomarkers of progressive structural CKD in children

Thank you