Antenatally Diagnosed (Renal) Abnormalities

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Antenatal Kidney anomalies:
Common, often require evaluation

Antenatal hydronephrosis

~0.5-7.7% of all pregnancies: Varies by definition; gestation

17–30% bilateral; natural history depends on etiology

4-15% cases require postnatal intervention

Bright kidneys, usually cystic kidney diseases

HNF1B related nephropathy

Congenital solitary kidney	**1 in 1400 births**
Unilateral renal agenesis	1 in 2000
Multicystic dysplastic kidney	1 in 4300

Other congenital anomalies of kidney & urinary tract

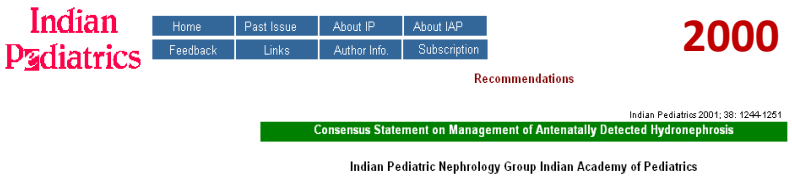
Causes of urinary tract dilatation

Etiology	All cases (%)	Significant ANH; Neonatal hydronephrosis
Transient hydronephrosis	41-88	
PUJ obstruction	10-30	35-45
Vesicoureteric reflux	10-20	20-30
VUJ obstruction, megaureter	5-10	10
Duplex kidneys (±ureterocele)	2-7	7-8
Posterior urethral valves	**1-2**	**4-9**
Multicystic dysplastic kidney	4-6	4-15
Others (urethral atresia, urogental sinus, prune belly, extrarenal tumors)		

Pediatr Radiol 2004; 34:519–29

SFU Consensus Statement. J Pediatr Urol 2010; 6: 212-31

Evidence Based Guidelines for India


Indian Pediatrics

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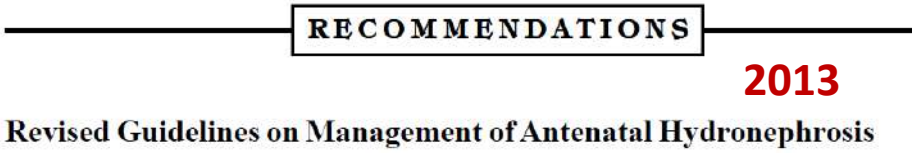
2000

Recommendations

Indian Pediatrics 2001; 38: 1244-1251

Consensus Statement on Management of Antenatally Detected Hydronephrosis

Indian Pediatric Nephrology Group Indian Academy of Pediatrics


RECOMMENDATIONS

2013

Revised Guidelines on Management of Antenatal Hydronephrosis

Strength of evidence: The AAP model

Evidence Quality	Preponderance of Benefit or Harm	Balance of Benefit and Harm
A. Well designed RCTs or diagnostic studies on relevant population	Strong Recommendation	Option
B. RCTs or diagnostic studies with minor limitations;overwhelmingly consistent evidence from observational studies	Recommendation	
C. Observational studies (case-control and cohort design)		
D. Expert opinion, case reports, reasoning from first principles	Option	No Rec
X. Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm	Strong Recommendation / Recommendation	

Level 1. Recommendation

Level 2. Suggestion or option

Revision of guidelines: 2022-23

Expert Group Meetings

Online: October 2022- February 2023

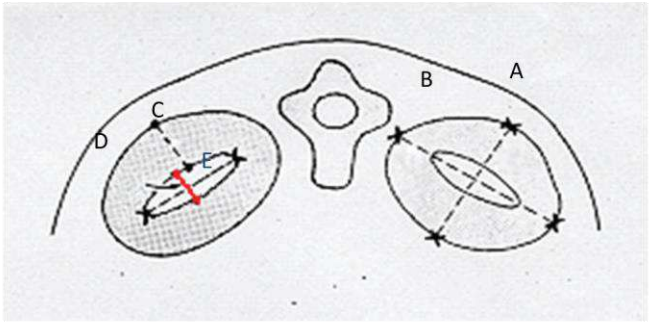
Physical: 25 November 2022

Methods

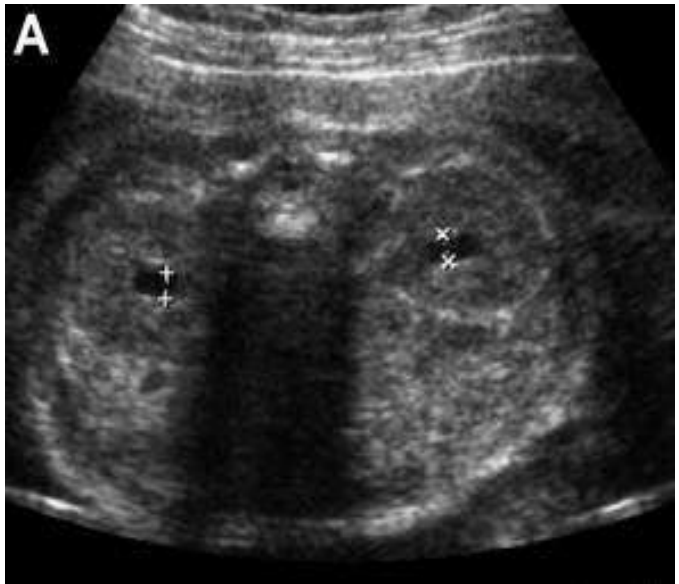
- **Literature searches: 2000-2022**
- **Evidence tables**
- **Rating of evidence**
  - AAP model; GRADE-PRO
  - Consensus thru' discussions
- **Revision of guidelines**

#1: Defining Fetal Hydronephrosis

Maximum anteroposterior diameter (APD) of renal pelvis in transverse plane



A	Anteroposterior diameter of kidney
B	Transverse diameter of kidney
C	AP diameter of renal cortex
D	**Anteroposterior diameter of renal pelvis**
E	Transverse diameter of renal pelvis.

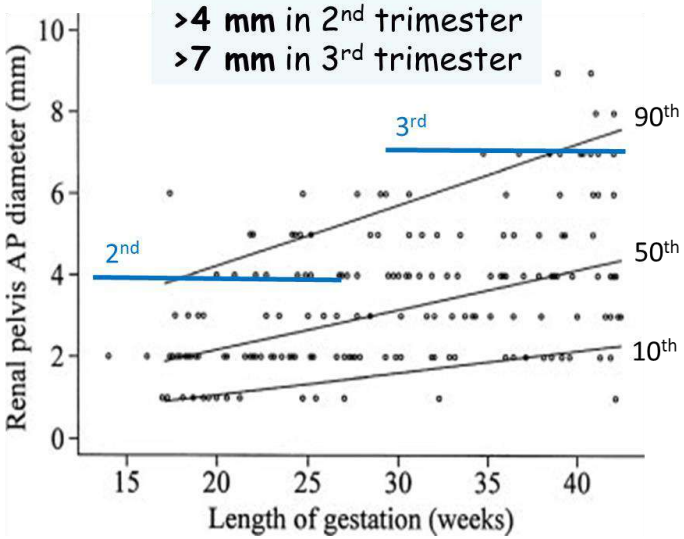


PRENATAL DIAGNOSIS
Prenat Diagn 2003; **23**: 891–897.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/pd.693

Charts of fetal size: kidney and renal pelvis measurements

Cross-sectional survey
663 fetuses, 14-42 wk

>4 mm in 2nd trimester
>7 mm in 3rd trimester



>4 mm in 2nd trimester; **>7 mm** in 3rd trimester

Determined by gestation, hydration, bladder distension

Objective, reproducible, low intra- & inter- observer variation

Disregards calyceal dilatation, parenchymal changes

Risk of pathology increases with severity

Meta-analysis: n=1308; 17 studies

TABLE 5 Risk of Pathology by Degree of ANH

Overall risk 36%

Postnatal Pathology, % (95% CI)[a]	Degree of ANH					Trend *P*[b]
	Mild (*N* = 587)	Mild-Moderate (*N* = 213)	Moderate (*N* = 235)	Moderate-Severe (*N* = 179)	Severe (*N* = 94)	
Any Pathology	11.9 (4.5–28.0)	39.0 (32.6–45.7)	45.1 (25.3–66.6)	72.1 (47.6–88.0)	88.3 (53.7–98.0)	<.001
UPJ	4.9 (2.0–11.9)	13.6 (9.6–18.9)	17.0 (7.6–33.9)	36.9 (17.9–61.0)	54.3 (21.7–83.6)	<.001
VUR	4.4 (1.5–12.1)	10.8 (7.3–15.7)	14.0 (7.1–25.9)	12.3 (8.4–17.7)	8.5 (4.7–15.0)	.10
PUV	0.2 (0.0–1.4)	0.9 (0.2–3.7)	0.9 (0.2–2.9)	6.7 (2.5–16.6)	5.3 (1.2–21.0)	<.001
Ureteral obstruction	1.2 (0.2–8.0)	11.7 (8.1–16.8)	9.8 (6.3–14.9)	10.6 (7.4–15.0)	5.3 (1.4–18.2)	.025
Other[c]	1.2 (0.3–4.0)	1.9 (0.7–4.9)	3.4 (0.5–19.4)	5.6 (3.0–10.2)	14.9 (3.6–44.9)	.002

PU
[a] P
stu
SE

lustering by
unadjusted

APD (mm) in T2	≤7	7-10	≥10
APD (mm) in T3	≤9	9-15	≥15

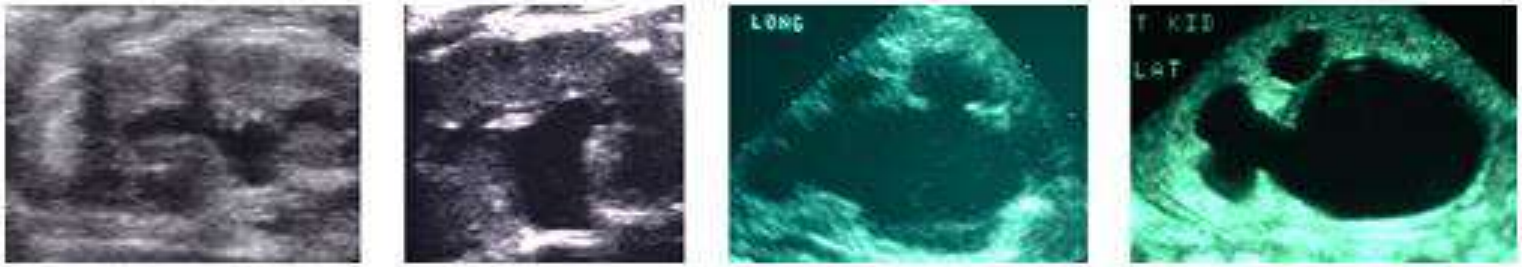
[b] Testing for trend in risks with increasing degree of ANH using logistic regression with robust SEs based on generalized estimating equations with a working independence correlation structure.
[c] Includes prune belly syndrome, VATER syndrome, solitary kidney, renal mass, and unclassified.

12% for mild; 45% for moderate; 88-90% for severe ANH

Exceptions: VUR, distal ureteral obstruction

Pediatrics 2006; 118: 586-93

Society of Fetal Urology grading system for hydronephrosis



Good intra-rater, but modest inter-rater, reliability

Grade	Renal pelvis	Parenchymal thickness
0	Intact	Normal
I	Mild splitting	Normal
II	Moderate splitting (confined to renal border) +/- dilatation of major calyces	Normal
III	Marked (outside renal border, dilatation ofminor calyces)	Normal
IV	Pelvicalyceal dilatation	Thin

Segmental (4A); diffuse (4B) cortical thinning

Pediatr Radiol 1993; 23: 478-80; Keays, J Urol 2008; 180:1680

Defining fetal hydronephrosis

Urinary tract Dilation (UTD) classification: 2014

Multidisciplinary Consensus: 8 Academic Societies

American College of Radiology
Society for Pediatric Urology
Society for Fetal Urology
Society for Pediatric Radiology
American Institute of Ultrasound in Medicine
American Society of Pediatric Nephrology
Society for Maternal–Fetal Medicine
Society of Radiologists in Ultrasound

	Antenatal	
	UTD A1	UTD A2-3
Anterior Posterior Renal Pelvic Diameter (APRPD)	4 - <7 mm (<28w) 7 - <10 mm (≥28w)	≥ 7 mm (<28w) ≥ 10 mm (≥28w)
		OR
Calyces		Any Dilation
		OR
Ureter		Any Dilation *(with APRPD ≥ 4mm or calyceal dilation)*
		OR
Parenchyma Abnl, Bladdder Abnl, or Oligohydramnios		Yes *(with APRPD ≥ 4mm or calyceal dilation)*

	16–27 weeks	≥28 weeks	Postnatal (>48 h)
Anterior-Posterior Renal Pelvis Diameter (APRPD)	<4 mm	<7 mm	<10 mm
Calyceal dilation			
Central	No	No	No
Peripheral	No	No	No
Parenchymal thickness	Normal	Normal	Normal
Parenchymal appearance	Normal	Normal	Normal
Ureter (s)	Normal	Normal	Normal
Bladder	Normal	Normal	Normal
Unexplained oligohydramnios	No	No	NA

Parenchyma abnormalities: cortical thinning, hyperechogenicity, or cystic dysplasia; indistinct corticomedullary differentiation

Bladder abnormalities: wall thickening, ureterocele, dilated posterior urethra

J Pediatr Urol 2014; 10: 982-99

#2A:Additional Evaluation

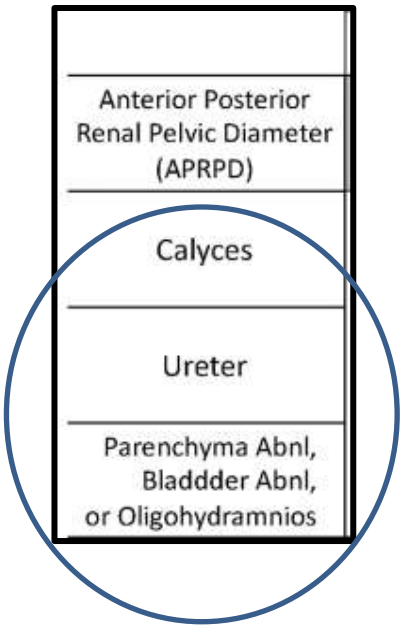
Lower urinary tract obstruction, renal dysplasia

2013

Features suggesting LUTO*; dysplasia

- **Bilateral hydronephrosis**
- **Dilated, thick-walled bladder**
- **Dilated posterior urethra**
- ?Key hole sign
- **Oligohydramnios**
- **Renal echogenicity**
- **Thin cortex**
- **Kidney cysts**

Captured in UTD



*Posterior urethral valves, urethral atresia

2013

#2B: Additional Evaluation

Look for soft signs or major anomaly on level II ultrasound

Increased risk of fetal aneuploidy
Thickened nuchal fold
Echogenic bowel
Mild ventriculomegaly
Echogenic focus in the heart
Choroid plexus cyst
Increased risk of non-chromosomal abnormalities
Single umbilical artery
Enlarged cisterna magna
Pyelectasis (APD 5-10 mm)*

ANH is associated with an increased risk of aneuploidy if there is *one* major structural anomaly or any *one additional* soft sign

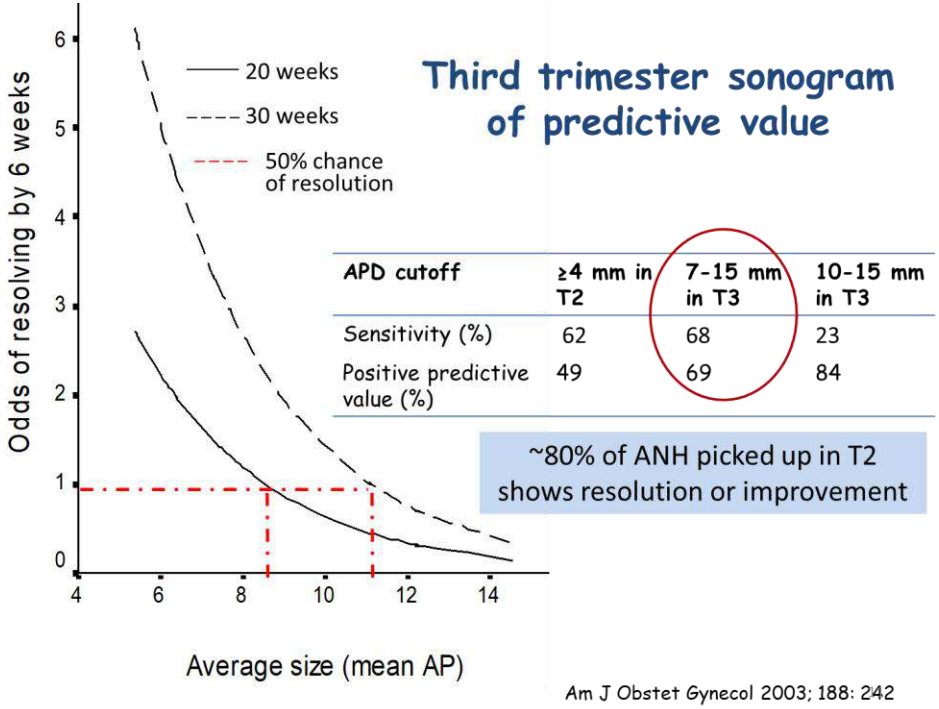
If any of above present, refer for genetic counseling and prenatal testing (karyotype, fetal ECHO) (1C)

Termination of pregnancy **not** recommended for unilateral or bilateral antenatal hydronephrosis, except in presence of extrarenal life threatening abnormality **(1D)**

SOGC Clinical Practice Guidelines. J Obstet Gynaecol Can 2005;27:592-612

2013

#3:Frequency of evaluation



APD cutoff	≥4 mm in T2	7-15 mm in T3	10-15 mm in T3
Sensitivity (%)	62	68	23
Positive predictive value (%)	49	69	84

Am J Obstet Gynecol 2003; 188: 242

Unilateral hydronephrosis

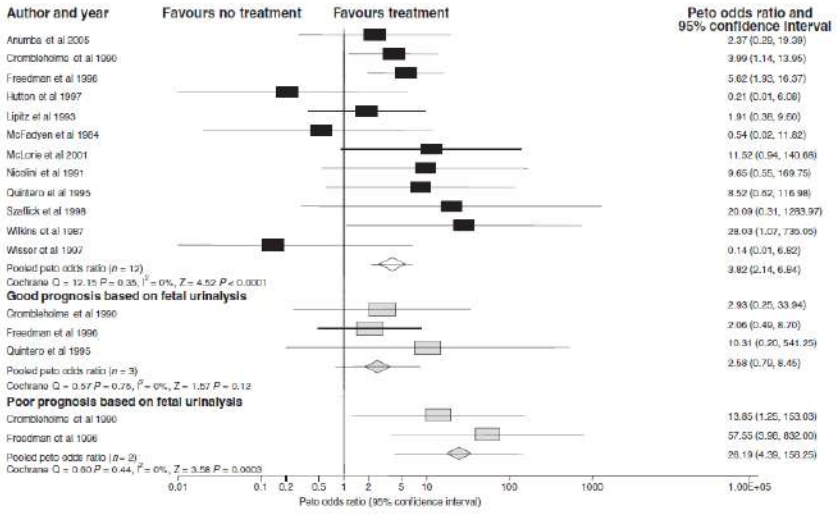
Recommend at least one ultrasound in third trimester (**1B**)

Bilateral hydronephrosis

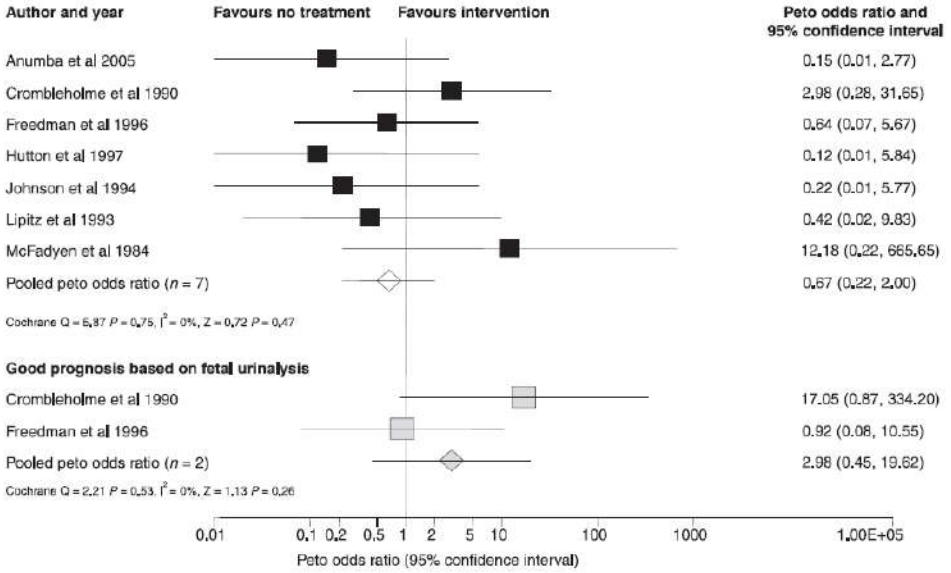
Suggest monitoring frequently, q 2-6 weeks, depending on gestation, severity, oligohydramnios (**2C**)

#4: Fetal intervention for LUTO

Perinatal survival



Postnatal survival with normal renal function



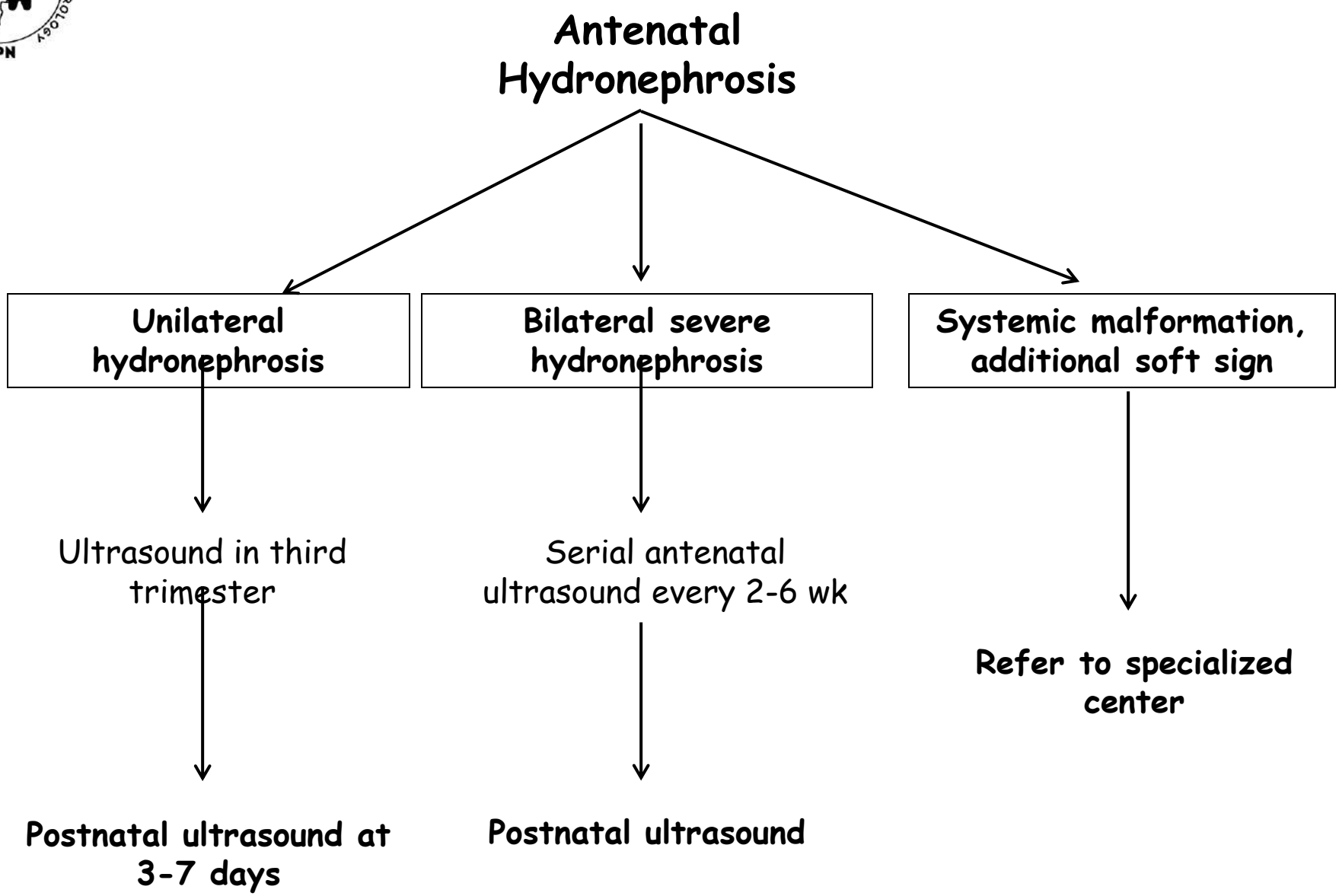
Risks: Preterm labour; fetal loss; chorioamnionitis; catheter displacement

Long term renal function: High risk of ESRD

Consider diagnostic and therapeutic interventions for suspected LUTO and oligohydramnios only at specialized centers, following one-to-one counseling (**2A**)

BJOG. 2010 Mar;117(4): 382-90.

2013


Antenatal Hydronephrosis
Unilateral hydronephrosis
Bilateral severe hydronephrosis
Systemic malformation, additional soft sign
Ultrasound in third trimester
Serial antenatal ultrasound every 2-6 wk
Refer to specialized center
Postnatal ultrasound at 3-7 days
Postnatal ultrasound

#5: Postnatal ultrasound

Meta-analysis, 25 studies

Risk of postnatal pathology

- 10.8% in infants with a normal postnatal ultrasound
- 54.7% in those with persisting hydronephrosis

Normal postnatal ultrasound has an NPV of 98.9% for UTI

Hydronephrosis that resolves postnatally has satisfactory outcome

Postnatal ultrasound necessary in neonates with suspected LUTO

Considerations

Neonatal dehydration

Loss to follow up

2013

#5: Newborns with antenatal hydronephrosis (including with prenatal resolution) should have postnatal ultrasonography (1B)

	Timing
Suspected lower tract obstruction, oligohydramnios, solitary kidney, bilateral	Within 24-48 hr of birth (1C)
Unilateral hydronephrosis	Within 2-7 days (1C)

One ultrasound before discharge from the hospital

If first US normal: Confirm at 4-6 weeks of birth

Good correlation between higher grades of hydronephrosis and risk of pathology

Multiple studies; meta-analysis

29.6% with milder APD, SFU
96.3% in severe hydronephrosis

5-times more likely to stabilize if associated with SFU grade 1-2 or APD <12 mm than with SFU grade 3-4 or APD >12 mm

J Pediatr Urol 2011;7:128-36
Pediatr Nephrol 2006;21:218-24

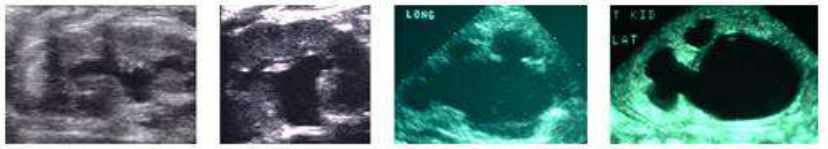
#6: Grading the severity of Neonatal Hydronephrosis

2013

APD based

No	**<7 mm**
Mild	**7-10** mm
Moderate	**10**-15 mm
Severe	≥15 mm

Society of Fetal Urology grading system for hydronephrosis



Grade 1 Grade 2 Grade 3 Grade 4

Grade 0: no dilation (not shown). Grade 1: renal pelvis is only visualized. Grade 2: renal pelvis as well as a few, but not all, calyces are visualized. Grade 3: virtually all calyces are visualized. Grade 4: similar to Grade 3 but, when compared to the normal centralateral kidney, there is parenchymal thinning.

2023

	Postnatal *(>48h)*		
	UTD P1	UTD P2	UTD P3
Anterior Posterior Renal Pelvic Diameter (APRPD)	10 - <15 mm	≥ 15 mm	≥ 10 mm
	OR	OR	OR
Calyces	Central Dilation	Peripheral Dilation	Any Dilation
		OR	
Ureter		≥ 4 mm *(with APRPD ≥ 10mm or calyceal dilation)*	
Parenchyma Abnl, Bladdder Abnl, or Oligohydramnios			AND Yes

#6: Grading the severity of Neonatal Hydronephrosis

2013

2023

Abnormal: SFU grade ≥1 or APD ≥7 mm or UTD P1-3

Mild if SFU 1-2 or APD 7-15 mm or UTD P1
Severe if SFU 3-4 or APD >15 mm or UTD P2-3

Suggest assessment of severity by the **UTD** classification rather than based on APD or proposed by SFU

Suggest including evaluation for calyceal or ureteric dilation, cortical cysts and enhanced renal echogenicity, and bladder wall abnormalities **(2D)**

#7: Postnatal monitoring

Recommend repeating ultrasound at 4-6 weeks for newborns with normal ultrasound in the first week of life (1C)

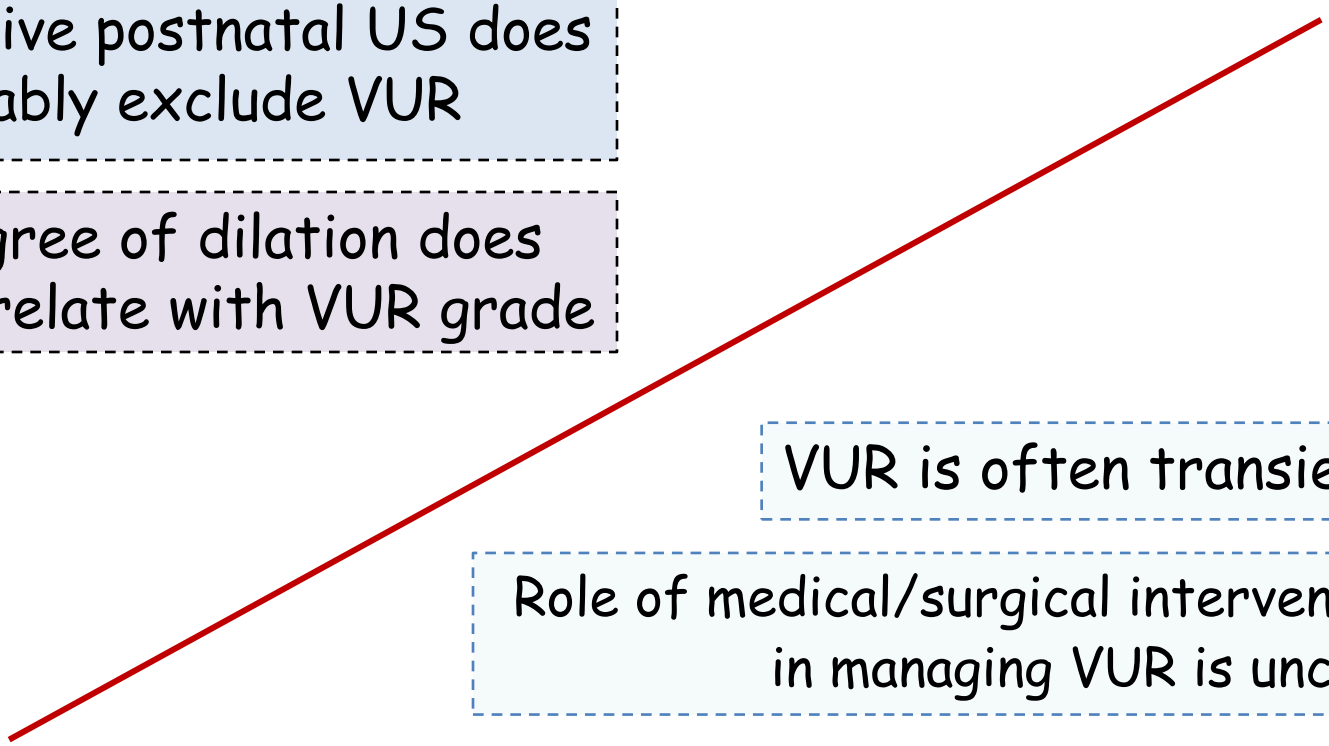
Recommend following neonates with **isolated <u>mild</u>** unilateral or bilateral **hydronephrosis** with sequential ultrasound alone, till resolution (1C)

2013	2023
APD 7-10 mm SFU 1-2	UTD 0-1 APD <10-15 mm SFU 1-2

Vesicoureteric reflux in 10-20% cases

A negative postnatal US does not reliably exclude VUR

The degree of dilation does not correlate with VUR grade



VUR is often transient

Role of medical/surgical intervention in managing VUR is unclear

Patients with two normal postnatal ultrasounds do not benefit from MCU

Pediatr Radiol 1997; Arch Dis Child Fetal Neonatal Ed 1999; Arch Dis Child 2002; Pediatr Nephrol 2005

#8: Micturating cystourethrography, if:

Bilateral hydronephrosis

Hydronephrosis in solitary kidney

Abnormal bladder, suspected lower tract obstruction

Within 24-48 hr

(1D)

Dilated ureter, dilated calyces

Ureterocele, duplex system

Moderate-severe unilateral hydronephrosis

Between 4-6 wk

(1B)

2013	2023
APD >10 mm SFU 3-4	UTD 2-3 APD >15 mm SFU 3-4

Renal dynamic scan: detects obstruction

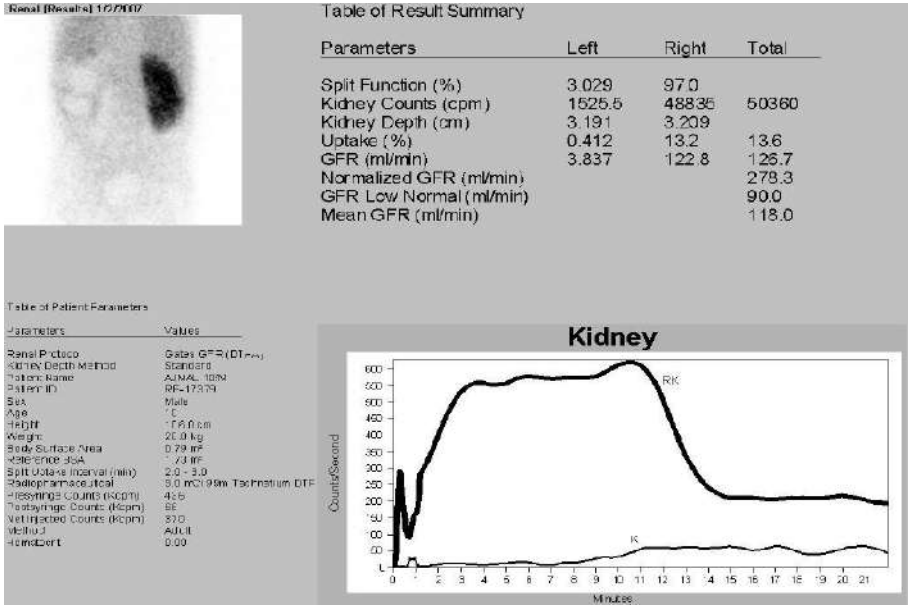
Unilateral moderate-severe hydronephrosis, calyceal/ureteric dilatation
Bilateral hydronephrosis

At ≥6 weeks; if MCU normal

Well-tempered diuresis renogram

Tc-MAG3 or Tc-DTPA

Differential function
Severity of obstruction



#9: Renal dynamic scan

Recommend diuretic renography for infants with moderate to severe unilateral or bilateral hydronephrosis (**UTD 2-3**, SFU 3-4, APD **>10-15** mm) who do not show VUR on MCU **(1C)**

Suggest diuretic renography for infants with hydronephrosis and dilated ureter(s) and no evidence of VUR **(2C)**

Use ^{99m}Tc-MAG3, ^{99m}Tc-EC or DTPA (**2D**)

Estimate differential function, inspect curve for pattern of drainage

Suggest to perform diuretic renography after 6-8 weeks of age **(2D)**

Suggest to repeat the procedure after 3-6 months if ultrasound shows worsening of pelvicalyceal dilatation **(2D)**

#10: Indications for surgery

Posterior urethral valve

Ureterocele

Ectopic ureter with reflux, obstruction

PUJ obstruction with low differential function

Solitary kidney with obstruction

Bilateral obstruction

Grade III-V VUR with breakthrough febrile UTI or new scars despite antibiotic prophylaxis

2023: Guidance on management of PUV, PUJ obstruction

#11: Antibiotic prophylaxis

Recommend

Vigilance of all infants with antenatal hydronephrosis: Risk of UTI; need prompt management (**1B**)

✓ Postnatally confirmed moderate to severe hydronephrosis (**UTD 2-3,** SFU 3-4; renal APD >10 mm) or dilated ureter while awaiting evaluation (**1C**)

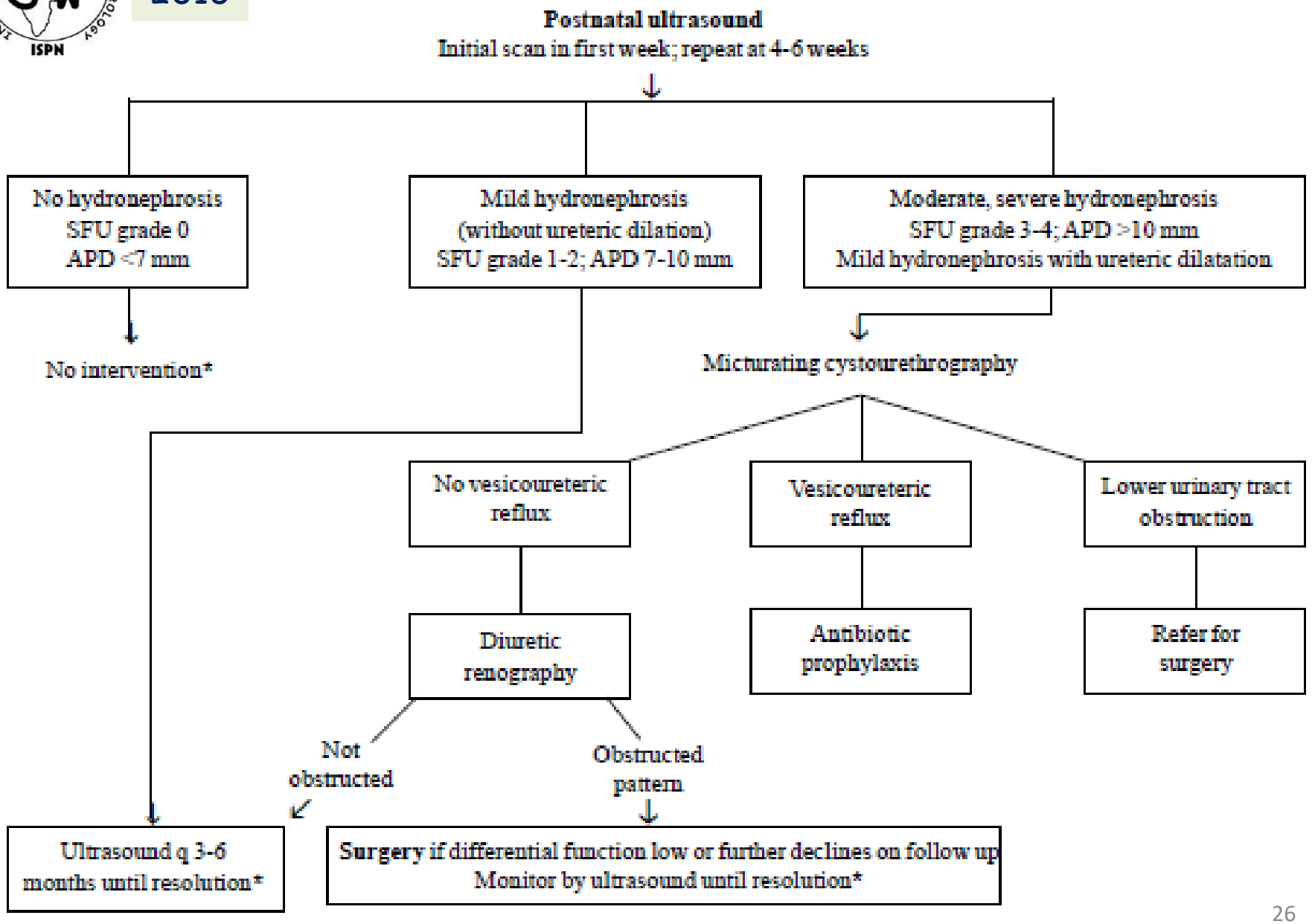
✓ All infants with VUR (by MCU), through the first year of life (**1B**)

ISPN 2022

Recommend <1-yr-old with VUR III–V identified through screening

May consider in <1-yr-old with VUR I–II identified through screening

2013


Postnatal ultrasound
Initial scan in first week; repeat at 4-6 weeks
No hydronephrosis
SFU grade 0
APD <7 mm
Mild hydronephrosis
(without ureteric dilation)
SFU grade 1-2; APD 7-10 mm
Moderate, severe hydronephrosis
SFU grade 3-4; APD >10 mm
Mild hydronephrosis with ureteric dilatation
No intervention*
Micturating cystourethrography
No vesicoureteric reflux
Vesicoureteric reflux
Lower urinary tract obstruction
Diuretic renography
Antibiotic prophylaxis
Refer for surgery
Not obstructed
Obstructed pattern
Ultrasound q 3-6 months until resolution*
Surgery if differential function low or further declines on follow up
Monitor by ultrasound until resolution*

2023

Postnatal ultrasound

Initial scan in first week; repeat at 4-6 weeks

UTD P0
No hydronephrosis (APD <10 mm) or additional renal abnormalities[1]

UTD P1
APD 10-15 mm without additional renal abnormalities[1]

UTD P2
APD ≥15 mm or peripheral calyceal dilatation without additional renal abnormality[1]

UTD P3
APD ≥10 mm with any additional renal abnormality[1]; antenatal oligohydramnios (UTD A2-3)

No intervention[2]

Ultrasound q 3-12 months follow up until resolution

Ultrasound q 3-12 months follow up until resolution

Micturating cystourethrography[3]

Normal

VUR

LUTO

Normal

DTPA/MAG3 scintigraphy[4]

Antibiotic prophylaxis[5]

Pediatric surgery consultation

Obstructive pattern; low differential function)

Guidelines on ANH: 2023 *versus* 2013

Definitions and grading: APD/SFU *versus* UTD

Similar intensity of antenatal monitoring and screening; no role for fetal interventions

Fewer indications for MCU & antibiotic prophylaxis

Best practices for MCU and scintigraphy

Management of individual entities refined

Congenital solitary kidney

Agenesis: Absent kidney absent on antenatal ultrasound at 18-22 weeks POG; confirmed postnatally

Aplasia: Rudimentary kidney on antenatal ultrasound at 18-22 weeks POG, with relative function <5% on postnatal DMSA

MCDK: Multiple non-communicating cysts of various sizes within a lobulated renal contour, pelvis and parenchyma not visible on postnatal ultrasound

Undefined CSK: Detection of an empty kidney fossa in the third trimester of pregnancy or after birth, with uncertain differential diagnosis

Pediatric Nephrology 2022; 37: 2185–2207

Congenital solitary kidney:

Additional renal and extrarenal anomalies in 1 in 3 cases

Author, year	Number of pts	CSK type (%)	Associated CAKUT, %	Total VUR, %	VUR grades III–V, %	UPJO, %	VUJO, %
Schreuder M. (2009) [1]*	3557	MCDK (100)	31.3 (of 2415 pts)	15 (of 2104 pts)	8	4.8 (of 2159 pts)	NR
Westland R. (2013) [2]*	1093	UKA (100)	32	24 (of 770 pts)	NR	6 (of 615 pts)	7 (of 605 pts)
La Scola C. (2016) [7]	146	MCDK (38), UKA (29), UKAP (16), Undefined (18)	21	11.5	10	2	3
Ross I. (2015) [42]	138	MCDK (63), UKA (37)	NR	36	17	NR	NR
Marzuillo P. (2017)[31]	322	MCDK (48), UKA (52)	14.6	9.3	5.6	0.3	4
Brown C. (2019) [43]	165	MCDK (100)	33	17 (of 77 pts)	NR	NR	NR
Blachman-Braun R. (2020) [41]	156	MCDK (100)	NR	16	6	NR	NR

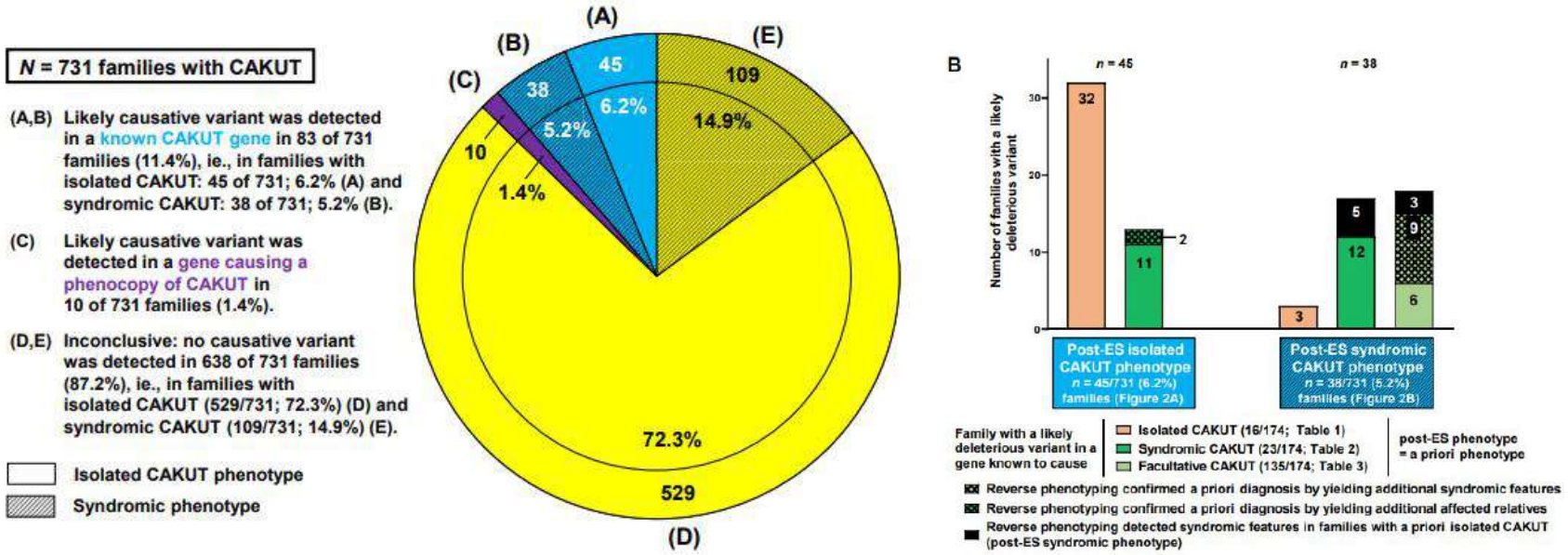
	Number of pts	Genital	Cardiac	Musculo-skeletal	Inguinal hernia	Haemato-poietic	Eye	Nervous	Endocrine	Gastro-intestinal	Respiratory	Syndromes	Total***
Schreuder M. (2009) [1]*	1340	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	**14.9%**
Mansoor O. (2011) [34]	101	-	3%	-	-	-	-	-	-	-	-	3%	**6%**
Westland R. (2013) [2]*	709	11%**	14%	13%	NR	NR	NR	NR	NR	16%	NR	NR	**31%**
La Scola C. (2016) [7]	146	9%	7.5%	7.5%	2%	1.4%	-	6.1%	5.5%	3.4%	1.4%	10.3%	**26%**
Groen in't Wood S. (2016) [50]	49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	**12.2%**
Marzuillo P. (2017) [31]	322	3.4%	3.1%	0.3%	1.2%	0.6%	0.6%	-	-	-	-	1.2%	**10.5%**

Pediatric Nephrology 2022; 37: 2185–2207

Syndromes associated with congenital solitary kidney

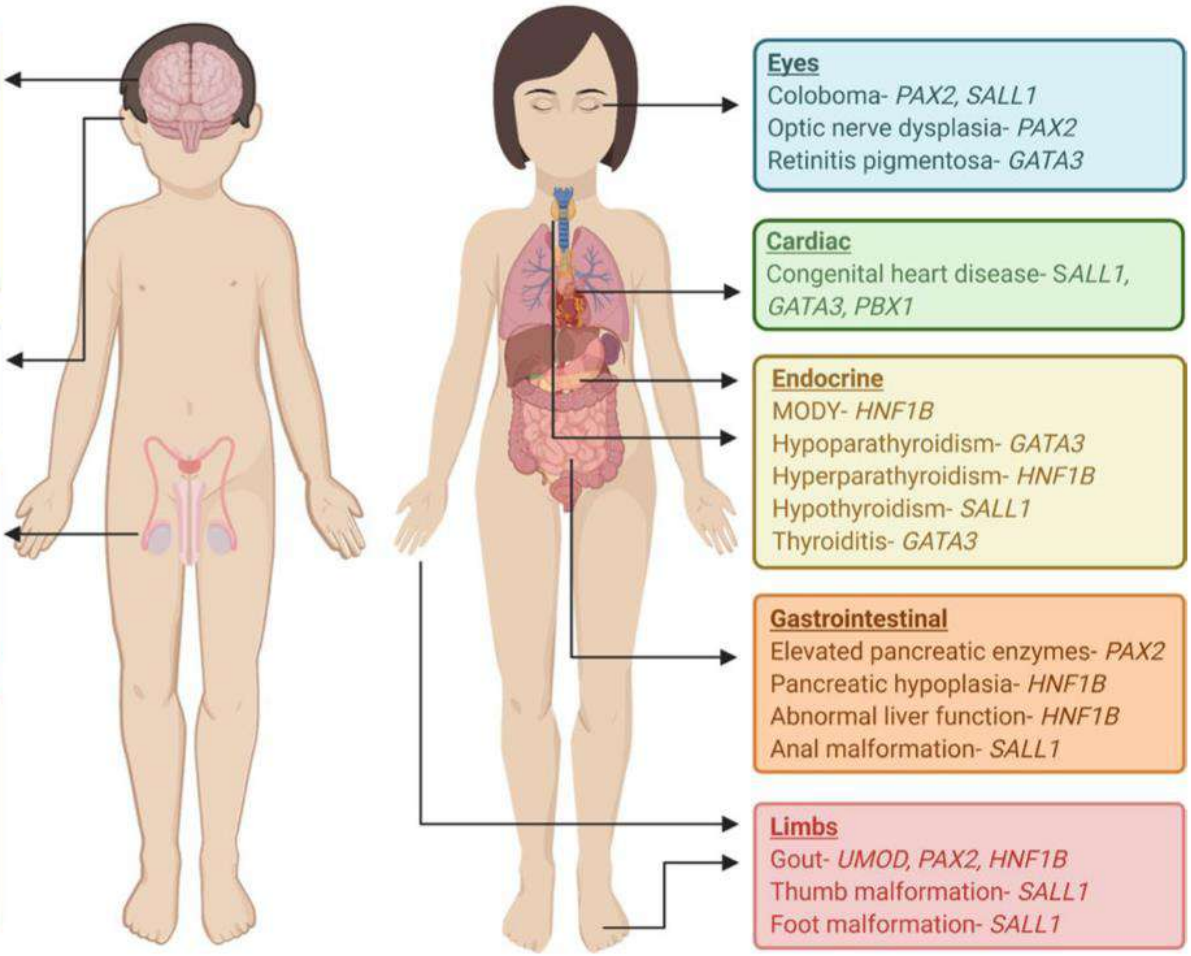
Syndrome		Extrarenal manifestations	Genes
Branchio-oto-renal	AD, except:	Sensorineural hearing loss, preauricular pits, branchial cysts, and microtia	*EYA1, SIX1, SIX5*
DiGeorge		Congenital heart disease, hypocalcaemia, immunodeficiency, and neurocognitive disorders	22q11 deletion
Fraser	AR	Cryptophthalmos, cutaneous syndactyly, occasionally malformations of the larynx, ambiguous genitalia, and mental retardation	*FRAS1, FREM2*
Herlyn-Werner-Wunderlich or OHVIRA (obstructed hemivagina and ipsilateral renal agenesis)		Obstructed hemivagina and uterus didelphys	Unknown
Kallmann 1	XR	Micropenis, bilateral cryptorchidism, and anosmia	*KAL1*
Klinefelter	Sporadic	Small, firm testis, gynaecomastia, azoospermia, and hypergonadotropic hypogonadism	47, XXY
MURCS (Mayer-Rokitansky-Kuster–Hauser type 2)		Müllerian duct aplasia-hypoplasia and cervicothoracic somite dysplasia	Unknown
Renal coloboma		Retinal and optic nerve coloboma	*PAX2*
Renal cysts and diabetes		Maturity-onset diabetes of the young type 5, hyperuricaemia, hypomagnesemia, and uterine malformations	*HNF1B*
Townes–Brocks		Thumb anomalies, imperforate anus, and sensorineural hearing loss	*SALL1*
VACTERL association	AR	Vertebral anomalies, anorectal malformations, cardiovascular disease, tracheoesophageal fistula, esophageal atresia, and limb defects	*TRAP1*
Williams–Beuren		Developmental delay, cardiovascular anomalies, mental retardation, and facial dysmorphology	7q11.23 deletion

Genetics in CAKUT



Genes	Clinical manifestations
HNF1β	MCDK, renal hypoplasia, renal cysts and diabetes syndrome
PAX2	Renal hypoplasia, VUR, renal coloboma, FSGS
SIX1/ SIX5	Renal hypodysplasia, VUR, branchio-oto-renal syndrome
SALL1	Townes-Brooks syndrome
GATA3	Renal dysplasia, Hypoparathyroidism-deafness-renal dysplasia syndrome
FREM2/ FRAS1	Renal agenesis, Fraser syndrome

Main extra-renal manifestations associated with monogenic CAKUT



CNS
Autism, Schizophrenia- 17q12 del, *GATA3*
Developmental delay- *PAX2, PBX1*
CNS malformations- *PAX2, SALL1, PBX1*
Cerebral infarction- *GATA3*
Basal ganglia calcifications- *GATA3*

Ears
Hearing loss- *PAX2, EYA1, SALL1, PBX1*
Dysplastic ear- *EYA1, SALL1, PBX1*

Genitourinary
Polycystic ovaries - *GATA3*
Urogenital anomalies- *HNF1B, SALL1, GATA3*
Cryptorchidism- *PBX1*
Hypomagnesemia- *HNF1B*

Others
Branchial fistula or cysts- *EYA1*
IUGR- *HNF1B, PBX1*
Palate abnormalities- *EYA1*
Skeletal defects- *PBX1, PAX2*
Diaphragm malformations, lung hypoplasia- *PBX1*

Eyes
Coloboma- *PAX2, SALL1*
Optic nerve dysplasia- *PAX2*
Retinitis pigmentosa- *GATA3*

Cardiac
Congenital heart disease- *SALL1, GATA3, PBX1*

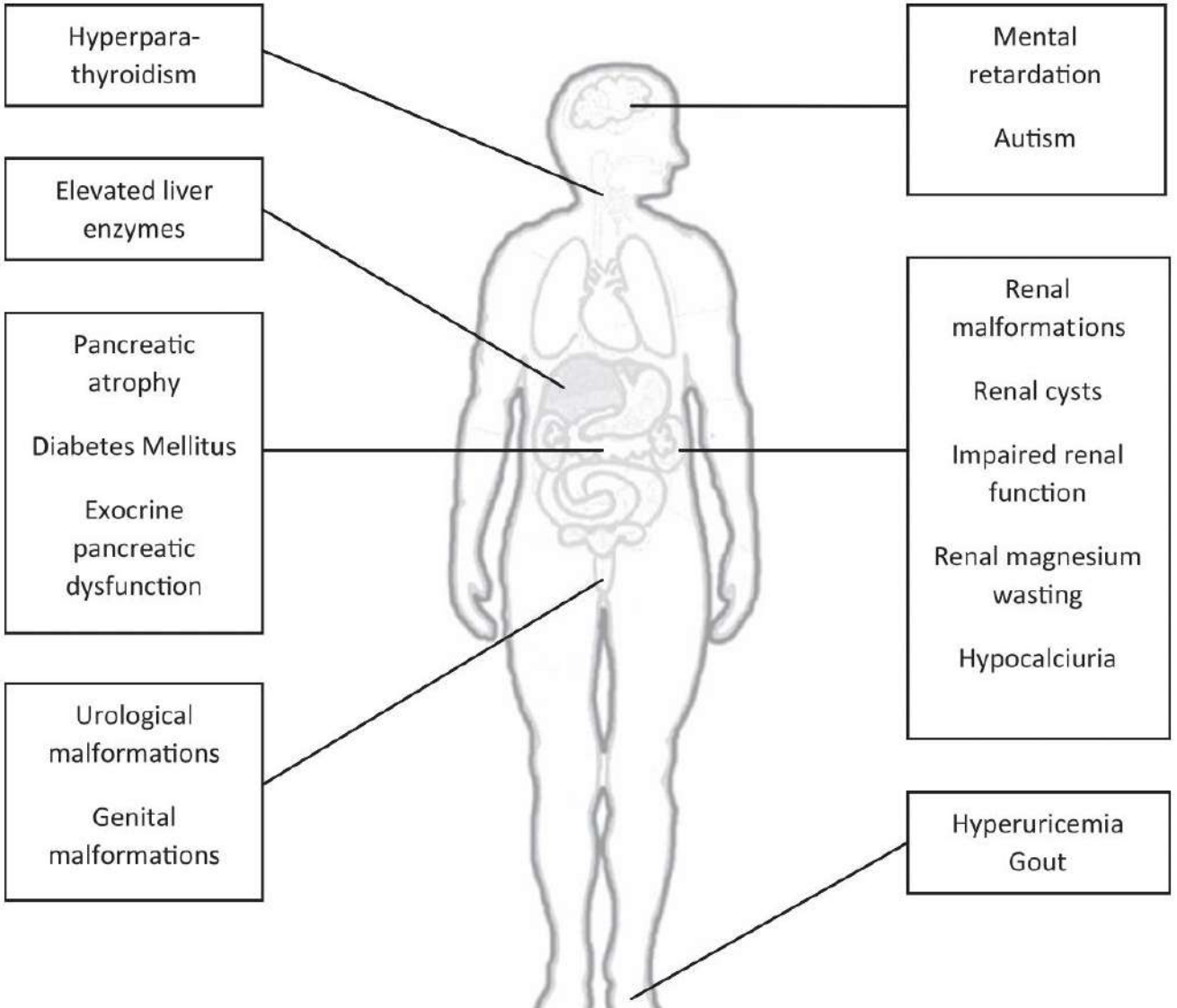
Endocrine
MODY- *HNF1B*
Hypoparathyroidism- *GATA3*
Hyperparathyroidism- *HNF1B*
Hypothyroidism- *SALL1*
Thyroiditis- *GATA3*

Gastrointestinal
Elevated pancreatic enzymes- *PAX2*
Pancreatic hypoplasia- *HNF1B*
Abnormal liver function- *HNF1B*
Anal malformation- *SALL1*

Limbs
Gout- *UMOD, PAX2, HNF1B*
Thumb malformation- *SALL1*
Foot malformation- *SALL1*

HNF1B-related kidney disease: Diverse phenotypes

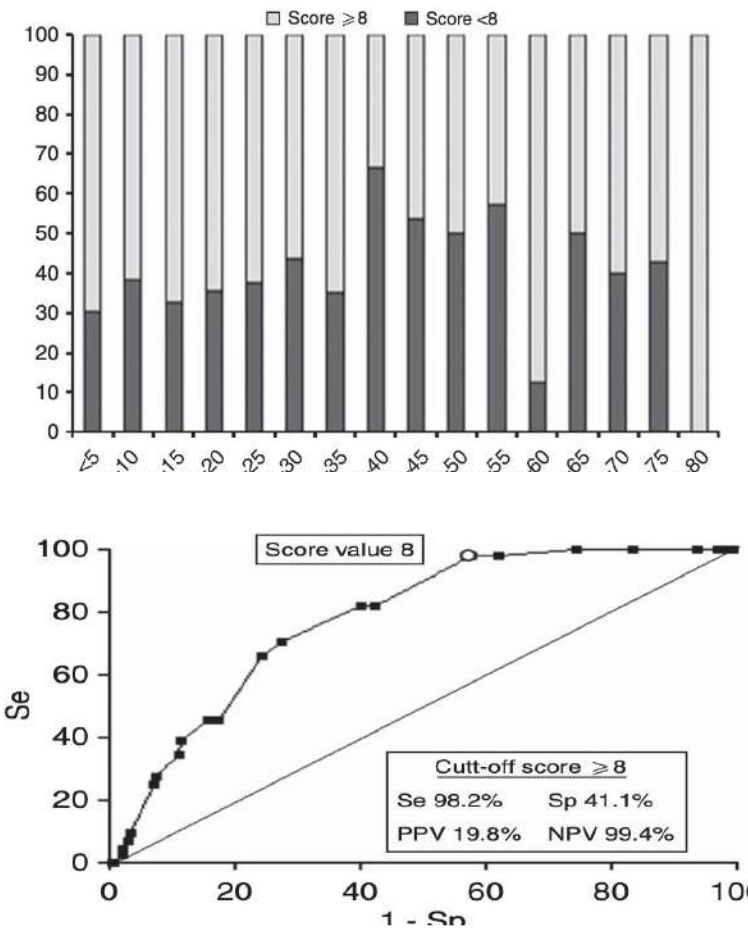
Family history (renal cysts and diabetes); hyperuricemia, hypomagnesemia



When to suspect *HNF1B-related* kidney disease?

HNF1B score

Characteristics	Item	Value
Family history		+2
Antenatal renal abnormalities	Uni/bilateral abnormality by renal echography	+2
Kidneys and urinary tract		
Left kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Right kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Electrolyte or uric acid disorders	Low serum Mg^{2+} (<0.7 mmol/l)	+2
	Low serum K^{+} (<3.5 mmol/l)	+1
	Early-onset gout (>30 years of age)	+2
Pathological findings	Oligomeganephronia or glomerular cysts	+1
Pancreas[a]	MODY or hypoplasia of tail and neck of the pancreas or pancreatic exocrine insufficiency	+4
Genital tract	Genital tract abnormality[b]	+4
Liver	Live test abnormalities of unknown origin[c]	+2



Kidney International 2014

Embryological classification of female genital malformations

Agenesis (or hypoplasia) of a urogenital ridge

Ipsilateral **absence of kidney**, ovary, Fallopian tube, hemiuterus & hemivagina

Mesonephric anomalies

(Absent opening in the urogenital sinus; non-development of corresponding ureteral bud; lack of inductor function of the mesonephric duct on uterus)

Unilateral renal agenesis, ipsilateral blind vagina; +/- ectopic ureter (with renal hypoplasia) opening into the blind vagina

Isolated Mullerian anomalies

(Probably also induced by minor mesonephric defect)

- Paramesonephric ducts: uterine and/or tuba! anomalies
- Mullerian tubercle: agenesis or atresia of the vagina
- All paramesonephric derivatives: Rokitansky-Kuster Hauser syndrome
- Anomalies of urogenital sinus: Persistent urogenital membrane (imperforate hymen)
- Combinations of the above malformations

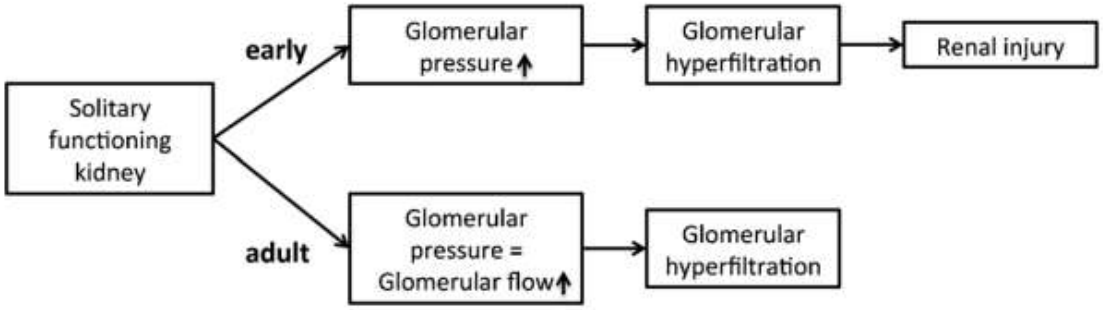
Hum Reprod 1992;7: 437-45

Adverse kidney outcomes in CSK quite common

10 studies; 2051 patients, assessed in childhood

Studies	GFR reduction (eGFR < 90)	Proteinuria#
Vu K.H 2008	10.7%	7.7%
Abou Jaoude P. 2011	11.4%	18%
Mansoor O. 2011	9.7%	17%
Hayes W.N 2012	43%	-
Westland R 2013	4%*	13%
Kolvek G 2014	11%*	7.4%
Siomou E 2014	44.7%	-
Le Scola C 2016	12%	4%
Marzuillo P 2017	1.3%	3.6%
Urisarri A 2018	2.3%*	3%

*eGFR reduction < 60 ml/1.73 m^2/min; #Assessed using various definitions of albuminuria/ protein creatinine ratio



Hypertension in congenital solitary kidney

10 studies, 381 patients at average age 8-13 years
Clinic hypertension: 7-33%
Ambulatory hypertension: 7-46%
Masked hypertension: 4-26%
White coat hypertension: 9-26%
Abnormal dipping: 14-82%

Author, year	N	Age at ABPM (yrs)	OBP hypertension	ABPM hypertension	Masked hypertension	WCH	Abnormal dipping
Seeman T. (2001) [70]	25	7.8 (3.8–17.7)	8/25 (33%)	5/25 (20%)	1/25 (4%)	4/25 (16%)	5/25 (20%)
Mei-Zahav M. (2001) [85]	18	9.6 ± 3.9	NR	NR	NR	NR	0/18
Seeman T. (2006) [28]	15	10.0 (4–17)	5/15 (33%)	1/15 (7%)	0/15	4/15 (26%)	2/15 (14%)
Dursun H. (2007) [71]	44	8.3 ± 4.2	NR	10/44 (23%)	NR	NR	13/44 (29.5%)
Westland R. (2014) [72]	28	12.5 ± 3.6	2/28 (7%)	7/28 (25%)	5/28 (18%)	0/28	8/28 (29%)
Tabel Y. (2015) [73]	44	10.9 ± 3.3	NR	19/44 (43%)	NR	NR	NR
Lubrano R. (2017) [74]	38	About 14.5	11/38 (29%)	11/38 (29%)	0/38	0/38	NR
Zambaiti E. (2018) [32]	50	9.5 ± 4.2	10/50 (20%)**	23/50 (46%)***	NR	NR	41/50 (82%)
La Scola C. (2020) [37]	81	11.8 ± 4.7	13/81 (16%)	27/81 (33.3%)	21/81 (25.9%)	7/81 (8.6%)	51/81 (64%)
Kasap-Demir B. (2021)[75]	36	11 ± 4.75	10/36 (28%)	7/36 (19%)	5/36 (14%)	8/36 (22%)	NR

Antenatally detected congenital solitary kidney

Antenatal

Classification, based on T2 and T3 ultrasound
(Agenesis, hypoplasia or MCDK)
Level II ultrasound for extrarenal anomalies; syndromic findings
If abnormal: Referral to consider ***fetal karyotype*** or ***microarray***
If abnormal: Referral to consider termination of pregnancy

Postnatal

Physical exam for extrarenal anomalies; syndromic findings
Follow-up ultrasound at 1 month
Contralateral kidney: Compensatory hypertrophy, echogenicity, hydronephrosis, cysts, ureter, bladder; genital tract anomalies
If abnormal: Consider **micturating cystourethrography**
Risk stratification

After thelarche and before menarche, in girls

Pelvic ultrasound
If abnormal: **III D ultrasound** or **magnetic resonance imaging**

J Pediatr Urol; doi: 10.1016/j.jpurol.2018.01.011

Congenital solitary kidney (CSK): Recommendations of the Italian Society of Pediatric Nephrology 2022

Low risk
CSK with compensatory enlargement

Medium risk
CSK without compensatory enlargement and/or additional CAKUT

High risk
Decreased GFR and/or proteinuria, and/or hypertension.

	Low risk*	Medium risk*		High risk*
		Without CAKUT	With ipsilateral CAKUT	
Setting	Primary pediatric care[1]	Pediatric nephrologist[1]/pediatric nephrology unit		Pediatric nephrology unit
Ultrasound[2]	Yearly until 3 years of age, then every 5 years	Yearly until 3 years of age, then every 3 to 5 years	Further work-up depending on additional ipsilateral CAKUT findings	According to kidney function and clinical data
Proteinuria by urinalysis[3]	Yearly until 3 years of age, then every 5 years	Yearly		
Office Blood pressure	Yearly ≥ 3 years	Yearly		
Serum creatinine/eGFR	Not necessary	Yearly		
Abdominopelvic ultrasound in girls	Between thelarche and menarche	Between thelarche and menarche		Between thelarche and menarche

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