Overview of congenital anomalies of the kidney and urinary tract (CAKUT)

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INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) constitute approximately 20 to 30 percent of all anomalies identified in the prenatal period [1]. Defects can be bilateral or unilateral, and different defects often coexist in an individual child.

An overview of CAKUT is presented here. The antenatal screening and postnatal evaluation of infants with CAKUT are discussed in greater detail separately. (See "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT)" and "Congenital ureteropelvic junction obstruction" and "Primary megaureter in infants and children" and "Ectopic ureter" and "Renal ectopic and fusion anomalies" and "Autosomal recessive polycystic kidney disease in children".)

ASSOCIATION WITH END-STAGE KIDNEY DISEASE (ESKD)

Because CAKUT play a causative role in 30 to 50 percent of cases of chronic kidney disease requiring kidney replacement therapy in children [2], it is important to diagnose these anomalies and initiate therapy to minimize kidney damage, prevent or delay the onset of end-stage kidney disease (ESKD), and provide supportive care to avoid complications of ESKD. Patients with malformations involving a reduction in kidney numbers or size are most likely to have a poor kidney prognosis [3]. (See 'Renal development and CAKUT' below and "Chronic kidney disease in children: Overview of management".)

EMBRYOLOGY

Normal embryology — Normal embryologic development of the kidney occurs in three stages (figure 1). Of note, in this discussion, embryonic age begins at conception and not at last menstrual period.

- Pronephros – Transient rudimentary and nonfunctioning system that begins in the fourth week of embryogenesis (ie, day 22) and disappears by end of the fourth week (ie, day 28). Degeneration of the pronephros is required for normal kidney development.
- Mesonephros – Derived from the intermediate mesoderm by day 26 and by the fifth week of embryogenesis develops into 20 paired tubules that produce small amounts of urine. The mesonephros ultimately fuses with the cloaca and contributes to the formation of the urinary bladder, and in the male, the genital system is derived from the mesonephric ducts and some tubules.
- Metanephros – The metanephros, which is composed of the metanephric mesenchyme and ureteric bud epithelium (caudal portion of the mesonephric duct), is the last stage of kidney development and forms the permanent kidney beginning at the fifth week of embryonic age.

Metanephros — The metanephros is the final stage of kidney development. It is first detected at five to six weeks of embryogenesis and begins to function at 6 to 10 weeks, with urine production beginning at nine weeks of embryonic age. The metanephros is initially positioned in the pelvis opposite the sacral somites and migrates from its caudal position, reaching its permanent location in the lumbar region at the eighth week of embryogenesis.

Reciprocal interactions between the metanephric mesenchyme (metanephros) and the ureteric epithelium induce organogenesis, resulting in the formation of the nephrons and the collecting system of the metanephric system [4]. This process is dependent on the coexpression of a number of signaling and transcription factors, including, but not limited to, Gdnf (glial-cell-line-derived neurotrophic factor) and its cognate receptor complex, RET/GFRa 1, Osr1, Eya1, Isl1, Foxc1, Pax2, Pax8, Gata3, Lim1, Gdf11, Sall1, Six1, BMP4, and WT1 [5-9].

The bladder develops from a separate, but contiguous, structure termed the urogenital sinus. The bladder is present in fetuses with renal agenesis (RA) but is empty because of absent urine production.

Renal development and CAKUT — CAKUT represent a broad range of disorders and are the result of the following abnormal renal developmental processes:

- Malformation of the renal parenchyma resulting in failure of normal nephron development, as seen in renal dysplasia, RA, renal tubular dysgenesis, and some types of nephronophthisis. Investigation utilizing molecular genetics has demonstrated that renal malformation results from defects in genes that encode signaling and transcription factors (table 1) [10-13]. Approximately 18 percent of children with CAKUT have an underlying monogenic abnormality [14]. However, not all studies demonstrate this quantitative contribution of monogenic defects to CAKUT, suggesting that the contribution of previously implicated genes to CAKUT risk was smaller than expected and development of renal malformations may be more complex than previously assumed [15]. Differences in these reports may be due in part to the variation of phenotypes represented within patient cohorts. Reviewing the results of these studies, it appears that monogenic defects have been demonstrated in 40 genes in patients with isolated forms of CAKUT and in 179 genes in patients with syndromic forms of CAKUT. Other cases, as yet defined with respect to pathogenesis, may be explained by mutations in rare genetic variants, nongenetic factors, or a complex combination of these factors.

- Environmental factors, such as prenatal exposure to teratogens, can also disrupt renal morphogenesis, resulting in CAKUT. (See 'Pathogenesis' below.)

- Abnormalities of embryonic migration of the kidneys, as seen in renal ectopy (eg, pelvic kidney), and fusion anomalies, such as horseshoe kidney. (See "Renal ectopic and fusion anomalies".)

- Abnormalities of the developing urinary collecting system, as seen in duplicate collecting systems, posterior urethral valves, and ureteropelvic junction obstruction.

EPIDEMIOLOGY

The overall rate of CAKUT in live and stillborn infants is 0.3 to 1.6 per 1000 [16-18]. The incidence is higher in offspring with a family history of CAKUT and maternal history of either kidney disease or diabetes [19,20].

Of all antenatal kidney anomalies, the most frequent abnormality is hydronephrosis (ie, upper urinary tract dilatation). The prevalence of different CAKUT is shown in the table (table 2) [17]. Kidney malformations are associated with nonrenal congenital anomalies in approximately 30

percent of cases [17]. A combination of CAKUT and nonrenal anomalies are found in more than 200 described syndromes [21].

KIDNEY PARENCHYMAL MALFORMATIONS

Malformations of the kidney parenchyma result in failure of normal nephron development, as seen in renal dysplasia, renal agenesis (RA), renal tubular dysgenesis, and cystic dysplasia.

Pathogenesis — The pathogenesis of kidney parenchymal malformations is thought to be multifactorial, involving genetic and environmental factors [12,22-25].

- **Genetic factors** – Several genes and epigenetic factors have been implicated in the pathogenesis of kidney malformations (table 1).
  - Examples specific anomalies and associated genes variants include:
    - Bilateral renal agenesis is associated with homozygous loss-of-function variants in *GFRA1* [26] and *NPNT* (nephronectin) [27].
    - Renal hypodysplasia is associated with variants in genes expressed during kidney development, including *EYA1* and *SIX1* (branchio-oto-renal syndrome), *FRAS1* (Fraser syndrome), *PAX2* (renal-coloboma syndrome), *SALL1* (Townes-Brocks syndrome), *HFN1b* and *TCF2* (renal cysts and diabetes mellitus), *TRAP1* (VACTERL syndrome) and *DSTYK* (renal hypodysplasia, ureteropelvic junction obstructions, and vesicoureteral reflux) [13,28-32].
    - Variants in the PBX homeobox 1 gene (*PBX1*), which is involved in kidney development, were detected by targeted exome sequencing in 5 of 204 unrelated patients with CAKUT [33].
  - Genetic copy-number disorders also are commonly associated with renal hypoplasia and CAKUT, especially in individuals with neurodevelopmental delay [34].
  - Whole-exome sequencing (WES) identified recessive mutations in nine known disease-causing genes not previously thought to be involved in renal development in patients with CAKUT from consanguineous families including *ZBTB24*, *WFS1*, *HPSE2*, *ATRX*, *ASPH*, *AGXT*, *AQP2*, *CTNS*, and *PKHD1* [35]. Using WES, an autosomal dominant mutation of the nuclear receptor interacting protein 1 (*NRIP1*) gene was identified in seven affected family members with CAKUT. *NRIP1* interacts with the retinoic acid receptors to modulate retinoic acid transcriptional activity [36]. Homozygous deletions in the *CBWD1*

gene were detected by whole genome sequencing in two children with CAKUT within two generations of a single family [37].

- Cystic dysplasia can be caused by mutations of genes involved in ciliary function, as seen in patients with nephronophthisis. In contrast, other ciliary gene mutations disrupt terminal epithelial differentiation and do not have renal dysplastic elements. Such disorders include autosomal recessive and dominant polycystic kidney disease. (See 'Genetic cystic diseases' below and "Renal hypodysplasia", section on 'Genetic disorders'.)

- **Environmental factors** – Environmental effects include exposure to teratogens and nutritional deficiencies. As an example, prenatal exposure to angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) have been associated with juxtaglomerular hyperplasia, diminished or absent differentiation of proximal convoluted tubules, and increased cortical and medullary fibrosis [23,24]. The proposed mechanism for the teratogenic effect of these medications is interference of the normal upregulation of the renin-angiotensin system during kidney development. (See "Adverse effects of angiotensin converting enzyme inhibitors and receptor blockers in pregnancy".)

  Animal models have demonstrated that vitamin A deficiency is associated with urogenital malformations and renal hypoplasia [38]. Additional data generated in genetic mouse models suggest that vitamin A plays a significant role in the signaling of ureteric bud branching and the development of the ureteric-bladder connection during embryogenesis [25]. Thus, vitamin A deficiency would disrupt this process, resulting in CAKUT. The contribution of vitamin A-dependent signaling to human CAKUT remains to be defined.

Simple renal hypoplasia — Simple renal hypoplasia, which consists of a lower number of structurally normal nephrons, is an entity distinct from renal dysplasia, which is characterized by kidney parenchymal malformations. Although it remains unknown what causes renal hypoplasia, genetic determinants are thought to play a role.

The clinical diagnosis of renal hypoplasia is suggested when all of the following criteria are met [12]:

- Reduction of kidney size by two standard deviations for the mean size by age
- Exclusion of kidney scarring by 99mTc-dimercaptosuccinic acid (DMSA) radionuclide scan

Unequivocal diagnosis is based upon histologic examination, which is rarely performed. (See "Renal hypodysplasia".)

Renal dysplasia and hypodysplasia — Renal dysplasia is characterized by the presence of malformed kidney tissue elements (picture 1). Characteristic microscopic abnormalities include geographic disorganization of nephron elements, maldifferentiation of mesenchymal and epithelial elements, decreased number of nephrons, and metaplastic transformation of metanephric mesenchyme to cartilage and bone (picture 1).

Dysplastic kidneys are variable in size, but most are smaller than normal, resulting in renal hypodysplasia. Size is often determined by the presence or absence of cysts. (See "Renal hypodysplasia".)

Renal dysplasia may be unilateral or bilateral and occurs in 2 to 4 per 1000 births. The male-to-female ratio for bilateral renal dysplasia is 1.3:1 and for unilateral dysplasia is 1.9:1 [39].

Presentation and clinical findings — Renal dysplasia may be discovered during routine antenatal screening or postnatally when kidney ultrasonography is performed in a dysmorphic infant. Bilateral dysplasia is likely to be diagnosed earlier than unilateral dysplasia, especially if oligohydramnios is present. Kidney ultrasound features include increased echogenicity as a result of abnormal kidney parenchymal tissue, poor corticomedullary differentiation, and parenchymal cysts.

Infants with bilateral dysplasia may have impaired kidney function at birth, and subsequent progressive kidney failure may occur. Associated urologic findings include abnormalities of the renal pelvis, calyces (eg, congenital hydronephrosis), and ureters (eg, duplicating collecting system megaureter, ureteral stenosis, and vesicoureteral reflux [VUR]) [22]. As a result, symptomatic presentation may occur due to complications associated with these urological anomalies, including urinary tract infection (UTI), hematuria, fever, and abdominal pain.

Evaluation — Because of the frequent association of renal dysplasia with a collecting system anomaly, voiding cystourethrography may be considered in patients with renal dysplasia with or without a UTI (see "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT)", section on 'Voiding cystourethrography'). If there is an associated urologic abnormality such as VUR in the normal contralateral kidney, children with unilateral renal dysplasia may be at increased risk of long-term sequelae of kidney scarring from recurrent UTI. DMSA radionuclide scan can provide further information on the differential function of each kidney (see "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT)", section on 'Static renal scan'). For example, multicystic dysplastic kidney (MCDK) (see 'Multicystic dysplasia' below) typically has no viable functional kidney tissue and, therefore, no detectable renal blood flow or kidney function. However, there may be rare variations of segmental dysplasia. Thus, these imaging studies may be useful in defining baseline kidney function and risk of future kidney damage.

A more detailed description of the postnatal evaluation in infants with CAKUT is discussed separately. (See "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT)", section on 'Postnatal evaluation'.)

Outcome and follow-up care — The prognosis of renal dysplasia depends on whether there is unilateral versus bilateral disease. In general, the long-term outcome of unilateral renal dysplasia is excellent, particularly if there is a normal contralateral kidney. Serial ultrasonography can assess compensatory kidney growth of a normal contralateral kidney and any further change in the size of the abnormal kidney.

Similar to patients with unilateral RA, patients with renal dysplasia, especially if compensatory hypertrophy is not observed, are at risk for chronic kidney disease (CKD). In these patients, ongoing monitoring of the patient is recommended with yearly assessment of blood pressure and urinalysis. In patients with elevated blood pressure or urinary protein excretion, kidney function should be assessed by obtaining a serum creatinine to estimate the glomerular filtration rate (GFR). (See "Chronic kidney disease in children: Clinical manifestations and evaluation", section on 'Laboratory testing'.)

Multicystic dysplasia — MCDK is a nonfunctioning dysplastic kidney with multiple cysts, which is thought to arise from an alteration in kidney parenchymal differentiation (image 1 and picture 2). MCDK consists of a nonreniform mass of cysts and connective tissue and is most commonly detected by routine antenatal screening. Most infants with unilateral MCDK are asymptomatic. The clinical manifestations, management, and natural course of MCDK are discussed in greater detail separately. (See "Renal cystic diseases in children", section on 'Multicystic dysplastic kidney'.)

Unilateral renal agenesis — RA is defined as congenital absence of kidney parenchymal tissue and results from major disruption of metanephric development at an early stage. The reported incidence ranges from 0.04 to 0.05 percent [40,41]. Males are more commonly affected than females, with a male-to-female ratio of approximately 2 to 1 [41-43].

Multiple factors are thought to be implicated in the pathogenesis of RA, including mutations in genes important in kidney development (eg, *Ret* or *Gdnf*) [22] and teratogenic and environmental agents (eg, retinoic acid and cocaine exposure) [42,44,45].

Unilateral RA accounts for 5 percent of kidney malformations [17]. When a solitary kidney is detected, it is usually an incidental finding as a result of an ultrasound performed antenatally or as part of an evaluation for a UTI. Although the majority of patients are asymptomatic, unilateral RA can be accompanied by other CAKUT and nonrenal anomalies and evidence of kidney injury [40,41,43].

In a 2013 systematic review of the literature that included 43 studies with 2684 patients associated CAKUT anomalies were observed in approximately one-third of patients with solitary kidneys, of which vesicoureteral reflux was the most common finding (24 percent of patients) [40]. Extra-renal malformations were also found in approximately one-third of patients. Nonrenal-associated anomalies include malformations of the heart, genitals, bone/skeleton, and gastrointestinal and respiratory tracts [42]. Presumed RA also may actually be an ectopic dysplastic renal nubbin associated with müllerian abnormalities such as uterus didelphys.

Evaluation — The evaluation of any child with unilateral RA is focused on detecting other kidney and nonrenal anomalies and evidence of kidney injury. It includes a comprehensive history, physical examination, and kidney functional testing.

- **History**
  - History of impaired hearing or abnormal hearing test is suggestive of Branchio-oto-renal syndrome (BOR syndrome, MIM #113650), also referred to as Melnick-Fraser syndrome. BOR syndrome is an autosomal dominant genetic disorder characterized by hearing loss, branchial cysts and fistulas, ear pits, and kidney anomalies including renal aplasia. The majority of cases are caused by mutations in the *EYA1* gene, with fewer cases due to mutations in *SIX1* [46]. (See "Renal hypodysplasia", section on 'Genetic disorders'.)
  - Family history of kidney disease and deafness is suggestive of BOR syndrome.
- **Physical examination**
  - Measurements of weight, height, and blood pressure to detect any growth impairment or increased blood pressure, which may be indicative of kidney function impairment or injury.
  - Detection of other congenital anomalies, which may indicate an underlying genetic disorder, such as:
    - Coloboma – Renal-coloboma syndrome (MIM #120330) is a genetic disorder characterized by renal hypoplasia, vesicoureteral reflux, and optic nerve coloboma and is due to mutations in the *PAX2* gene. (See "Renal hypodysplasia", section on 'Genetic disorders'.)
    - Branchial defects are suggestive of BOR syndrome, as discussed above. (See "Renal hypodysplasia", section on 'Genetic disorders'.)

- Müllerian abnormalities – Müllerian defects (eg, uterine didelphys and/or vaginal duplication) are common in girls with RA because the Wolffian and müllerian ducts are contiguous [47]. These patients are 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. (See "Renal agenesis: Prenatal diagnosis", section on 'Syndromes, associations, and sequences in which renal agenesis may be present'.)

- Microphallus and/or cryptorchidism – 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. Unilateral RA is commonly found in these patients. (See "Isolated gonadotropin-releasing hormone deficiency (idiopathic hypogonadotropic hypogonadism)".)

- Other chromosomal disorders have been associated with RA including trisomies 13 and 18 and Turner syndrome. (See "Renal agenesis: Prenatal diagnosis", section on 'Syndromes, associations, and sequences in which renal agenesis may be present'.)

- **Tests**

  - Kidney ultrasound In all patients with a solitary kidney, a kidney ultrasound is the initial imaging study that measures the size of the solitary kidney and determines if there are any other kidney abnormalities. If there is no compensatory renal hypertrophy, further imaging, particularly in the pelvic area, should be performed to determine whether or not an ectopic kidney is present. In a retrospective review of 13,705 fetuses with antenatal ultrasounds, 24 of 40 cases with an empty kidney fossa were caused by renal ectopy [48]. In the remaining cases, unilateral RA was detected in 13, horseshoe kidney in 2, and crossed fused renal ectopy in 1.

    Thus, a finding of an empty renal fossa should direct the search for an ectopic kidney. The diagnosis of renal agenesis can be confirmed by performing magnetic resonance imaging or a static renal scan with DMSA. However, a renal scan may miss nonfunctional kidney tissue. (See "Renal ectopic and fusion anomalies", section on 'Renal ectopy' and "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT)", section on 'Static renal scan'.)

  - Voiding cystourethrogram – Some clinicians obtain a voiding cystourethrogram (VCUG) in infants who are diagnosed by antenatal ultrasound because of the association of

vesicoureteral reflux (VUR) with unilateral RA. However, VUR is typically low grade and appears to have little clinical significance, particularly in the absence of UTI.

- Urinalysis – Urinalysis is performed to detect proteinuria. If there is evidence of kidney injury (eg, hypertension or proteinuria), a serum creatinine is obtained to assess kidney function by estimating GFR. (See "Chronic kidney disease in children: Clinical manifestations and evaluation", section on 'Serum creatinine and GFR'.)

Chronic kidney disease — Children with a solitary kidney are at risk for long-term CKD, which is thought to be due to glomerular hyperfiltration [40,41,43,49-52]. Obesity appears to increase the risk of CKD in patients with unilateral RA [41,53].

- In the previously discussed systematic review, evidence of kidney injury included microalbuminuria (21 percent), hypertension (16 percent), and reduced kidney function defined as an estimated GFR (eGFR) <60 mL/min/1.73 m^2 (10 percent) [40].

- Two subsequent studies reported findings suggestive of kidney injury in 40 percent of patients with a solitary kidney:

  - A case series of 407 patients reported that approximately one-third of the cohort had evidence of kidney injury defined as proteinuria, hypertension (reduced estimated creatinine clearance, or the use of medication for kidney protection (eg, angiotensin-converting enzyme inhibitors [ACEI]) [49]. In this cohort, kidney length was inversely associated with kidney injury at a median time of 14.8 years.

  - In a population-based study, 353 of 979,630 screened 17-year old conscripts were identified with a solitary kidney. Kidney injury was more common in the group with a solitary kidney compared with those with two kidneys (42 versus 24 percent) and all three components of kidney injury were more prevalent in the group with a solitary kidney; high BP (32 versus 23 percent), proteinuria (18 versus 0.4 percent), and eGFR <90 mL/min/1.73 m^2 (12 versus 0.1 percent) [41]. In this cohort, multivariate analysis showed higher body mass index, male sex, and smaller kidney length were associated with kidney injury.

Follow-up care — In patients with unilateral RA, the contralateral normal kidney is expected to undergo compensatory hypertrophy, defined as kidney size at or above the 50th percentile for age (figure 2 and table 3). While no evidence-based guidelines for long-term follow-up of these children exist, a review of published evidence and expert opinion supports serial investigation by ultrasound and urinalysis.

Follow-up care is dependent on the response of the contralateral kidney and whether there are other risk factors for CKD:

- For those with compensatory hypertrophy, serial ultrasounds and urinalysis are performed within the first two years of life to monitor kidney growth, and then intermittent examination of kidney growth, blood pressure, and urine protein excretion via urinalysis are conducted through the end of puberty [54].

- For those without compensatory hypertrophy is not observed, serial ultrasounds and urinalysis are performed within the first two years and then ongoing monitoring of the patient is recommended with yearly assessment of blood pressure and urinalysis as these individuals are at risk for CKD.

- In patients with elevated blood pressure or urinary protein excretion, kidney function should be assessed by obtaining a serum creatinine to estimate the GFR. (See "Chronic kidney disease in children: Clinical manifestations and evaluation", section on 'Laboratory testing'.)

  If there is an elevation in either blood pressure or serum creatinine, management should be focused on interventions to slow or prevent progression towards CKD. (See "Chronic kidney disease in children: Overview of management", section on 'Slow progression of CKD'.)

The low incidence of traumatic injury in contact sports does not preclude the participation of children with a solitary kidney in contact/collision sports [55]. (See "Sports participation in children and adolescents: The preparticipation physical evaluation", section on 'Targeted physical examination'.)

Renal tubular dysgenesis — Renal tubular dysgenesis (RTD), an uncommon, severe disorder, is characterized by the absence or poor development of proximal tubules and is accompanied by thickening of the renal arterial vasculature from the arcuate to the afferent arteries [56,57]. Both sporadic and familial cases have been reported.

This disorder may be inherited or acquired [57].

- Mutations in the genes that encode renin, angiotensinogen, angiotensin-converting enzyme (ACE), and angiotensin II receptor type 1 (AT1 receptor) have all been associated with autosomal recessive RTD [56,57]. Mutations may be inherited in an autosomal recessive pattern, or two different mutations affecting the same allele may result in a compound heterozygote.

- Acquired causes include twin-twin transfusion syndrome, which can occur in monochorionic twin pregnancies, prenatal exposure to ACEI or angiotensin II receptor blockers (ARBs), and severe liver disease due to congenital hemochromatosis [57].

Clinical manifestations of RTD due to genetic mutations or prenatal exposure to ACEI and/or ARBs are similar. They include early onset of oligohydramnios, detected at or before 20 weeks embryonic age, persistent postnatal anuria with kidney failure, ossification defects (hypocalvaria) with large fontanelles, refractory arterial hypotension, and, in severe cases, Potter sequence (oligohydramnios, lung hypoplasia, and characteristic facies of pseudoepicanthus, recessed chin, posteriorly rotated, flattened ears, and flattened nose) (picture 3). Kidney ultrasonography is characteristically normal in infants with RTD.

The diagnosis of RTD is based on morphologic examination of the kidneys that demonstrates the absence or significant reduction in the number of differentiated proximal tubules with preservation of the glomerular architecture. The majority of patients die in the perinatal period secondary to kidney failure or lung hypoplasia [58].

Genetic cystic diseases — Genetic cystic renal diseases are due to mutations of genes involved in primary ciliary function.

- **Polycystic kidney disease** (PKD) is typically due to terminal epithelial differentiation disruption and includes:

  - **Autosomal recessive polycystic kidney disease (ARPKD**) – ARPKD is characterized by multiple microscopic cysts, principally involving the distal collecting ducts. It is caused by mutations in the *PKHD1* gene, which codes for fibrocystin. Clinical manifestations include oligohydramnios, pulmonary hypoplasia, hypertension, congestive cardiac failure, liver disease, and kidney failure. The perinatal prognosis depends on the pulmonary status. (See "Autosomal recessive polycystic kidney disease in children".)

  - **Autosomal dominant polycystic kidney disease (ADPKD**) – ADPKD is characterized by bilateral kidney enlargement secondary to multiple cysts. It is caused by mutations in either *PKD1* (85 percent of patients) or *PKD2* genes (15 percent), which encode polycystin 1 and polycystin 2, respectively. These proteins are localized to the primary cilia of renal epithelial cells. There is a greater variability in clinical manifestations of ADPKD, with most patients having significant clinical findings only in adulthood. However, there is a subset of children who have an early onset of disease (in utero or in the first year of life) with symptoms similar to those with ARPKD. These include gross or microscopic hematuria, hypertension, proteinuria, cyst infection, and kidney insufficiency. (See "Autosomal dominant polycystic kidney disease (ADPKD) in children"

and "Autosomal dominant polycystic kidney disease (ADPKD): Genetics of the disease and mechanisms of cyst growth".)

- **Nephronophthisis** (NPH), the more common form of recessive cystic dysplastic kidney disease, is characterized by abnormal renal tubules, interstitial inflammation, and fibrosis. Several gene mutations have been identified for proteins involved with primary ciliary function, basal body function, and planar cell polarity. The genetic mutations and clinical manifestation of nephronophthisis are discussed separately. (See "Genetics and pathogenesis of nephronophthisis" and "Clinical manifestations, diagnosis, and treatment of nephronophthisis".)

ANOMALIES OF RENAL EMBRYONIC MIGRATION

Disruption of the normal embryologic migration of the kidneys results in renal ectopia (eg, pelvic kidney) and fusion anomalies (eg, horseshoe kidney (image 2)). In general, patients with an ectopic or fused kidney(s) are asymptomatic and diagnosed coincidentally, usually by antenatal ultrasonography. In patients diagnosed symptomatically with either anomaly, symptoms at presentation are generally related to associated complications including urinary tract infection (UTI), obstruction, and kidney calculi.

Patients with renal ectopy or fused kidneys are at increased risk for other anomalies, especially genitourinary abnormalities, such as vesicoureteral reflux (VUR). Renal ectopic and fusion anomalies are discussed in detail separately. (See "Renal ectopic and fusion anomalies".)

ANOMALIES OF THE COLLECTING SYSTEM

Anomalies of the collecting system include abnormalities of the following:

- Renal pelvis (eg, ureteropelvic junction obstruction) (see "Congenital ureteropelvic junction obstruction")
- Ureter (eg, megaureter, ectopic ureter, ureterocele, or vesicoureteral reflux) (see "Primary megaureter in infants and children" and "Ectopic ureter" and "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux" and "Ureterocele")
- Bladder (eg, bladder exstrophy) (see "Clinical manifestations and initial management of infants with bladder exstrophy")

- Urethra (eg, posterior urethral valve) (see "Clinical presentation and diagnosis of posterior urethral valves")

Anomalies of the collecting system are often associated with primary or secondary kidney parenchymal changes.

Duplication — Complete or partial duplication of the renal collecting system, also referred to as duplex system, is the most common congenital anomaly of the urinary tract [59]. Autopsy studies report an estimated incidence of 0.8 to 5.0 percent [60]. Double collecting systems are thought to result from duplication of the ureteric bud, with the superior bud associated with the upper renal pole and the inferior bud with the lower renal pole.

In complete duplication, the kidney has two separate pelvicaliceal systems and two ureters. The ureter from the lower collecting system usually enters the bladder in the trigone, whereas the ureter from the upper collecting system can have a normal insertion in the trigone or be inserted ectopically in the bladder or elsewhere. In boys, insertion can occur in the posterior urethra, ejaculatory ducts, or epididymis, and in girls, into the vagina or uterus. Ectopic insertion of the ureter can result in obstruction (picture 4) or vesicoureteral reflux (VUR). Depending upon the location of the ectopic insertion, incontinence also may be present.

Partial duplication is more common than complete duplication. In these cases, the kidney has two separate pelvicaliceal systems, with either a single ureter or two ureters that unite prior to insertion into the bladder.

In patients with asymptomatic uncomplicated (no dilation) duplication of the collecting system, no further intervention or referral is needed. However, if there is a history of urinary tract infection (UTI) or dilatation (typically due to obstruction), referral to a pediatric urologist is warranted for surgical repair (picture 5).

SUMMARY

- **Introduction** – Congenital anomalies of the kidney and urinary tract (CAKUT) constitute approximately 20 to 30 percent of all anomalies identified in the prenatal period.
- **Epidemiology** – The reported incidence of CAKUT in live and stillborn infants is 0.3 to 1.6 per 1000. Nonrenal anomalies are seen in 30 percent of infants with CAKUT. A combination of CAKUT and nonrenal anomalies are found in more than 200 described syndromes. (See 'Epidemiology' above.)

- **Pathogenesis** – CAKUT represent a broad range of disorders that result from abnormal embryogenic kidney development due to kidney parenchymal malformations, abnormalities in renal migration, or abnormalities in the developing collecting system. (See 'Embryology' above.)

- **Renal parenchymal malformations** – Malformations of the kidney parenchyma result in failure of normal nephron development, as seen in renal dysplasia, renal agenesis (RA), renal tubular dysgenesis, and polycystic renal diseases. The pathogenesis of kidney parenchymal malformations is multifactorial involving genetic (table 2) and environmental factors. (See 'Kidney parenchymal malformations' above and "Renal cystic diseases in children", section on 'Multicystic dysplastic kidney' and "Autosomal recessive polycystic kidney disease in children" and "Genetics and pathogenesis of nephronophthisis" and "Autosomal dominant tubulointerstitial kidney disease (medullary cystic kidney disease)".)

- **Renal ectopia and fusion** – Disruption of the normal embryologic migration of the kidneys results in renal ectopia (eg, pelvic kidney) and fusion anomalies (eg, horseshoe kidney). (See 'Anomalies of renal embryonic migration' above and "Renal ectopic and fusion anomalies".)

- **Collection system anomalies** – Abnormalities in the development of the collecting system result in anomalies of the renal pelvis (eg, ureteropelvic junction obstruction), ureter (eg, megaureter, ectopic ureter, or vesicoureteral reflux), bladder (eg, bladder exstrophy), and urethra (eg, posterior urethral valve). (See "Congenital ureteropelvic junction obstruction" and "Primary megaureter in infants and children" and "Ectopic ureter" and "Clinical manifestations and initial management of infants with bladder exstrophy" and "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux".)

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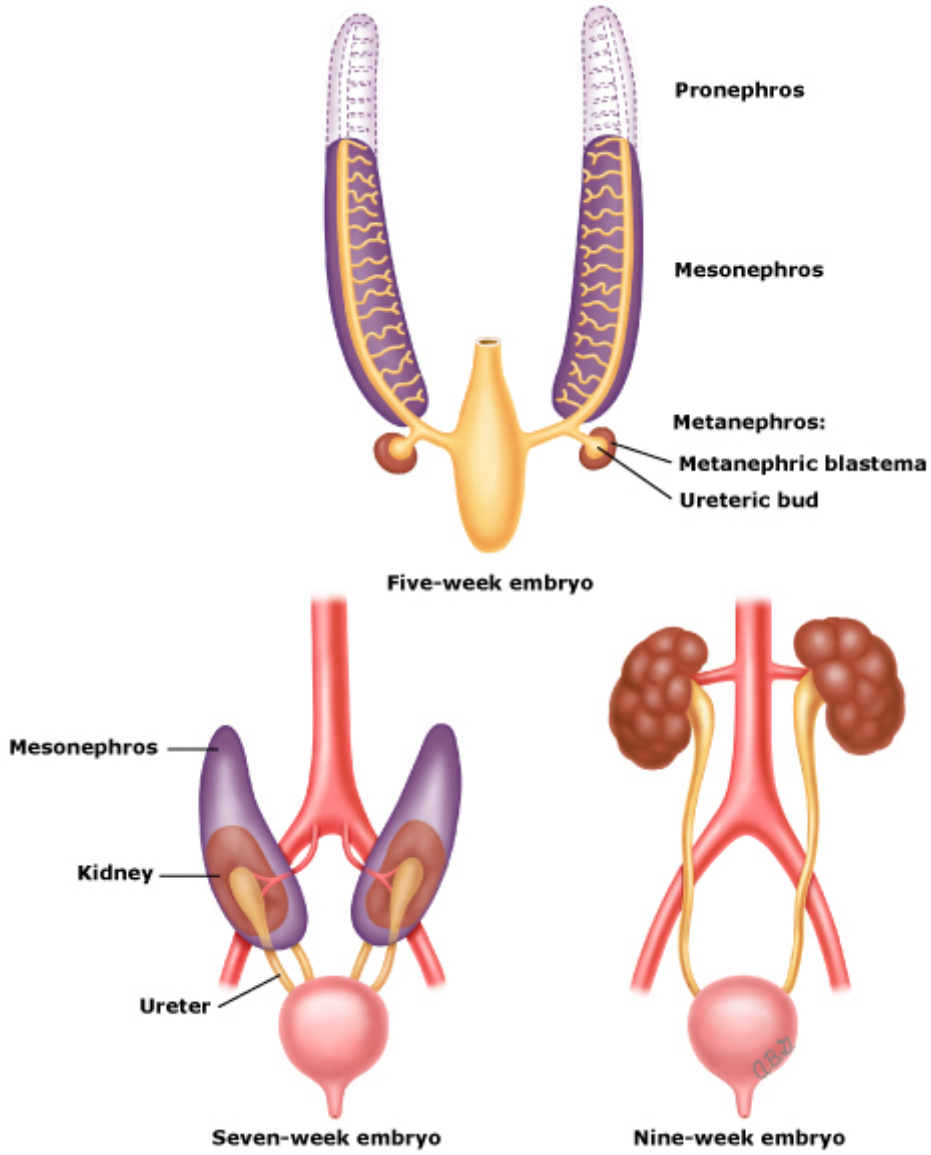
Topic 6110 Version 38.0

GRAPHICS

Embryology of the kidney



Graphic 68500 Version 2.0

Human gene mutations associated with defects in renal morphogenesis

Primary disease	Gene	Kidney phenotype
Alagille syndrome	*JAGGED1*, *NOTCH2*	Cystic dysplasia
Apert syndrome	*FGFR2*	Hydronephrosis
Bardet-Biedl syndrome	*BBS1*	Cystic dysplasia
Beckwith-Wiedemann syndrome	Dysregulation of imprinting in chromosome 11p15.5	Medullary dysplasia
Branchio-Oto-Renal syndrome (BOR)	*EYA1*, *SIX1*, *SIX5*	Unilateral/bilateral agenesis/dysplasia, hypoplasia, collecting system anomalies
Campomelic dysplasia	*SOX9*	Dysplasia, hydronephrosis
Cenani-Lenz syndrome	*LRP4*	Agenesis, UPJO
DiGeorge syndrome	22q11.2 deletions	Agenesis, dysplasia
Fraser syndrome	*FRAS1*, *FREM2*, *GRIP1*	Agenesis, dysplasia
Hypoparathyroidism, sensorineural deafness, and renal anomalies (HDR)	*GATA3*	Dysplasia
Kallmann syndrome	*KAL1*, *SEMA3A*	Agenesis
Mammary-Ulnar syndrome	*TBX3*	Dysplasia
Meckel Gruber syndrome	*MKS1*, *MKS3*, *NPHP6*, *NPHP8*	Cystic dysplasia
Nephronophthisis	*CEP290*, *GLIS2*, *RPGRIP1L*, *NEK8*, *SDCCAG8*, *TMEM 67*, *TTC21B*	Cystic dysplasia
Okihiro syndrome	*SALL4*	Unilateral agenesis, VUR, malrotation, cross-fused ectopia
Pallister-Hall syndrome	*GLI3*	Agenesis, dysplasia, hydronephrosis
Renal coloboma syndrome	*PAX2*	Hypoplasia, VUR
Renal cysts and diabetes syndrome	*HNF1b*, *TCF2*	Dysplasia, hypoplasia
Renal dysplasia, isolated (cystic or non-cystic)	*DACH1*, *BICC1*, *CDC5L*, *NRIP1*	Dysplasia
Renal hypoplasia, isolated	*BMP4*, *RET*, *DSTYK*	Hypoplasia, VUR; DSTYK mutations also associated with UPJO
Renal tubular dysgenesis	Renin, angiotensinogen, ACE,	Tubular dysgenesis

	AT1 receptor	
Rubinstein-Taybi syndrome	*CREBBP*	Agenesis, hypoplasia
Simpson-Golabi Behmel syndrome	*GPC3*	Medullary dysplasia
Townes-Brock syndrome	*SALL1*	Hypoplasia, dysplasia, VUR
Zellweger syndrome	*PEX1*	Cystic dysplasia
Smith-Lemli-Opitz syndrome	*DHCR7*	Renal hypoplasia, cysts, and aplasia

ACE: angiotensin converting enzyme; AT1: angiotensin II receptor type 1; VUR: vesicoureteral reflux; UPJO: ureteropelvic junction obstruction.

Graphic 52772 Version 11.0

Prevalence of renal anomalies detected by ultrasonography in 709,030 births*

Type of renal malformation	Number of cases detected antenatally¶ (percent of antenatal diagnoses)	Total number of cases, detected antenatally and postnatally (percent of total cases)	Percent of total cases detected antenatally
Dilatation of upper tract	259 (28)	309 (27)	84
Unilateral multicystic dysplastic kidney	102 (11)	105 (9)	97
Unilateral renal agenesis	36 (4)	58 (5)	62
Bilateral renal agenesis/dysgenesis	86 (9)	95 (8)	91
Polycystic kidney disease	27 (3)	31 (3)	87
Supernumerary kidney	37 (4)	39 (3)	95
Ectopic kidney	15 (2)	27 (2.5)	56
Posterior urethral valves	19 (2)	27 (2.5)	70
Solitary cyst	19 (2)	25 (2)	76
Bladder exstrophy	10 (1)	19 (2)	53
Syndrome with chromosomal defect	107 (12)	128 (11)	84
Syndrome without identified chromosomal defect	54 (6)	64 (6)	54
Multiple malformations$^{\Delta}$	130 (14)	176 (16)	74
Total	924 (100)	1130 (100)	82

* Total number of births included live births, stillbirths, and abortions.

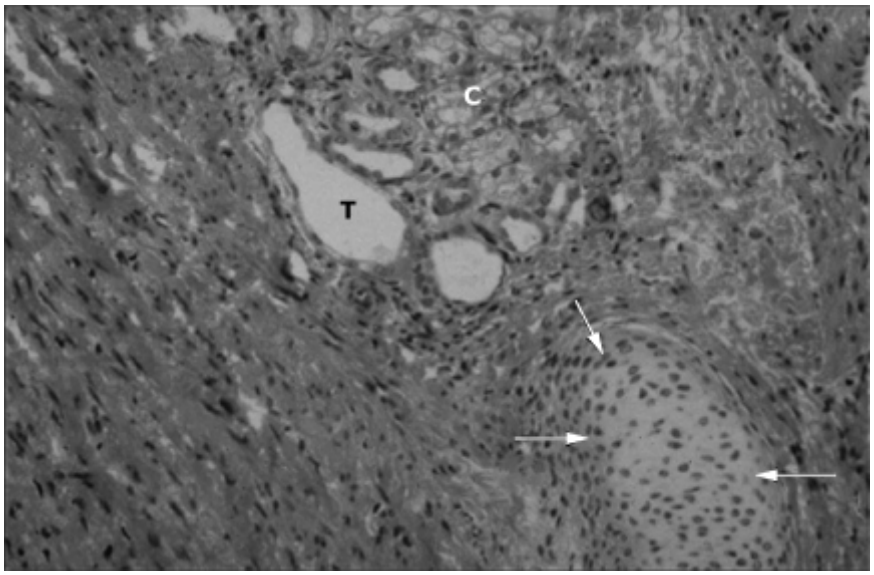
¶ Mean gestational age of antenatal detection 24.3 weeks (range 18.5 to 28.3).

Δ Multiple malformations defined as at least one renal malformation and one or more major malformation of another system.

Data from: Wiesel A, Queisser-Luft A, Clementi M, et al. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. Eur J Med Genet 2005; 48:131.

Graphic 75351 Version 6.0

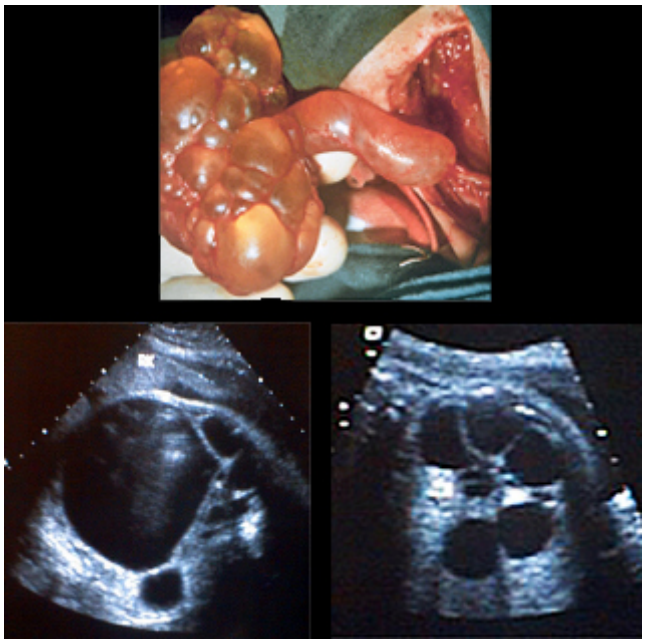
Renal dysplasia: microscopic section



Microscopic section of a dysplastic kidney showing cartilage (arrows). Tubules (T) are poorly formed with cystic changes (C).

Graphic 54805 Version 2.0

Multicystic dysplastic kidney

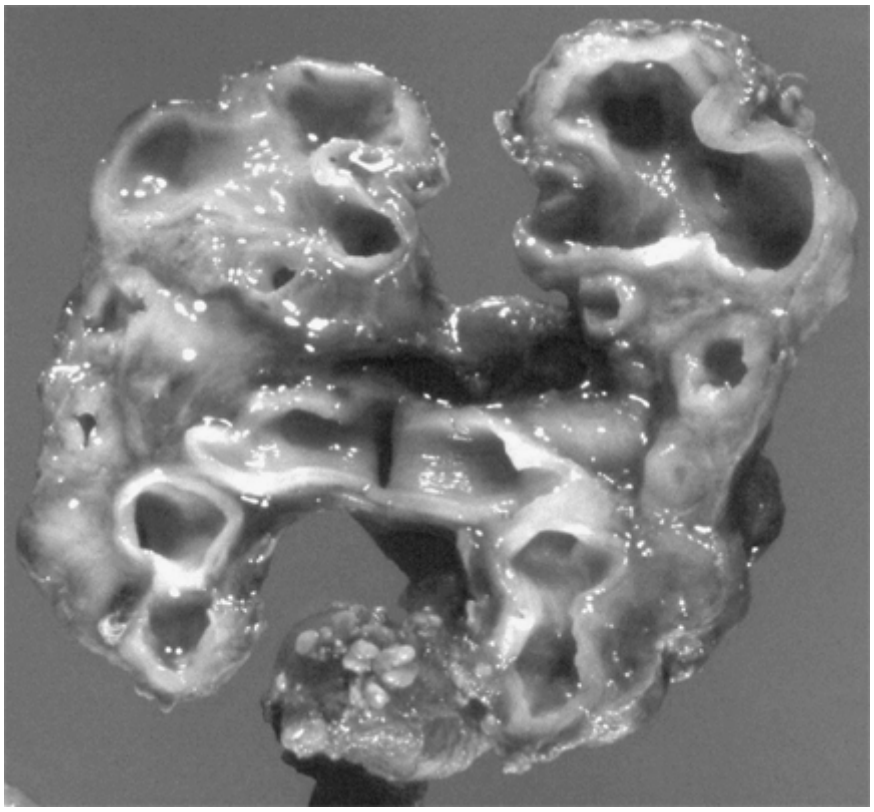


Intraoperative multicystic dysplastic kidney and its corresponding ultrasound images.

Courtesy of Laurence Baskin, MD.

Graphic 68485 Version 3.0

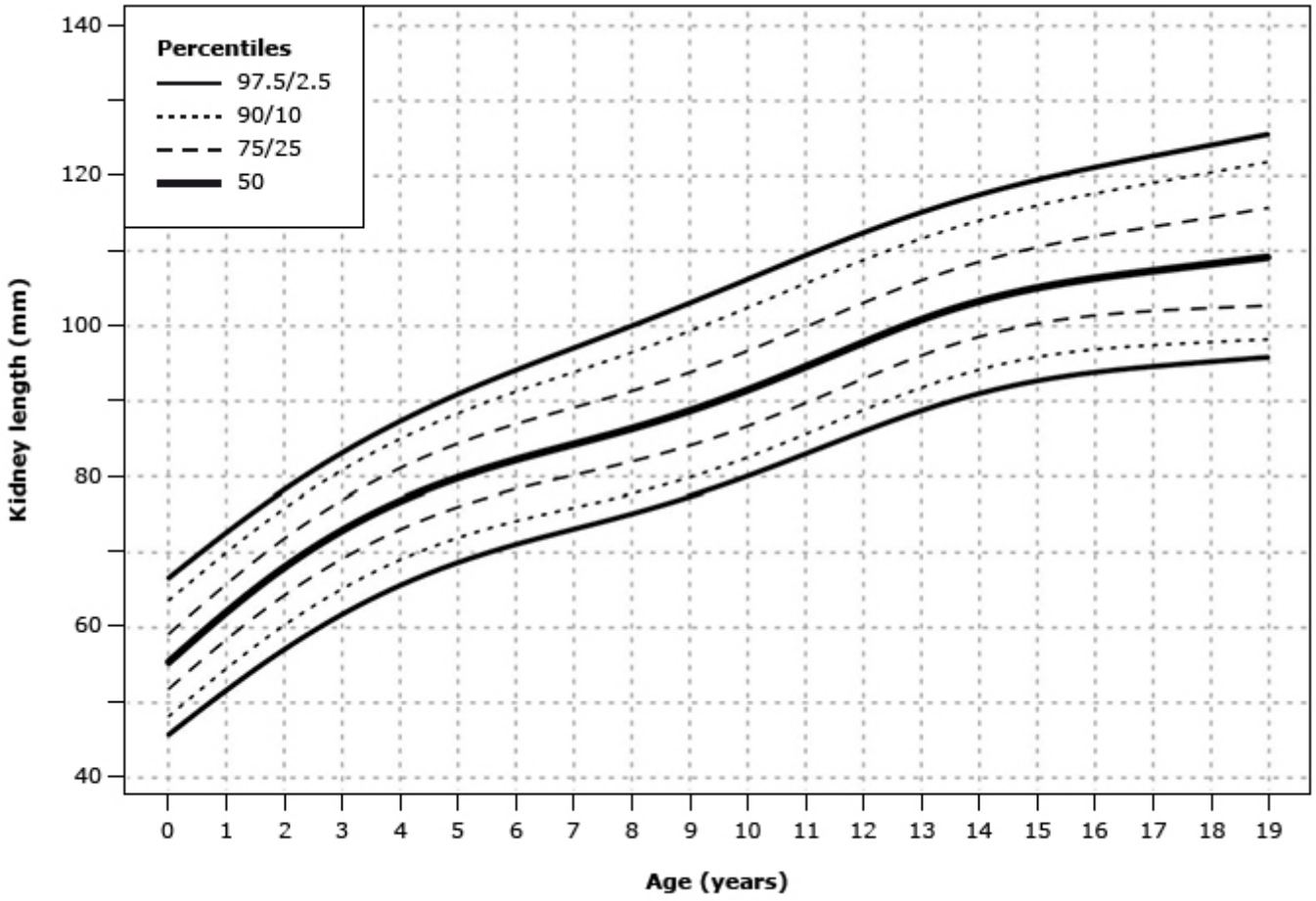
Multicystic dysplastic kidney: gross pathology



Gross pathologic features observed in the multicystic dysplastic kidney. Poorly defined renal archectiture, loss of corticomedullary differentiation, and multiple cysts are evident.

Graphic 59147 Version 3.0

Sonographic renal length plotted against age



From: Obrycki L, Sarnecki J, Lichosik M, et al. Kidney length normative values in children aged 0-19 years - a multicenter study. Pediatr Nephrol 2021. Copyright © 2021 The Authors. Available at: https://link.springer.com/article/10.1007%2Fs00467-021-05303-5 (Accessed on December 7, 2021). Reproduced under the terms of the Creative Commons Attribution License 4.0.

Graphic 79848 Version 10.0

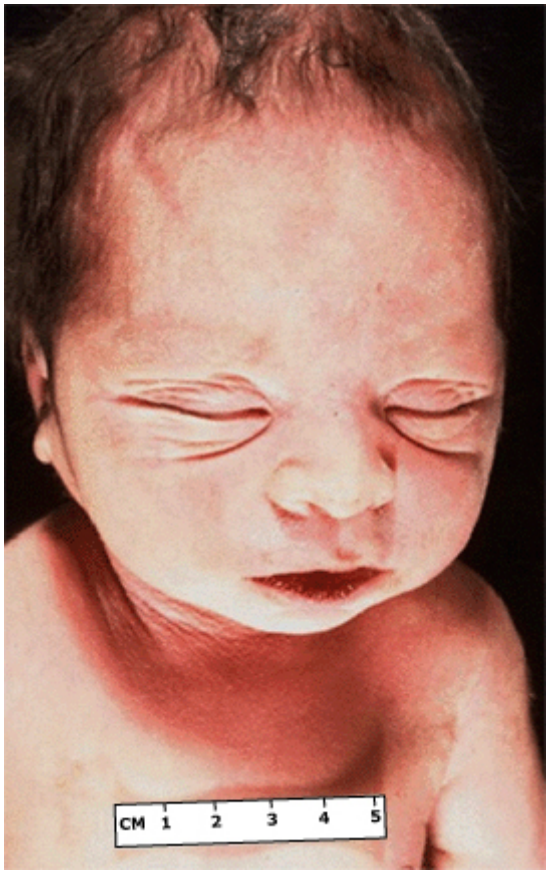
Normal fetal renal lengths

Gestational age, weeks	Mean kidney length, cm	95% CI, cm
18	2.2	1.6 - 2.8
19	2.3	1.5 - 3.1
20	2.6	1.8 - 3.4
21	2.7	2.1 - 3.2
22	2.7	2.0 - 3.4
23	3.0	2.2 - 3.7
24	3.1	1.9 - 4.4
25	3.3	2.5 - 4.2
26	3.4	2.4 - 4.4
27	3.5	2.7 - 4.4
28	3.4	2.6 - 4.2
29	3.6	2.3 - 4.8
30	3.8	2.9 - 4.6
31	3.7	2.8 - 4.6
32	4.1	3.1 - 5.1
33	4.0	3.3 - 4.7
34	4.2	3.3 - 5.0
35	4.2	3.2 - 5.2
36	4.2	3.3 - 5.0
37	4.2	3.3 - 5.1
38	4.4	3.2 - 5.6
39	4.2	3.5 - 4.8
40	4.3	3.2 - 5.3
41	4.5	3.9 - 5.1

From: Cohen HL, Cooper J, Eisenberg P, et al. Normal length of fetal kidneys: sonographic study in 397 obstetric patients. AJR Am J Roentgenol 1991; 157:545. Reprinted with permission from the American Journal of Roentgenology.

Graphic 74636 Version 11.0

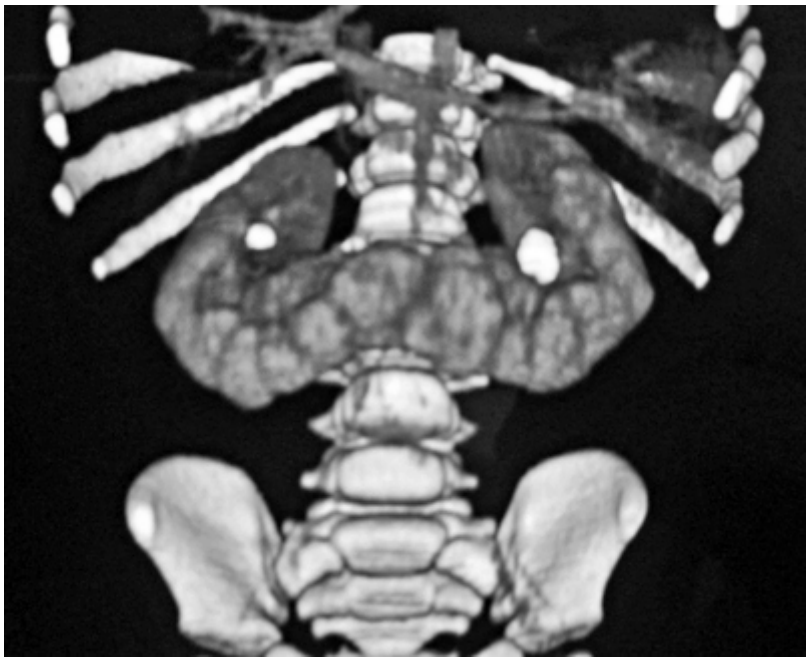
Facial appearance of a patient with Potter sequence



Typical facial appearance observed in Potter sequence. Characteristic abnormalities include pseudoepicanthus, recessed chin, posteriorly rotated, flattened ears, and flattened nose.

Graphic 72847 Version 3.0

Computed tomographic scan of horseshoe kidney

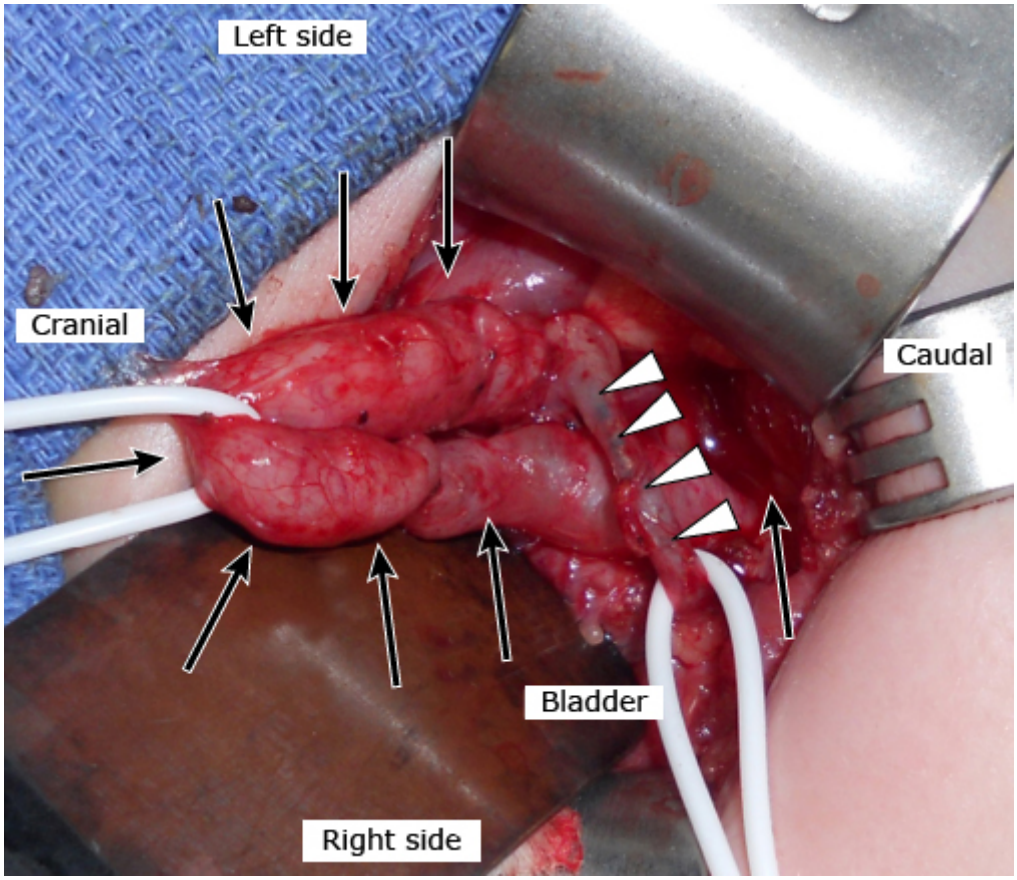


Unenhanced computed tomographic scan of horseshoe kidney with bilateral calculi.

Courtesy of Laurence Baskin, MD.

Graphic 73581 Version 6.0

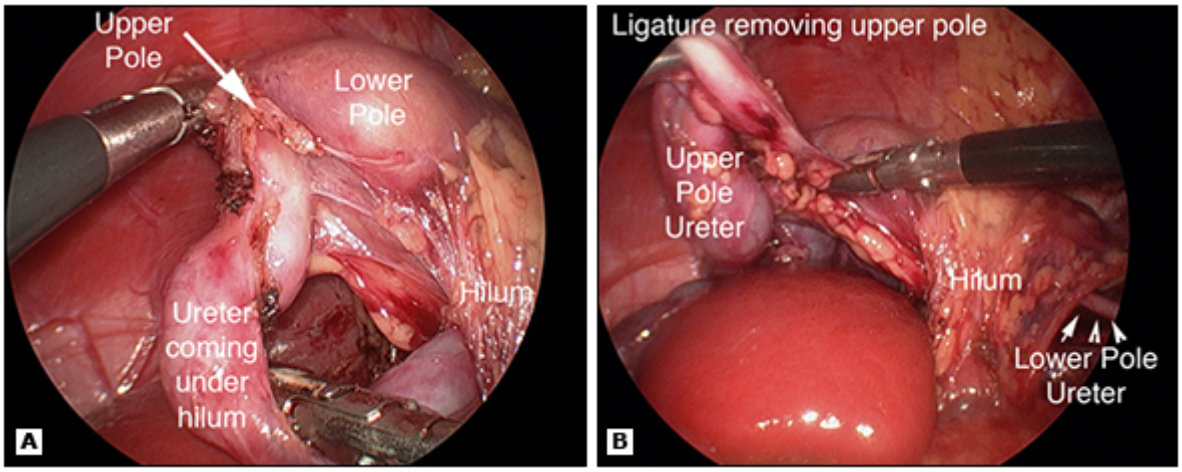
Duplex renal system with upper pole obstructed ectopic ureter



Intraoperative image of duplex renal system with upper pole obstructed ectopic ureter (black arrows). The dilated upper pole ureter is ~6 times the normal size compared to normal lower pole ureter (white arrowheads). Note the course of the ectopic ureter is underneath the normal lower pole ureter. It is headed to an ectopic location past the bladder, which is mostly covered by the metal retractor blade.

Graphic 86773 Version 1.0

Nephrectomy of nonfunctional upper pole of a duplex system



(A) Laparoscopic view of a nonfunctional dysplastic upper pole segment and dilated ureter in a duplex collecting system. This patient had obstruction due to a non-refluxing ureter. (B) Laparoscopic view of the ligature removal of the nonfunctional upper pole segment.

Graphic 97115 Version 1.0

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