## SECTION 16

# The patient with structural and congenital abnormalities

# CHAPTER 343

# Human kidney development

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## Introduction

The kidneys perform functions that are essential for normal postnatal life including excretion of nitrogenous waste products, homeostasis of water, electrolytes and acid–base balance, and hormone secretion. The simplest functional unit within the kidneys is the nephron, which consists of specialized segments from glomerulus, through proximal tubule, loop of Henle, and distal tubule. These are connected to the tree-like collecting duct system, and all segments are intimately associated with an extensive vascular and lymphatic system. The average mature human male kidney measures around 11 × 6 × 2.5 cm in size and weighs up to 170 g; females have slightly smaller organs. The paired kidneys are located in the retroperitoneum lateral to, and extending between the 12th thoracic and 3rd lumbar vertebrae. Urine produced within the kidney passes into the renal pelvis medially which drains into the ureter, itself extending caudally to the bladder.

A key determinant of eventual renal function is nephron endowment. Estimates of total, final nephron number vary, perhaps because of different counting techniques, ranging from 0.6 to 1.3 million per kidney (Bertram et al., 2011), and this is clearly important in not just severe kidney diseases but also less obvious conditions such as primary hypertension (Keller et al., 2003). In contract, mice and rats have 10,000–20,000 nephrons. Glomeruli are located in the cortex, a 1 cm thick strip which forms the outermost part of the kidney, whereas other nephron components extend into the medulla towards the centre of the organ. The cortex is continuous in humans, whereas the medulla consists of around 14 discrete pyramids. This is termed 'multipapillary' and contrasts with the 'unipapillary' kidneys found in rodents and rabbits.

### Timetable of nephrogenesis

Kidney formation, usually termed 'nephrogenesis', begins around 22 days after fertilization and completes in the 8th month of gestation. There are three pairs of 'kidneys' in the mammalian embryo: the pronephros, mesonephros, and metanephros, which arise sequentially from intermediate mesoderm on the dorsal body wall. The human pronephros and mesonephros are transient structures, which degenerate and are resorbed during fetal life, but they are essential precursors to the metanephros and normal adult kidneys will not form if they are disrupted. Timing of key events in human and mouse nephrogenesis is outlined in Table 343.1. It is noteworthy that the pronephros is the functioning kidney of adult hagfish and some amphibians, as is the mesonephros in adult lampreys, some fishes, and amphibians. Conservation of gene function across species means that valuable information pertinent to human development can still be gleaned from these different stages in animals; many recent investigations, for example, involve functional experiments in zebrafish larvae which have a pronephros containing two glomeruli fused in the midline (Drummond and Davidson, 2010).

## Anatomy

### Early kidneys—the pronephros and mesonephros

The human pronephros develops from 22 days after fertilization (Fig. 343.1). It comprises simple tubules along with the pronephric duct from the intermediate mesoderm lateral to the notochord adjacent to the ninth somite. This duct elongates caudally to fuse with the cloaca on day 26 but, confusingly, its name changes to the mesonephric or Wolffian duct as mesonephric tubules develop; further kidney development will not occur without this duct. Pronephric tubules (nephrotomes) and the cranial part of the duct involute by day 25.

The long sausage-shaped mesonephros reiterates a duct with adjacent tubular structures, but glomeruli can also be identified from around 24 days of gestation as the duct grows towards the cloaca. The mesonephric duct is initially thought to be a solid rod of cells which then develops a lumen after fusion with the cloaca. Mesonephric tubules develop from intermediate mesoderm medial to the duct by 'mesenchymal-to-epithelial' transformation, a process which is subsequently reiterated during nephron formation in metanephric development. In humans, a total of around 40 mesonephric tubules are produced (several per somite), but the cranial tubules regress at the same time as caudal ones are forming, hence there are never more than 30 pairs at any time.

Each human mesonephric tubule consists of a medial cup-shaped sac encasing a knot of capillaries, analogous to Bowman's capsule and glomerulus of the mature kidney, and a lateral portion draining into the mesonephric duct. Other segments of the tubule resemble mature proximal and distal tubules histologically but there is no loop of Henle. Small quantities of urine are thought to be made in the human mesonephros, whereas the murine organ is much more rudimentary and does not contain well-differentiated glomeruli. Most mesonephric structures involute during the third month of gestation, except in males where some tubules contribute to the efferent ducts of the epididymis and the mesonephric duct is incorporated into ductular parts of the epididymis, the seminal vesicle and ejaculatory duct.

### The definitive kidney—the metanephros

The adult human kidney develops from the metanephros (Figs 343.2 and 343.3), comprising two cell lineages at its inception: the

**Table 343.1** Summary of important events during nephrogenesis in mice and humans. Rat timing is around 1 day later than mice. Note that kidney development continues after birth in rodents but is complete, in terms of formation of structures, before birth in humans

| Structure | | Human | Mouse |
|---|---|---|---|
| Pronephros | Appears | 22 days | 9 days |
| | Regresses | 25 days | 10 days |
| Mesonephros | Appears | 24 days | 10 days |
| | Regresses | 16 weeks | 14 days |
| Metanephros | | 32 days | 11.5 days |
| Renal pelvis | | 33 days | 12.5 days |
| Collecting tubules/nephrons | | 44 days | 13 days |
| Glomeruli | | 9 weeks | 14 days |
| Nephrogenesis ceases | | 34–36 weeks | 7–10 days after birth |
| Length of gestation | | 40 weeks | 20 days |

epithelial cells of the ureteric bud, and the mesenchymal cells of the metanephric mesenchyme. Reciprocal interactions promote ureteric bud branching to form the ureter, renal pelvis, calyces, and collecting tubules whilst the mesenchyme has a more varied fate; most undergoes epithelial conversion to form the nephrons from glomerulus to distal tubule, but other mesenchymal cells contribute to vascular development and give rise to interstitial cells/stroma in the mature kidney.

In humans, metanephric kidney development begins at day 28 when the ureteric bud sprouts from the distal mesonephric duct. By day 32 the tip (ampulla) of the bud penetrates the metanephric blastema, a specialized area of sacral intermediate mesenchyme, and the first layer of condensed mesenchyme settles around the growing ampulla. Glomeruli form from 8–9 weeks and nephrogenesis continues in the outer rim of the cortex until 34 weeks (Potter, 1972). Nephrons elongate and continue to differentiate postnatally

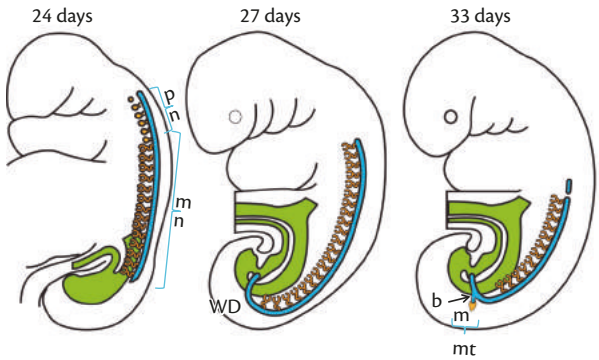


**Fig. 343.1** Early development of the human kidney and urinary tract demonstrating pronephric (pn), mesonephric (mn) and metanephric phases between 23 and 33 days post fertilization. The nephric duct (in blue) originates in the thoracic region, along with pronephric tubules. It migrates caudally stimulating mesonephric glomeruli and tubules, and is renamed the mesonephric or Wolffian duct (WD). It eventually fuses with the cloaca and the ureteric bud (b) branches from it into the metanephric mesenchyme (m) to form the metanephros (mt) which will generate the adult kidney.

but new nephrons are not formed. In mice, the ureteric bud enters the metanephric mesenchyme by embryonic day 10.5, the first glomeruli form by embryonic day 14, and nephrogenesis continues for 7–10 days after birth (note that most older texts incorrectly state 14 days after birth).

### Ureteric bud/collecting duct lineage

The solitary ureteric bud grows into the metanephric blastema (Figs 343.2 and 343.3) and signalling from this mesenchyme stimulates the ampulla to divide into a T-shape with two tips, then repeated cycles of elongation and branching occurs repeatedly during nephrogenesis to generate a tree-like collecting duct system. Around 9–10 rounds of branching occur in mice and a further 10 generations in humans. Each connects to a nephron proximally, whilst distal collecting ducts drain into minor calyces, which connect to the major calyces of the renal pelvis and then the ureter. The latter structures are formed by fusion and remodelling of early bud branches by apoptosis; Potter provided a rough estimate that the first three to five generations form the pelvis and the next three to five give rise to the minor calyces and papilla but it is difficult to confirm this in humans (Potter, 1972).

### Mesenchyme

Every nephron develops from mesenchyme adjacent to an ampullary tip of the ureteric bud. The mesenchyme is initially loosely arranged but the cells destined to become nephrons grow closely together and compact/condense around the bud tips before undergoing phenotypic transformation into epithelial renal vesicles. Each vesicle elongates to form a comma shape which folds back on itself to become an S-shaped body (Saxen, 1987). The proximal S-shape develops into the glomerulus whilst the distal portion elongates and differentiates into all nephron segments from proximal convoluted tubule to distal convoluted tubule. Other mesenchymal cells give rise to renal interstitial cells and contribute to vessel development.

### Vessels

Up to a fifth of cardiac output passes through the kidneys in humans, and there is specialized vascular patterning in different areas for specific functions including glomerular capillaries adapted for filtration, the juxtaglomerular apparatus, and vasa rectae which pass alongside loops of Henle into the medulla. There are two potential sources of these vessels: vasculogenesis, in which mesenchyme differentiates *in situ* to form capillary endothelia, or angiogenesis, which involves ingrowth of existing capillaries. Renal capillaries were initially hypothesized to arise by angiogenesis, because glomeruli formed in organ culture are avascular which suggests that exogenous vessels may be needed and the capillary loops that develop when mouse metanephroi are grafted onto avian chorioallantoic membranes come from the host. Donor vessels may also play a part, however, because these generate the vasculature in grafting experiments into the anterior eye chamber and under the capsule of neonatal mouse kidneys. Further support for vasculogenesis comes from recent reports that molecules characteristically expressed by endothelia are present in the metanephros from the inception of nephrogenesis. These results suggest that both vasculogenesis and angiogenesis have roles in the developing kidney and the complex interactions between different signalling systems are only just beginning to be unravelled (Sequeira Lopez and Gomez, 2011).

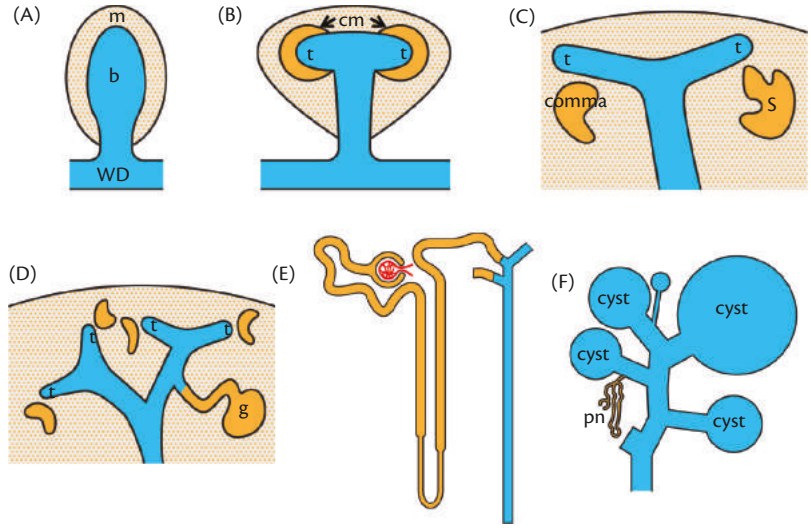


**Fig. 343.2** (A) The first step in meta-nephrogenesis is ingrowth of the epithelial ureteric bud (b; blue) into the metanephric mesenchyme (m; yellow). (B) Mutual induction between the bud and mesenchyme causes the former to branch serially and bud tips (t) reiteratively stimulate the mesenchyme to condense (cm) and undergo epithelial conversion. (C–E) The newly formed epithelia go through vesicle, comma, and S-shaped (S) stages as the nephron is formed from glomerulus (g) through distal tubule. (F) Dysplastic kidneys arise when induction fails or is incomplete; in the extreme case of multicystic dysplastic kidneys there are multiple cysts arising from ureteric structures and a few primitive nephrons (pn) but no normal functioning renal tissue.

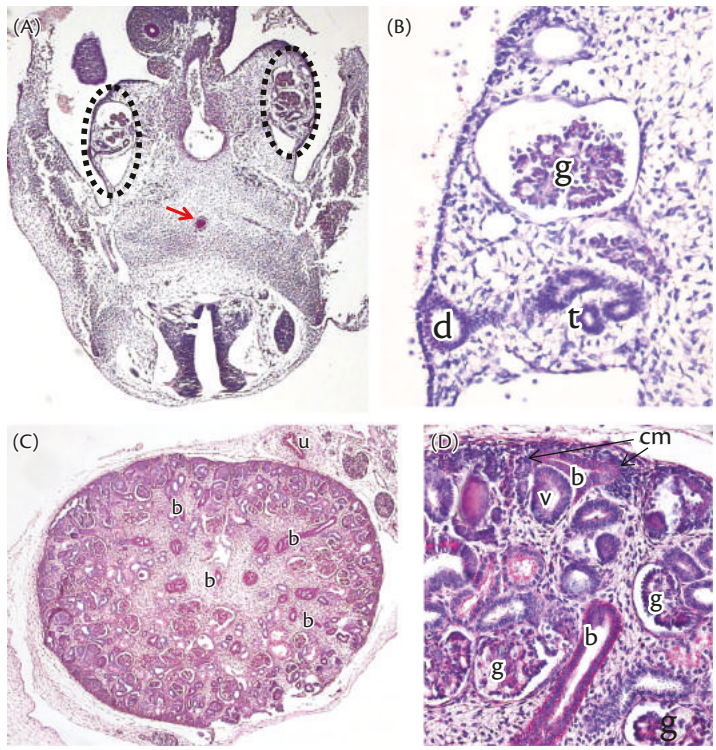


**Fig. 343.3** Histology of human developing kidneys, stained with periodic acid–Schiff. (A, B) At 5 weeks of gestation; low- and high-power views of the mesonephros (dotted lines in (A) showing glomeruli (g), tubules (t), and the mesonephric duct (d). (C, D) At 8 weeks of gestation; low- and high-power views of the metanephros ureteric bud branches (b) with condensing mesenchyme (cm) around bud tips, renal vesicles (v) and developing glomeruli (g).

Note: anonymized human tissues were obtained for this figure with ethical permission from the MRC/Wellcome funded Human Developmental Biology Resource at the UCL Institute of Child Health, London, UK.

## Basic processes during nephrogenesis

Nephrogenesis balances cell proliferation, death, and differentiation, all controlled by regulated gene expression. There is extensive cell proliferation as the adult mammalian kidney develops from less than a thousand cells at its inception to many millions in the mature organ, but this is mainly confined to the narrow rim of cortex containing actively branching ureteric bud tips and adjacent condensing mesenchyme (Winyard et al., 1996a and b). Fine tuning of cell numbers occurs by apoptosis, with as many as 50% of the cells produced in the developing kidney deleted via this process. The major sites of apoptosis are early nephron precursors such as comma and S-shaped bodies and the medulla to facilitate collecting duct remodelling. Markedly increased apoptosis occurs in major diseases such as polycystic kidney disease but more subtle effects may occur with external factors such as perturbed maternal diet and blood sugar control which decrease eventual nephron number (Stewart and Bouchard, 2011). Several levels of differentiation occur during normal nephrogenesis ranging from early mesenchymal–epithelial differentiation to form renal vesicles through to terminal differentiation where different cells in the same nephron segments acquire different functions (e.g. the α- and β-intercalated versus principal cells in collecting ducts).

### Genes controlling nephrogenesis

Outgrowth of the ureteric bud into a pre-specified area of metanephric mesenchyme must occur just once but at the right time and place for normal development. The kidney may not form without it, or the whole pattern of nephrogenesis can be disrupted by slight deviation from the regular programme, which can include other perturbations such as lower urinary tract pathology. The molecular controls of these developmental stages are beginning to be understood, although the pathways are often better worked out in mice and other animals than in humans because tissues and experimental models are more easily accessed. It is assumed that the same factors are important across mammalian species, but this is not always the case; for example, the X-linked Kalmann syndrome has a high frequency of renal dysplasia/agenesis and it is caused by mutations in *KAL1*, but there is no mouse orthologue of this factor (Hardelin and Dode, 2008). A comprehensive list of genes implicated in nephrogenesis is beyond the scope of this article but Potter and colleagues have started to compile this complex list for mice (Potter et al., 2010), whilst several recent articles focused on heritable human mutations that cause kidney and urinary tract malformations (Song and Yosypiv, 2011; Weber, 2012); examples of these are given in Table 343.2. Here, I will concentrate on the main gene families and signalling pathways important for normal human development.

### The GDNF/RET system: critical for controlled ureteric outgrowth and bud branching (and in Hirschsprung syndrome)

Initiation and growth of the ureteric bud involves positive inducers/stimulating signals counterbalanced against negative repressor molecules (Costantini, 2010). The glial cell line-derived neurotrophic factor (GDNF)/RET pathway is the most important initiator, and even the genes such as *SPRY1*, *SLIT2/ROBO*, and semaphorins which act as negative regulators generally work by modulating GDNF/RET signalling.

**Table 343.2** Examples of inherited congenital human renal malformations

| Gene | Phenotype |
|---|---|
| *ACE* | Renal tubular dysgenesis |
| *AGT* | Renal tubular dysgenesis |
| *AGTR1* | Renal tubular dysgenesis |
| *BBS* | Multiple Bardet–Biedl syndrome mutations causing tubulointerstitial and glomerular changes with or without cysts and dysplasia |
| *BMP4* | Renal hypodysplasia/agenesis |
| *CHRM3* | Functional bladder outlet obstruction/prune-belly syndrome |
| *EYA1* | Branchio-oto-renal syndrome |
| *FOXC1/FOXC2* | CAKUT |
| *FRAS1* | CAKUT |
| *FREM1* | CAKUT |
| *GDNF* | Hirschsprung disease/CAKUT |
| *GPC3* | Simpson–Golabi–Behmel syndrome |
| *HNF1B* | Renal hypodysplasia, frequently with renal cysts; renal cyst and diabetes syndrome, maturity onset diabetes of the young |
| *HPSE2* | Urofacial syndrome/Ochoa syndrome with dysmorphic, poorly emptying bladder |
| *KAL1* | Renal agenesis and hypodysplasia |
| *NPHP1* | Renal hypodysplasia, nephronophthisis |
| *OFD1* | Oral-facial-digital syndrome with glomerulocystic kidneys |
| *PAX2* | Renal coloboma syndrome, renal hypodysplasia, vesicoureteric reflux |
| *PKD1/PKD2* | ADPKD; a few large cysts arising from all nephron segments |
| *PKHD* | ARPKD; many cysts arising from collecting ducts only |
| *REN* | Renal tubular dysgenesis |
| *RET* | Hirschsprung disease/CAKUT |
| *ROBO2* | Vesicoureteral reflux/CAKUT |
| *SALL1* | Townes–Brocks syndrome; digital and kidney anomalies, imperforate anus, inner ear deafness |
| *SIX1* | Branchio-oto-renal syndrome |
| *SIX2* | Renal hypodysplasia |
| *SIX5* | Branchio-oto-renal syndrome |
| *SOX17* | Pelviureteric junction obstruction/vesicoureteral reflux |
| *UMOD* | Renal hypodysplasia, occasional cysts |
| *UPIIIA* | Renal hypodysplasia |
| *WT1* | Denys–Drash, WAGR, and Frasier syndromes; mesangial sclerosis, focal glomerular sclerosis or Wilms tumours with other urogenital abnormalities |
| *XPNPEP3* | Nephronophthisis, tremor, sensorineural hearing loss, mitochondriopathy |

ADPKD = autosomal dominant polycystic kidney disease, ARPKD = autosomal recessive polycystic kidney disease; CAKUT = congenital anomalies of the kidneys and urinary tract; WAGR = Wilms tumour, aniridia, genitourinary abnormalities, and mental retardation.

GDNF binds to the RET receptor tyrosine kinase in association with an adapter molecule, GDNF receptor α (GFRα), and it was first observed in neuronal growth with mutations linked to Hirschsprung syndrome. Genetic ablation of any of these factors causes either complete failure of metanephric development or severe dysplasia (Michos et al., 2010). RET and GFRα are expressed along the entire nephric/mesonephric duct, in the ureteric bud which arises from it and also in branching bud tips in the metanephros. GDNF, on the other hand, is found in restricted sites in the mesenchyme where it is handily placed to act upon RET-expressing actively developing renal epithelia, namely adjacent to:

1. the site where the ureteric bud is about to form. Here, the function of GDNF is to stimulate bud outgrowth but too much of the growth factor causes ectopic buds in mice *in vitro* and *in vivo*.
2. the bud tips in the metanephros which are about to branch. Several roles have been postulated for GDNF here in addition to the obvious positive effects on branching including prevention of apoptosis and maintenance of *WNT11* expression in the bud as part of an autoregulatory feedback loop involving to coordinate/regulate ureteric branching (Reginensi et al., 2011).

It is remarkable how many factors conspire to limit GDNF/RET signalling. The axon guidance factors SLIT2 and its receptor ROBO2 regulate *GDNF* expression at initiation of ureteric bud outgrowth: mice lacking these factors develop ectopic ureteric buds because the *GDNF* expression domain is widened near the mesonephric duct (Grieshammer et al., 2004), and *ROBO2* mutations cause vesicoureteric reflux in humans which may reflect aberrant origin or development of the lower ureter. *Spry1* null-mutant mice also have extra ureteric buds (Basson et al., 2005) but Spry1 also restricts later branching of the ureteric bud lineage, being negatively regulated by angiotensin II via the angiotensin II type 1 receptor. Semaphorin3a is another factor that downregulates both GDNF signalling (and hence ureteric branching) and growth of the vascular tree, in contrast to semaphorin 3c which promotes branching (Reidy and Tufro, 2011).

Other systems involved in both ureteric bud outgrowth and ureter formation include the *FRAS1* (mutated in Fraser syndrome (Pitera et al., 2008)) and Teashirt (*TSHZ*) genes (Lye et al., 2010).

## The PAX–EYA–SIX transcription factor cascade in kidney and multiorgan congenital malformations

Part of *GDNF* expression is also under the control of an interlinked group of transcription factors including PAX2, EYA1, and several SIX and SALL genes (Costantini, 2010; Reidy and Rosenblum, 2009). Coordinated expression of a cascade of several of these factors is required for development of many organs including the ear, eyes, and branchial arches.

*PAX* genes are well preserved from *Drosophila* through zebrafish to human, but only PAX2, -3, and -8 are expressed in the developing kidney. *PAX2* was identified early because it is absolutely essential for kidney development and there is a direct correlation between expression and kidney phenotype (Harshman and Brophy, 2011; Winyard et al., 1996a). Mice with decreased Pax2 have aberrant kidney development: heterozygous mutations cause hypoplasia whilst *Pax2* knockouts lack mesonephric tubules and the metanephroi fail to form because the ureteric buds are absent. In contrast, overexpression of *Pax2* causes cystic kidneys with proteinuria and renal failure. Frank human *PAX2* mutations generate the 'renal coloboma' syndrome, which consists of optic nerve colobomas, renal anomalies, and vesicoureteric reflux (see Chapter 360), whilst polymorphisms with reduced *PAX2* expression are associated with smaller kidneys which are assumed to have fewer nephrons (Quinlan et al. 2007). As well as functions upstream of GDNF, the key roles for *PAX2* in the kidney involve support for actively proliferating tissues such as the tips of the ureteric bud and adjacent mesenchyme and to promote mesenchymal condensation and epithelial transformation. *PAX2* expression is upregulated by factors such as Yin Yang 1 and VEGF (Gao et al., 2005; Patel and Dressler, 2004), but a key downregulator in the kidney is the Wilms tumour gene, *WT1*: PAX2 binds to two sites in the *WT1* promoter sequence and causes up to a 35-fold increase in *WT1* expression which acts in a negative feedback loop to decrease PAX2 levels.

*PAX8* and *PAX3* are also expressed in nephrogenesis: PAX8 appears to be a co-factor in very early kidney development since the mesenchymal–epithelial transformation required for nephric duct formation does not occur in double *PAX8*/*PAX2* mutants, whereas *PAX3* is upregulated in some Wilms tumours, suggesting a PAX–WT1 negative regulatory loop (Hueber et al., 2009).

The SIX genes are important as part of developmental complexes with PAX. SIX1 forms a developmental pathway comprising SIX1–EYA1–PAX2, important for upregulating GDNF, and also mediates ureteral smooth muscle formation (Nie et al. 2010). *SIX2* expression maintains a proportion of undifferentiated progenitors in the renal mesenchyme so that there are self-renewing progenitors throughout nephrogenesis (Self et al. 2006).

*EYA1* is the mammalian homologue of the *Drosophila* transcriptional co-activator 'eyes absent' gene, and *EYA1* mutations occur in a quarter of branchio-oto-renal syndrome patients (see Chapter 358), whilst others may have *SIX1* mutations disrupting the SIX1–EYA1–PAX2 pathway (Ruf et al. 2004). Homozygous *EYA1* null mutant mice die at birth with multiple abnormalities including renal agenesis because of defective ureteric bud outgrowth and subsequent metanephric induction.

## The Wilms tumour gene, *WT1*—more important for kidney development than tumours

The *WT1* gene (Chapter 379) was first discovered in Wilms tumours (Chapter 173), but is only mutated in about 15% of these cancers with several other mutant genes implicated in a greater proportion such as *WTX, CTNNB1*, and *IGF2* (Md et al. 2011). WT1 is a transcription factor expressed in mesonephric glomeruli, condensing metanephric mesenchyme and then becomes restricted to developing and mature podocytes. Complete lack of WT1 is incompatible with life because of heart and lung defects; renal defects are reduced numbers of mesonephric tubules, failure of ureteric bud branching, and death of the presumptive metanephric blastema by apoptosis. Three human syndromes are associated with WT1 mutations:

1. Denys–Drash syndrome consists of genitourinary abnormalities, including ambiguous genitalia in 46 XY males, nephrotic syndrome with mesangial sclerosis leading to renal failure, and a predisposition to Wilms tumour. This is caused by point mutations of *WT1*, predominantly affecting the zinc finger DNA-binding domains.
2. WAGR syndrome consists of Wilms tumour, aniridia, genitourinary abnormalities including gonadoblastoma and mental retardation.

3. Frasier syndrome has focal glomerular sclerosis with progressive renal failure and gonadal dysgenesis. This is caused by intronic point mutations of *WT1*, which affect the balance between different WT1 splice isoforms.

*WT1* has multiple isoforms generated by alternative splicing, RNA editing, and alternative translation initiation sites. *PAX2* is the major downstream repression target but other classical nephrogenic molecules include WNT/beta catenin, IGFs, SPRY1, SALL1, and BMPs (Kreidberg, 2010).

## Hepatocyte nuclear factor 1B: the renal cysts and diabetes syndrome, and the commonest known genetic cause of congenital renal malformations

Mutations of the *TCF2* gene, encoding the transcription factor hepatocyte nuclear factor 1B (HNF1B), cause the renal cysts and diabetes (RCAD) syndrome and are a major cause of human congenital kidney malformations (Adalat et al., 2009; Decramer et al., 2007). *TCF2* is expressed in the mesonephric duct, ureteric bud lineage and early nephron epithelia, and adjacent paramesonephric ducts which should differentiate into the uterus and fallopian tubes. Renal malformations in RCAD are highly variable, ranging from grossly cystic dysplastic kidneys, through hypoplasia with oligomeganephronia to apparent unilateral agenesis and, in females, are accompanied by similarly diverse uterine abnormalities. Absence of HNF1B at the very tips of the branching ureteric tree has led to speculation that it is a 'maturation factor' rather than a 'branching factor', but investigation of this potential role has been difficult since mouse null mutants die in early embryogenesis. More subtle abnormalities do occur with *TCF2* mutations and experimentally perturbed function including defects in primary cilia and renal magnesium handling (Adalat et al., 2009). Potential factors regulated by HNF1B include DCoH, E4F1 and ZFP36L1, and a recent study suggests a link between TGFβ, HNF1B, and microRNA-192 (miR-192) (Jenkins et al., 2012).

## *WNT* genes—important for both early differentiation and later cell specification

The WNT family comprises > 20 genes, many expressed in normal nephrogenesis with key roles in both mesenchymal and epithelial lineages (Schmidt-Ott and Barasch, 2008). WNT signalling occurs via canonical or non-canonical pathways, usually via interaction with specific Frizzled (FZ) receptors, followed by recruitment of the intracellular protein, Dishevelled (DVl), and activation of specific co-receptors (Grumolato et al., 2010; Lancaster and Gleeson, 2010). Canonical WNT signalling results in activation of β-catenin-mediated transcription, and alternatives are the WNT/$Ca^{2+}$ or WNT/planar cell polarity (PCP) non-canonical pathways.

- WNT4 is upregulated during mesenchymal–epithelial differentiation, stimulated by PAX2, and mice lacking Wnt4 do not progress beyond the condensate stage. WNT4 alone can induce tubulogenesis in isolated metanephric mesenchyme. A loss-of-function WNT4 mutation has been described in Mayer–Rokitansky–Kuster–Hauser syndrome, which comprises defects in Mullerian-derived structures and renal agenesis (Biason-Lauber et al., 2004).
- WNT11 is expressed at the tips of the ureteric bud, but is not sufficient to induce tubulogenesis. *WNT11* mutations disrupt ureteric branching morphogenesis which leads to kidney hypoplasia, perhaps by disrupting WNT11/GDNF/RET feedback. Dickkopf-1, a canonical inhibitor, disrupts ureteric bud branching in a similar pattern. The Townes–Brocks syndrome (ear, limb, heart, and renal anomalies (see Chapter 359) results from mutations in *SALL1*, which activates canonical WNT signalling and ureteric bud tip differentiation (Kiefer et al., 2010).
- WNT9b is expressed by the ureteric bud, and is implicated in both canonical and PCP signalling (Karner et al., 2011). One effect of WNT9b is to stimulate WNT4 expression in the mesenchyme, leading to mesenchymal–epithelial transformation. Both WNTs can be replaced by activating the Notch pathway which is normally involved in specifying proximal epithelial fate during later nephron differentiation and differentiation of principal cells in collecting ducts (Sirin and Susztak, 2012).

## Further important genes

Bone morphogenetic proteins (BMPs) are part of the TGFβ family, often expressed alongside WNTs in kidney development (Itasaki and Hoppler, 2010). They are important in (a) control of ureteric bud outgrowth and elongation, (b) prevention of apoptosis in metanephric mesenchyme, and (c) promotion of ureteric smooth muscle development. BMPs signal via BMP type-1 (BMPRIA, BMPRIB) and type-II (BMPRII) receptors, and there is evidence that BMPR1A (also known as activin-like kinase 3, ALK3) is not only important during development but also in kidney regeneration and fibrosis (Sugimoto et al., 2012). BMP antagonists such as GREMLIN (GREM1) modulate ureteric bud outgrowth/branching via GDNF/WNT11 systems (Goncalves and Zeller, 2011).

Forkhead/winged helix transcription factor genes are implicated in both kidney and urinary tract development: mutations in murine *Foxc1* cause ectopic mesonephric tubules and anterior ureteric buds, often leading to duplex kidneys and ureters, whilst *Foxd1* (previously known as BF2) is expressed in renal stroma and essential for both mesenchymal–epithelial transition and ureteric tree patterning (Levinson et al., 2005).

Fibroblast growth factors (FGF) bind the receptor tyrosine kinases, FGFR1 and -2, activating Ras-GTPase and ERK, and promoting cell proliferation (Bates, 2007; Sims-Lucas et al., 2012). FGF2 is expressed in renal mesenchyme and protects it from apoptosis whilst FGF7 and -10 modulate ureteric bud branching. Perturbed *FGF8* expression disrupts nephron epithelialization, and deletions of this or *FGFR1* account for a small proportion of Kalmann syndrome patients (Hardelin and Dode, 2008). FGFs are bound, and can be sequestered, by matrix and adhesion molecules and aberrant expression of these can perturb nephrogenesis (Harvey, 2012). Glypican-3 mutations occur in Simpson–Golabi–Behmel syndrome, and heparan sulphate has a regulatory role in ureteric patterning via modulation of FGF signalling (Steer et al., 2004).

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# CHAPTER 344

# Kidney stem cells

Oren Pleniceanu and Benjamin Dekel

## Introduction

The adult mammalian kidney is considered an organ with low regenerative capacity. This is in contrast with highly regenerating organs such as the haematopoietic system, skin, and gut (Weissman, 2005).

Nevertheless, cell genesis must occur in the adult mammalian kidney as we are estimated to lose 68,000–72,000 epithelial cells per hour under steady-state conditions due to cell shedding into the urinary space (Prescott, 1966) and therefore have to replete this loss. In addition, the neonatal kidney significantly increases in size to attain adult dimensions and while mainly attributed to hypertrophy and elongation of nephrons, cell proliferation may also account for this phenomenon (Rosenblum, 2008). In addition, clinicians are well aware of the compensatory kidney growth in those born with a single kidney (McCrory, 1972; Kaufman et al., 1975). Moreover, renal repair has been documented following extreme conditions of toxic or ischaemic and even mechanical kidney damage; for instance, a kidney suffering acute ischaemic injury which is harmful to the nephron's proximal tubules can re-build a proximal tubule (Humphreys et al., 2011). In addition, even after prolonged unilateral ureteric obstruction (UUO), involving considerable inflammation, tubular necrosis, and apoptosis, the renal cortex can substantially remodel (Cochrane et al., 2005), suggesting that some regeneration and cell genesis of nephron compartments takes place in the diseased kidney.

Studies of normal renal development identify nephrogenesis, the controlled process of generating *whole* new nephrons, to exclusively occur in discrete regions in the outer layers of the developing mammalian kidney collectively termed the nephrogenic cortex/zone (Hopkins et al., 2009) (see Chapter 343). The nephrogenic cortex ceases to exist in mice (first postnatal days) and in humans (34th gestational week) presumably exhausting its developmental progenitors (Hartman et al., 2007; Hopkins et al., 2009). Therefore, we are estimated to be born with 300,000–1,000,000 nephrons and are unable to generate additional whole nephron units under physiological or pathological conditions (Rosenblum, 2008). This is in sharp contrast to the fish which continues to add whole new nephrons in maintenance and disease throughout its entire lifetime (Diep et al., 2011). Importantly, the epithelia of the collecting system arise from a separate cell lineage than that of nephron epithelia (Fig. 344.1). In addition, there exist other non-epithelial cell lineages in the mammalian kidney apart from nephrons including renal vasculature and renal interstitium (interstitial cells, smooth muscle cells, pericytes). All of these lineages are considered restricted very early on in development meaning that they do not cross boundaries and trans-differentiate from one cell type to the other. This means that an angioblast which represents an endothelial progenitor cell or an embryonic stromal progenitor cell do not give rise to nephron or collecting system epithelia during renal development (Al-Awqati and Oliver, 2002). One would need to employ whole embryonic kidney rudiment transplantation in order to simultaneously 'catch' all cell lineages that make up the kidney and grow a miniature functional kidney (Hammerman, 2000; Dekel et al., 2003a). Alternatively, to isolate a single lineage such as the epithelial stem/progenitors that are committed to generating nephron epithelia in development, the nephrogenic zone containing embryonic/fetal kidney (see Chapter 343) must be separated into a single cell suspension and biomarkers that characterize epithelial stem/progenitor cells residing in the nephrogenic zone can be utilized to sort out these cells via immunoselection (Harari-Steinberg et al., 2013). Progenitor cell types have been also previously isolated from embryonic mouse kidneys by means of a supply of the epithelial nephrogenic inducer, Wnt4, to cells growing as clones (Osafune et al., 2006), or by growing cells in non-adherent conditions as nephrospheres (Lusis et al., 2010).

In the case of human tissues, surface markers and not intracellular transcription factors such as SIX2 (a nephron stem/progenitor marker in the developing mammalian kidney) are required for the isolation of human nephron stem/progenitors (Pleniceanu et al., 2010). Accordingly, we have previously interrogated the signature of the progenitor population of the developing human kidney and pinpointed surface markers suitable for progenitor cell isolation such as neural cell adhesion molecule 1 (NCAM1) (Dekel et al., 2006a; Metsuyanim et al., 2009). Strikingly, these early molecular markers were re-activated in regenerating kidneys (Metsuyanim et al., 2008) and were shared with cancer stem cells isolated from human paediatric kidney malignancies termed Wilms tumours in which transformed embryonic renal stem cells accumulate (Dekel et al., 2006b; Metsuyanim et al., 2008, 2009; Pode-Shakked et al., 2012). Importantly, the growth of human fetal kidneys in serum-free defined conditions and prospective isolation of NCAM1 cells selects for early nephron epithelial lineage identifying a mitotically active population with in *vitro* clonogenic and stem/progenitor properties. These developmental human nephron stem/progenitors were shown to generate mature kidney structures and halt progression of chronic renal disease in mice (Harari-Steinberg et al., 2013).

Taking the lineage separation/restriction in development into account, a realistic approach is to try and define (if it exists) a separate tissue stem/progenitor cell in the *adult* kidney for each of the following: nephron epithelia, collecting system epithelia, endothelium, smooth muscle, interstitial cells, and so on. Moreover, within nephron epithelia multiple epithelial lineages exist (glomerular

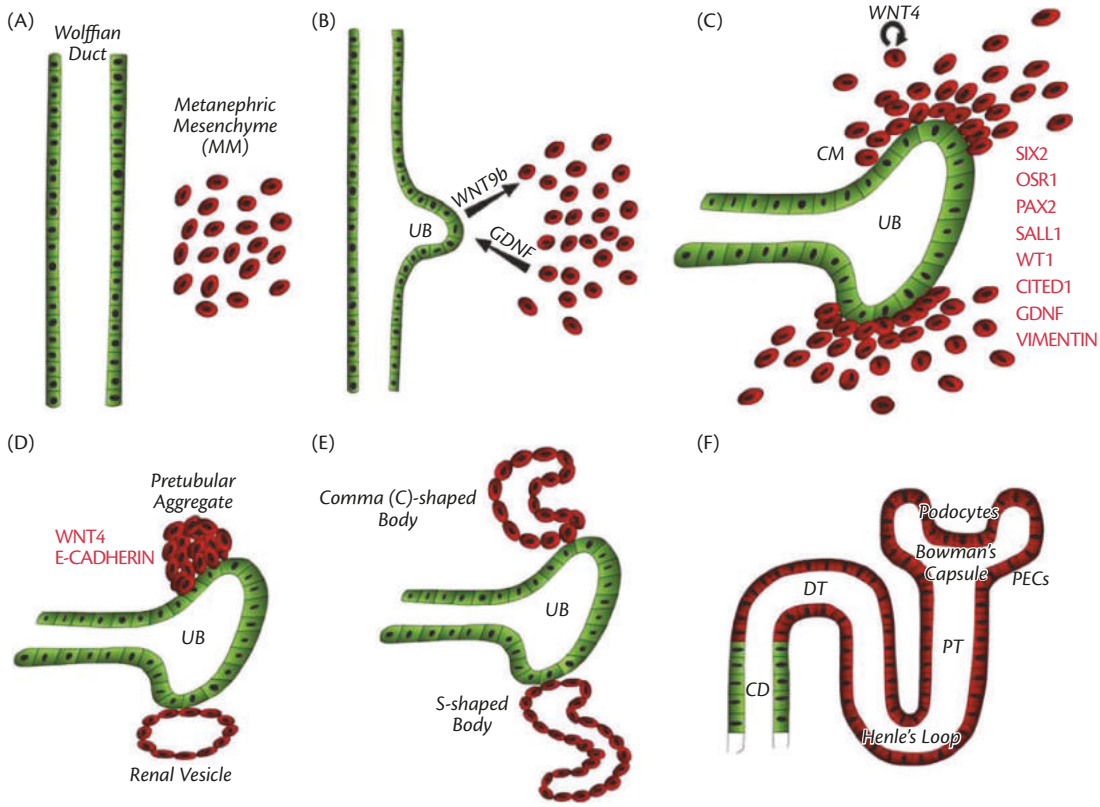


**Fig. 344.1** Kidney development. (A) The kidney is formed via reciprocal interactions between two precursor tissues derived from the intermediate mesoderm: the Wolffian duct and the MM. (B) MM-derived signals, mainly the glial-derived neurotrophic factor, induce an outgrowth from the Wolffian duct, termed the UB. The UB then invades the MM and secretes WNT9b, thereby attracting MM cells. (C) MM cells condense around the tips of the branching UB, forming the condensed or CM. The CM expresses a unique combination of genes (red) and the mesenchymal marker, Vimentin. The CM contains the kidney stem cells and is capable of self-renewal. In response to UB signals, CM cells start to produce WNT4, which acts in an autocrine fashion, leading to epithelialization of the cells. (D–F) The induced cells acquire an epithelial phenotype. This change is accompanied by the shutting down of the major transcription factors described before (B) and by the acquisition of the epithelial marker E-cadherin. The cells sequentially form the pretubular aggregate, renal vesicle, C-, and S-shaped bodies, and finally the mature nephron. The cells derived from the CM form most of the nephron body (from glomerulus to distal tubule), whereas the UB-derived cells form the collecting duct. CD = collecting duct; CM = cap mesenchyme; DT = distal tubule; PECs = parietal epithelial cells; PT = proximal tubule; UB = ureteric bud.

podocytes, glomerular parietal epithelia, proximal tubules, distal tubules, loop of Henle) that are diversified during development and therefore uni-potent cell precursors may operate in each of these compartments giving rise to segment-specific epithelial cells.

## Nephron epithelial stem/progenitor cells

A myriad of interesting publications have addressed various cellular models for epithelial neogenesis in the kidney (nephrons and collecting system) during maintenance and repair. In simple models, multipotent epithelial stem cells were shown to maintain the adult *Drosophila* malpighian tubules, which function as the fly kidney (Singh et al., 2007). In the zebrafish, multipotent adult nephron stem/progenitor cells capable of kidney regeneration and reminiscent of those located at the mammalian nephrogenic cortex were identified (Diep et al., 2011). In the mammal, the source of epithelial cell genesis has been controversial (Pleniceanu et al., 2010), implicating (a) circulating extrarenal cells, (b) intrinsic renal epithelia that dedifferentiate into stem-like cells and proliferate to repair damaged tissues (Witzgall et al., 1994; Bonventre, 2003; Vogetseder et al., 2005), and (c) multipotent adult kidney epithelial stem cells that reside in specific anatomic niches within the kidney (similar to epithelial stem cells found in gut and skin) and may respond to injury cues (Oliver et al., 2004; Bussolati et al., 2005; Dekel et al., 2006c; Maeshima et al., 2006; Sagrinati et al., 2006). Importantly, investigation of the repair processes in the ischaemically injured mouse kidney has suggested that re-building of nephron epithelia (mainly, proximal tubules) comes only from intrinsic epithelial cells and not from extrarenal cells such as bone marrow stem cells and mesenchymal stem cells (MSCs) (Humphreys et al., 2008). Thus, while extrarenal cells can contribute to resident haematopoietic cells (most likely of the monocytic lineage), some interstitial cells, and endothelial cells (Dekel et al., 2004, 2006; Garcia-Ortega et al., 2010) in the adult kidney, they completely fail to generate kidney epithelial parenchyma (Dekel et al., 2006a; Li et al., 2010).

The process of epithelial cell genesis may involve the dedifferentiation and proliferation of mature adult cells after acute injury. After an increase in cell proliferation, undifferentiated regenerating cells are believed to repopulate the damaged area and then re-differentiate into mature epithelial cells to reconstruct the functional integrity of nephrons (reviewed in Bonventre and Yang, 2011). In favour of this option is the post-ischaemic activation, at least in part, of renal developmental programmes including the appearance of early stem/progenitor cell markers during

de-differentiation (Dekel et al., 2003b, 2006b; Metsuyanim et al., 2008). For instance, NCAM1 which is strongly expressed in the nephrogenic cortex and is not expressed in the mature nephron has been shown to be reactivated in the rat following ischaemic injury in the S3 segment of the proximal tubule (Abbate et al., 1999), an area with a high regenerative response, recapitulating its expression in the developing kidney. In fact, re-activation of the renal developmental marker NCAM1 in cultures of human adult kidneys defines a subset of adult kidney epithelial cells that can be isolated from cultures and shown to function as renal progenitors (Buzhor et al., 2013). Similarly, when human adult kidney cells were grown *in vitro* as floating spheres this method selected for cells that acquire progenitor function (Buzhor et al., 2011).

Alternatively, a rarer population of quiescent bona fide epithelial stem cells may be present *in vivo*. This option involves the presence of specifically designated intratubular/intranephron cells that exclusively can clonally divide (originate from a single cell) in maintenance or disease to give rise to differentiated epithelial cells of a specific renal compartment and possibly to an adjacent or multiple compartments (a specific cell that, for instance, gives rise at the clonal level to glomerular parietal and visceral epithelia—podocytes). Multipotent epithelial stem have been demonstrated in malpighian tubes (an excretory organ) of *Drosophila* and were therefore predicted to exist in the mammalian kidney (Singh et al., 2007). In support of this option are studies that derive epithelial cells from specific nephron compartments such as parietal glomerular epithelium, proximal tubules, and collecting system epithelia of the renal papilla (Oliver et al., 2004; Kitamura et al., 2005; Sagrinati et al., 2006) and show *in vitro* that the derived cells harbour various 'stemness' traits. Examples for such traits include *in vitro* clonogenic capacity (Pleniceanu et al., 2010), a slowly proliferative rate *in vivo* (Metsuyanim et al., 2008; Pleniceanu et al., 2010), and expression of stem cell surface markers (Dekel et al., 2006a; Metsuyanim et al., 2008). However, these studies were unable to demonstrate long-term self-renewal and multipotency to various nephron or collecting system cell lineages at the clonal levels nor do they trace the fate of single cells *in vivo* and therefore interpretation to stem/progenitors is difficult. Indeed, clonal analysis of individual cells is extremely important for stem cell biology as cell populations with progenitor and stemness properties may represent heterogeneous cells comprised of various lineage-restricted progenitors that only together generate a mature structure that is comprised of several lineages. This is in contrast to multipotential stem cells in which a single self-renewing cell can also differentiate to give rise to all cell lineages.

Recently, genetic techniques for the concurrent *in vivo* labelling of multiple individual cells have been developed; these systems mark individual cells with a broad palette of distinct colours that result from combinations of fluorescent proteins generated by gene recombination (Fig. 344.2). Accordingly, one can inject a chemical such as tamoxifen at any mouse age to induce gene recombination, and fix a different colour gene in each cell (Rinkevich et al., 2011).

As the animal grows or regenerates, the clonal progenitors provide a single colour region. The clonal descents can then be analysed to determine whether they are restricted comprising a single lineage or alternatively multipotential comprising several lineages. Such long-term *in vivo* clonal analysis will assist in definitely answering critical questions in renal maintenance and repair: do clonal progenies exist in the adult mammalian kidney *in vivo* and if so does their cell of origin represent a rare population of multipotent kidney stem cells or alternatively multiple lineage-restricted progenitors? It is also possible that differentiated tubular cells can act as precursors to other adult nephron cells giving rise to limited clonal progeny and imitating acting like a progenitor cell (e.g. progenitor cell characteristics).

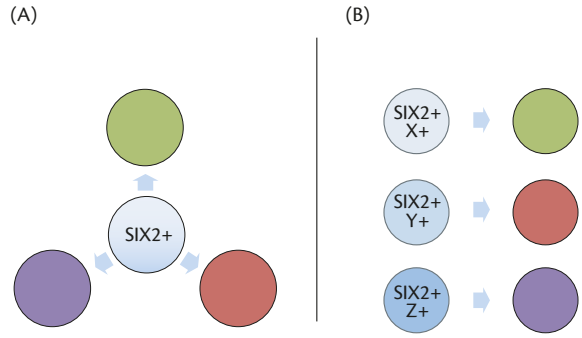


**Fig. 344.2** Clonal analysis and multi-potentiality. (A) Assessing multipotentiality at the *clonal* level, whereby any single cell (for instance, a SIX2+ nephron-forming cell) can give rise to several types of more differentiated cells. (B) Multi-potentiality at the *population* level. The SIX2 population, for instance as a whole can give rise to three types of more differentiated cells, as three distinct sub-populations (X+, Y+ and Z+) within the SIX2+ cells can each give rise to one type of cell. In this scenario, a colony derived from single SIX2+ cell will therefore not contain three types of cells, but only one indicating that the SIX2 population represents a heterogeneous population of progenitors.

## Adult stromal progenitors or kidney-resident multipotent stromal cells

While the presence of epithelial stem cells in the adult kidney is questionable there may exist stem/progenitors for other lineages. For instance, the presence of a spindle-shaped population of cells that is localized to the interstitial space and expresses the Sca-1 but not haematopoietic markers has been shown (Dekel et al., 2006c). This population shares markers of bone marrow MSCs and behaves like MSCs being clonogenic, multipotent, and differentiating to mesoderm lineages such as fat, bone, and smooth muscle. Cells with similar stromal progenitor characteristics have also been shown to reside in glomeruli (Bruno et al., 2009). All of these findings are in line with reports showing MSCs in most parenchymal organs apart from bone marrow (da Silva Meirelles et al., 2006). Importantly, these cells do not generate epithelia and their function as supporting cells and as cells that may participate in a renal regenerative process remain to be explored. In addition their relation to the Foxd1 stromal progenitor population that exists in embryonic kidneys is unknown. Kidney pericytes, which have features of both fibroblasts and smooth muscle cells, have established roles in sodium homeostasis and blood flow regulation. Lately, however, it has been suggested that pericytes have progenitor cell functions, although much of the data are indirect (2012). Very recent studies have shown that pericytes do give rise to multipotent MSCs (Crisan et al., 2008). Several studies have implicated this cell population in kidney fibrosis (e.g. diabetic nephropathy-related kidney fibrosis) (Humphreys 2012; Ren and Duffield, 2013). Thus, although the

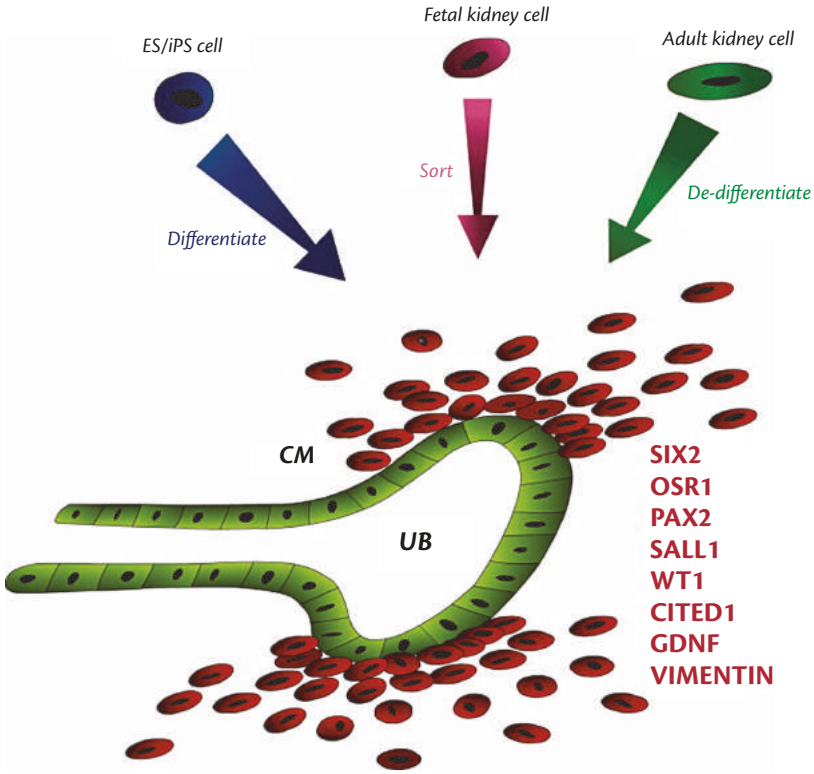


**Fig. 344.3** Regenerating nephrons: generation of cap mesenchyme cells (red) which include self-renewing nephron-forming cells are the ultimate goal of renal regenerative medicine and therefore different strategies are envisioned to obtain these cells or create an equivalent population of cells with nephrogenic potential: differentiation from pluripotent cells (ESCs or iPS cells), sorting of these cells from human fetal kidneys and de-differentiation via genetic reprogramming of adult kidney cells. CM = cap mesenchyme; ESCs = embryonic stem cells; Ips = induced pluripotent stem cell; UB = ureteric bud.

exact nature of these cells remains to be elucidated, their targeting as an antifibrotic mechanism or their use for therapeutic purposes still remain valid options.

## Adult kidney endothelial progenitors

Endothelial progenitors are present in various organs in embryonic life, especially haematopoietic organs such as the fetal liver, and in adults have been shown to reside in the bone marrow and to express *CD133* and *CD34* (Dome et al., 2008). It has been hard to demonstrate the existence of tissue-resident endothelial progenitors, partly because their phenotype has not been agreed upon. Detection of cells in the interstitial space of the adult kidney that express the *SCL/TAL1* gene, a transcription factor that confers a cell of haemangioblastic progenitor activity has been demonstrated (Dekel et al., 2004). Also Adriamycin® (doxorubicin) nephropathy in mice has been suggested to deplete local endothelial progenitors and damage the kidney via that mechanism (Yasuda et al., 2010). It seems that for vascular regeneration in the kidney, endothelial progenitor cells derived from non-renal sources are suitable (Garcia-Ortega et al., 2010). Importantly, while tissue hypoxia exacerbates chronic kidney disease (CKD), the repair of vasculature during CKD and hypoxic damage could have a secondary effect on the healing of the epithelial compartment and diseased kidney parenchyma (Fine, 2010).

## The future of renal regeneration by stem/progenitor cells

An important advancement for regenerative nephrology would be to derive and generate an unlimited supply of kidney epithelial stem/progenitor cells to be used directly in cell therapy or in combination with tissue engineering (Harari-Steinberg et al., 2013). This can be achieved via several methods, including differentiation of pluripotent stem cells (embryonic stem cells or their equivalent induced pluripotent stem cells) into renal epithelial cells or epithelial stem/progenitor cells, isolation of epithelial progenitor cells from within fetal kidneys, dedifferentiation via genetic reprogramming of adult cells into renal stem/progenitor cells, and finally, the isolation of putative progenitors with a more limited differentiation potential from adult kidney (Harari-Steinberg et al., 2011). In this last option as discussed above, the adult kidneys may not actually harbour true multipotential stem cells but just 'regenerating' cells—cells that can be activated to proliferate and assume progenitor characteristics and thus perform in renal repair. Each of these methods affords its own advantages and limitations (Fig. 344.3 and Table 344.1).

Of note, extrarenal stem cells, most importantly multipotent MSCs are currently being investigated for their potential to assist in renal repair in humans (Togel and Westenfelder et al., 2010) following acute tubular necrosis induced by cardiac surgery. While

**Table 344.1** Three cell sources for kidney regeneration

| Cell type | Tissue specific stem cell | | ESCs | Extra-renal |
|---|---|---|---|---|
| | Adult | Fetal | | |
| Potency | Multipotent | Multipotent | P1uripotent | Multipotent |
| Availability | Existence questionable, requires biopsy | Exist but rare, paucity of markers | Available | Readily available |
| Ethical problems | None | Problematic | Problematic | None |
| Immunogenicity | Autologous | Allogeneic | Allogeneic | Autologous |
| Expansion | Limited | Limited | Unlimited | Scalable |
| Renal differentiation | Inherent | Inherent | Possible, currently impractical | None |
| Maldifferentiation | Unlikely | Unlikely | Possible (e.g. teratoma) | Possible (e.g. mesoderm) |

devoid of true nephrogenic potential, they might be of use due to their paracrine and immunomodulatory effects and/or contribution to reversal of renal ischaemia, which in turn attenuates kidney damage.

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# CHAPTER 345

# Anatomical types of congenital anomalies: overview of obstruction

Michiel F. Schreuder

The suspicion of a urinary tract obstruction is mostly based on antenatal ultrasound screening showing hydronephrosis. In about 1/100 to 1/500 pregnancies, a dilatation of the renal pelvis is detected (Docimo et al., 2007). These numbers are highly variable per region (with an incidence as low as 1/5000 pregnancies) and largely depend on the definition of hydronephrosis (Garne et al., 2009). Such a dilatation of the renal collecting system may indeed be based on obstruction, but can represent a normal anatomical variation as well in addition to several non-obstructive causes (Table 345.1). Furthermore, dilatation is not a *condicio sine qua non* for the diagnosis of obstruction, especially in cases of oliguria, acute obstruction, and extrinsic causes.

Urinary tract obstruction, especially during kidney development, may lead to a disturbance of normal development and result in dysplasia with functional decline (Klein et al., 2011). When both kidneys are affected, this may present as renal failure at birth, as can be seen in patients with severe posterior urethral valves. In an even more extreme situation, both kidneys fail to form functionally (aplasia, renal agenesis, or multicystic dysplastic kidney) leading to oligohydramnios and subsequent pulmonary hypoplasia, almost inevitably a fatal condition. However, most cases of urinary tract obstruction in antenatal hydronephrosis represent a much less severe obstruction still capable of damaging renal tissue and function. To prevent such damage to the kidney, relief of the high pressure in the renal collecting system through surgery is indicated.

The diagnosis of urinary tract obstruction cannot be made by renal ultrasound. This may only lead to the suspicion of obstruction and the potential site of urine flow impairment. The combination of a dilated renal pelvis alone suggests an obstruction at the pyeloureteric junction. Combining hydronephrosis with a megaureter suggests obstruction at a lower level: if this is found bilaterally, an obstruction in the outflow tract of the bladder can be expected (lower urinary tract obstruction. A single-side megaureter with hydronephrosis suggests an obstruction in the distal ureter, such as a vesicoureteric junction obstruction.

The size of the renal pelvis dilatation predicts the necessity for surgical treatment. For both extremes of the renal dilatation spectrum, management is quite clear. An anterior–posterior (AP) diameter > 50 mm in a neonate predicts a poor outcome for the kidney, whereas an AP diameter of < 6 mm does not pose a threat. Unfortunately, there is still no consensus on the dimension of the AP diameter of the renal pelvis between 6 and 50 mm that can be considered safe, that is, not influencing kidney development and function. Table 345.2 shows the risk for surgical intervention in categories of AP diameter, based on the experience from a single UK centre (Dhillon, 1998).

Other diagnostic imaging that has been used in cases of suspected urinary tract obstruction includes intravenous pyelography and the Whitaker test (Docimo et al., 2007). However, these are currently replaced by diuretic renography, the main diagnostic imaging to evaluate upper urinary tract obstruction (Gordon et al., 2011). Several tracers can be used, all with their specific characteristics, but in daily practice technetium-99m mercaptoacetyltriglycine ($^{99m}$Tc MAG3) or $^{99m}$Tc diethylenetriamine pentaacetic acid (DTPA) are most widely used. As interpretation of renography relies on a fast elimination of the tracer, this may be hampered by a reduction in renal function as can be seen in neonates or patients with chronic kidney disease.

**Table 345.1** Causes of (prenatal) hydronephrosis

| | |
|---|---|
| Obstructive | Pelviureteric junction obstruction |
| | (Fetal) urolithiasis |
| | Vesicoureteric junction obstruction |
| | Ureterocele |
| | Urethra obstruction |
| | Posterior urethral valves |
| | Urethral atresia or stricture |
| | Anterior urethral valves |
| | Urethral diverticulum |
| Non-obstructive | Vesicoureteral reflux |
| | Non-obstructive megaureter |
| | Neurogenic bladder |
| | Residual dilatation after surgical relief of obstruction |
| Conditions mimicking hydronephrosis | Extrarenal pelvis |
| | Sonolucent medulla and pyramids (in fetus or neonates) |
| | Multicystic dysplastic kidney |
| | Peripelvic cysts |

**Table 345.2** Predictive value of the anterior–posterior (AP) diameter of the renal pelvis for the need for surgical intervention (Dhillon, 1998)

| Maximal renal pelvis AP diameter (mm) | Patients requiring surgical intervention (%) |
|---|---|
| < 15 | 2 |
| 15–20 | 7 |
| 20–30 | 29 |
| 30–40 | 61 |
| 40–50 | 67 |
| > 50 | 100 |

Even though a diuretic renography may assist in diagnosing obstruction, for instance, by a reduced drainage of the tracer, it may still be difficult to differentiate between kidneys that can be safely observed and kidneys that need to be surgically relieved in order to prevent additional damage. Sequential renography with a decrease in differential renal function (DRF) may provide an indication for surgery, and a DRF < 35–40% is generally considered such an indication. However, up to 20% of kidneys with a DRF > 40% show microscopic damage, whereas one out of three kidneys with a DRF < 20% do not show such damage (Elder et al., 1995).

Finally, magnetic resonance urography (MRU) can provide information on both the anatomy and functional capacity of the kidney and urinary tract, especially with gadolinium-enhanced MRU. A serious drawback of this superior imaging technique is the need for sedation, as with most magnetic resonance imaging in infants, which has limited its application in clinical practice (Docimo et al., 2007).

This illustrates that it is still not possible to unequivocally predict renal damage, and thereby the need for surgery, in patients with a urinary tract obstruction. To overcome this problem, urinary markers of renal tubular damage have been used, such as transforming growth factor beta 1, *N*-acetyl-beta-D-glucosaminidase, gamma-glutamyl transferase, and endothelin-1 (Madsen et al., 2011). Due to unacceptable low predictive values, this has not been helpful, but such an approach may be very helpful in clinical practice when proper markers have been identified.

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# CHAPTER 346

# Renal agenesis

Michiel F. Schreuder

In renal agenesis, the kidney never forms due to the absence of interaction in the developing embryo between the ureteric bud and the metanephric mesenchyme (Potter, 1972). (Nephrogenesis is detailed in Chapter 343.) The bud fails to form the ureter, renal pelvis, and collecting ducts, and the mesenchyme fails to form nephrons, leading to an absent kidney and ureter. Most cases of renal agenesis are unilateral, for which the reported incidence in both prenatal ultrasound as well as post-mortem studies varies widely between 1/12,000 (Wiesel et al., 2005) and 1/500 (Potter, 1972), respectively, with an average of 1/3,000. The male:female ratio is around 55:45%, and 56% of renal agenesis occurs on the left side. However, there is a subgroup of female patients that have associated ipsilateral genital tract anomalies, especially a uterus bicornis-bicollis, and these malformations appear predominantly on the right side (Vercellini et al., 2007).

Bilateral cases of renal agenesis show an estimated incidence of 1/4,800 to 1/7,500. As this condition is associated with the absence of renal function and therefore urine production by the fetus, resulting in oligohydramnios and pulmonary hypoplasia, most cases of bilateral renal agenesis lead to a termination of pregnancy (Wiesel et al., 2005).

The prenatal diagnosis of unilateral renal agenesis is based on the absence of a recognizable kidney, either at the normal or an ectopic site. However, such cases of an empty renal fossa can also be explained by an involuted multicystic dysplastic kidney, or by renal aplasia. The latter is defined as abnormal renal elements that involute, and it has been suggested that most cases of renal agenesis are in fact renal aplasia (Hiraoka et al., 2002). In daily clinical practice, it is not possible to differentiate between these two conditions.

Postnatal evaluation of a neonate with an empty renal fossa consists of confirmation by ultrasound of the prenatal suspicion, mostly followed by renography to confirm the presence of a solitary functioning kidney. The size of the solitary functioning kidney is increased in the majority of patients. Whether this increase in size is solely based on hypertrophy, or is accompanied by formation of additional nephrons remains to be determined. Fetal nephrectomy in sheep has been shown to result in an increase in nephron numbers in the solitary kidney (Douglas-Denton et al., 2002), and there is some evidence of additional nephrogenesis in humans as well (Hartshorne et al., 1991).

As there is an increased risk of vesicoureteral reflux of around 30%, most authors recommend evaluation with a voiding cystourethrogram. In addition to the urogenital anomalies, other organ (systems) may show anomalies as well (up to 44%), mainly cardiac and gastrointestinal anomalies (Woolf and Hillman, 2007). Many underlying genetic causes and syndromes have been identified that can explain the multiorgan associations (Song and Yosypiv, 2011), but these are discussed elsewhere in this section.

Relatives of patients with unilateral renal agenesis have an increased risk of having a renal anomaly as well, with risks of 7%, 4%, and 2.5% for offspring, parents, and sibs, respectively (McPherson, 2007). Based on these data, it may be advisable to perform a renal ultrasound in all first-degree relatives of a patient with renal agenesis.

Having a solitary functioning kidney has long been considered to have no influence on future health or (renal) survival. However, based on the hyperfiltration hypothesis (Brenner et al., 1996), glomerular hyperfiltration can be expected, resulting in hypertension, albuminuria with renal damage, and chronic renal failure in the long run (see Chapter 351). Indeed, data on a group of 71 patients with one absent kidney showed that at the age of 30 years there is only an approximately 60% renal survival (Sanna-Cherchi et al., 2009). Evaluation and long-term follow-up of all patients with renal agenesis is therefore desirable.

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# CHAPTER 347

# Renal dysplasia

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Renal dysplasia refers to abnormal and incomplete development of the kidney (Potter, 1972): rather than normal nephrons, incompletely branched ducts are surrounded by undifferentiated and metaplastic stroma. (Nephrogenesis is detailed in Chapter 343.) Dysplasia may be segmental, for instance, in the upper part of a duplex kidney, or affect the entire kidney, which can present as an aplastic, very small kidney. A dysplastic kidney may present with cysts as well, which is often referred to as cystic dysplastic kidneys.

A separate entity that combines cysts with renal dysplasia is a multicystic dysplastic kidney (MCDK), in which multiple non-communicating cysts of varying size are found amongst undifferentiated and metaplastic cells such as cartilage- and smooth muscle-like cells. Even though no nephrogenic zone at any stage of nephrogenesis, and hence complete absence of nephrons, was described by Potter (1972), MCDKs sometimes do contain some functional renal tissue with recognizable glomeruli and proximal tubules (Schreuder et al., 2009). An alternative explanation for the origin of MCDK is that normal nephrogenesis is largely disrupted by an impaired fetal urine flow early in development, which is consistent with the general finding of non-patent or atretic ureters attached to MCDKs (Woolf et al., 2004).

Renal dysplasia can also be found in patients with urine obstruction *in utero*, such as posterior urethral valves, pelviureteric junction obstruction (PUJO), or vesicoureteral reflux (VUR). Whether the dysplasia in such circumstances is caused by the high urine pressure or is a parallel presentation of the same congenital anomaly (and therefore cannot be prevented by relief of the pressure) remains to be determined.

Dysplasia is by definition a histological diagnosis, but in most patients diagnosis is made on the basis of evaluation with ultrasound and renography. This typically shows cysts and/or a small kidney with decreased corticomedullary differentiation and a reduced split renal function. The latter can also be found in other conditions, such as hypoplasia, vascular insults, renal post-infectious damage, or polycystic kidney disease, making it difficult to establish the diagnosis and thereby estimate the incidence of renal dysplasia. MCDK presents as a distinct radiological entity, as long as involution has not yet fully occurred, has an average incidence of 1/4300, and is slightly more prevalent in the left kidney and in males (Schreuder et al., 2009). Complete involution has been noted before birth in approximately 5% of patients, and is seen increasingly (up to 50%) in the first decade of life; most other MCDK will regress. Differential diagnosis of MCDK includes PUJO, in which the largely dilated calices may appear to be cysts. Differentiation may be made on the basis of communication between the dilated calices and the renal pelvis, whereas there is no communication between the cysts in a MCDK.

The clinical consequences of renal dysplasia depend upon the residual renal function and may range from hypertension to chronic kidney disease. Bilateral MCDK indicates that no fetal or neonatal renal function is present and leads to oligohydramnios with severe pulmonary hypoplasia, and is therefore considered a lethal entity. In contrast, unilateral MCDK does not lead to clinical signs, except for the rare occasion where the large abdominal mass leads to gastrointestinal or pulmonary complaints. Partially based on the supposed increased risk of hypertension and malignancy of which no evidence is found (Narchi, 2005a, 2005b), nephrectomy was performed routinely until recently, whereas nowadays most cases of MCDK are left *in situ* and followed with serial ultrasound (Docimo et al., 2007). In patients with MCDK, associated anomalies are frequently found both outside the urinary tract (in 15%) and within the urinary tract (~1/3 patients) (Schreuder et al., 2009). The majority of urinary tract abnormalities consists of VUR (~1/5 patients), of which 40% is at least grade 3, and in small numbers PUJO, ureterocele, and horseshoe kidneys are described.

As there is a congenital solitary functioning kidney in patients with a unilateral MCDK, please refer to Chapter 351 for the long-term consequences, which include an increased risk of hypertension, proteinuria, and chronic kidney disease in the long run, with about 20% of patients with MCDK needing renal replacement therapy by the age of 30 years (Sanna-Cherchi et al., 2009). Patients with associated urinary tract anomalies or not showing hypertrophy of the solitary kidney, which may indicate some degree of dysplasia, may be at increased risk of such long-term sequelae (Westland et al., 2011).

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# CHAPTER 348

# Renal hypoplasia

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Nephrogenesis (see Chapter 343) leads to the formation of nephrons, the functioning units of the kidney. In renal hypoplasia, normal nephrons are formed but with a deficit in total numbers. However, it is difficult to define a low number of nephrons as there is an almost 10-fold range of normal numbers, varying from 250,000 to over 2 million (Luyckx and Brenner, 2010). In addition, nephron number estimation *in vivo* (using gold standard stereological methodology) is not possible (yet). As a surrogate marker, renal size is used, in clinical practice generally measured by ultrasound. A widely used definition of renal hypoplasia is kidneys with a normal appearance on ultrasound but with a size less than two standard deviations below the mean for gender, age, and body size (Cain et al., 2010).

Unfortunately, differences in renal size explain only about 10% of the variation in nephron numbers. This illustrates that the definition based on renal size is useful for daily practice, but may not necessarily identify the renal anomaly that it is intended for. As renal dysplasia may also result in small kidneys and current imaging techniques are not capable of differentiating between pure hypoplasia and (hypo)dysplasia, it is difficult to estimate the incidence of true hypoplasia. Similarly, the clinical consequences are not easily delineated, even though hypodysplasia accounts for 35–50% of the causes for chronic kidney disease in children (Harambat et al., 2012). In a small cohort of 19 patients diagnosed with bilateral hypodysplasia, renal survival at the age of 30 years was only around 70% (Sanna-Cherchi et al., 2009).

A distinct and severe form of renal hypoplasia is called (congenital) oligomeganephronia, which is characterized by small but normal-shaped kidneys with a marked reduction in nephron numbers (to as low as 10–20% of normal), a distinct enlargement of glomeruli (Broyer et al., 1997), and a reduced renal function. Before the era of prenatal ultrasound screening, most patients presented with polyuria/polydipsia or signs of renal dysfunction such as anaemia or growth stunting. With the increasing metabolic demands on the kidney during growth, a decline in renal function is seen resulting in chronic renal failure at a mean age of 10 years (range 6 months to 17 years) (Broyer et al. 1997).

The wide inter-individual range of nephron numbers may point towards a more subtle form of renal hypoplasia. Indeed, a lower nephron endowment has been associated with hypertension, proteinuria, and renal damage with chronic renal failure in the long term (Brenner et al., 1996). In their landmark study, Keller et al. studied nephron numbers in individuals that died of non-renal causes (Keller et al., 2003). Comparing individuals known to be hypertensive with normotensive matched controls, a twofold difference in nephron numbers was found (700,000 vs 1.4 million nephrons per kidney, respectively). Of note, no difference in renal size was found, illustrating the lack of predictive value of renal size.

Within the normal range, many genetic and environmental factors have been identified that influence nephron numbers (see Chapter 349). Individuals with a nephron endowment at the lower end, irrespective of the cause, may be considered susceptible to the long-term consequences of glomerular hyperfiltration, leading to hypertension, proteinuria, renal damage with a further reduction in functioning nephrons, and eventually chronic renal failure (Brenner et al., 1996). In order to interrupt this vicious cycle, pharmaceutical interventions aiming to block the renin–angiotensin system have been studied to retard progression of proteinuria or renal failure. Ramipril was indeed found in a prospective study to lower proteinuria and blood pressure in children with renal dysplasia and/or hypoplasia (Wuhl et al., 2004), even though no effect on the progression to chronic kidney disease was found (Ardissino et al., 2007). It is therefore still debatable whether strict control of blood pressure and proteinuria can delay renal functional impairment in children with renal hypoplasia, as is well established in adult cohorts irrespective of the underlying cause (Ritz et al., 2010). Even without such evidence, it is advised to follow patients with hypodysplasia longitudinally and monitor blood pressure, renal function, and proteinuria.

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# CHAPTER 349

# Normal variation in nephron numbers

Michiel F. Schreuder

Nephrogenesis (see Chapter 343) is the process leading to the formation of nephrons, starting around the 9th week of gestation. No new nephrons are formed after the 36th week of gestation, indicating that the number of nephrons that are present at term birth will have to suffice for the entire life. On average, about 900,000–1,000,000 nephrons are formed per kidney, but nephron endowment shows an almost 10-fold variation (from 210,000 to about 2,000,000 nephrons per kidney) (Luyckx and Brenner, 2010). During life, nephrons are lost at a rate of approximately 4500 per year (Hoy et al., 2005), whereas ageing over the age of 60 years leads to a more rapid decline in nephron numbers (Nyengaard and Bendtsen, 1992).

A low nephron number leads to glomerular hyperfiltration with glomerular and systemic hypertension, glomerular sclerosis, and proteinuria with further loss of nephrons (see Chapter 138) (Brenner et al., 1996). Indeed, Keller et al. showed that accident victims with hypertension had about half the nephron number (median 702,379 glomeruli per kidney) from normal-blood pressure controls(median 1,429,200 glomeruli per kidney) (Keller et al., 2003). Subsequent studies confirmed the association between nephron number and blood pressure in Caucasians (Hughson et al., 2006) and Australian Aborigines (Hoy et al., 2006), but such an association was not clear in African Americans (Hughson et al., 2006). This may be just due to inadequate power, or other factors that influence the association between nephron number and blood pressure as all African Americans had a higher blood pressure.

These studies indicate that a higher number of nephrons at the beginning of life is highly preferable. In addition, the level of hyperfiltration is significantly higher when a lower number of nephrons presents itself in infancy than in adulthood (Larsson et al., 1980). This may explain, at least in part, the difference between the good prognosis in adult kidney donors (Ibrahim et al., 2009) and the progressively reduced renal survival in many cohorts with reduced nephron numbers from birth (Sanna-Cherchi et al., 2009).

Many circumstances have been identified that influence final nephron numbers (see Chapter 138). Men have on average 17% more nephrons than women and some races have been associated with a lower nephron endowment (Aborigines compared with Africans, African Americans, and Caucasians) (Luyckx and Brenner, 2010). The influence of (low) birth weight has been studied in more extent, as the Developmental Origins of Health and Disease hypothesis states that intrauterine factors may influence diseases later in life. For the kidney, low birth weight could therefore be expected to lead to a reduced nephron number. In fact, there is a direct linear association between birth weight and nephron numbers (~250,000 nephrons less per kg decrease in birth weight) (Hughson et al., 2003). In addition, maternal diseases, such as hypertension and diabetes, some maternal drugs (i.e. inhibitors of the renin–angiotensin system, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase inhibitors) and intoxications (smoking and alcohol) are all known to influence nephrogenesis (Schreuder et al., 2011). Being born prematurely, that is, before termination of nephrogenesis, may also inhibit nephron formation, for instance, by extrauterine growth restriction or the use of drugs in premature neonates such as aminoglycosides or NSAIDs (for closure of a patent ductus arteriosus).

Besides such environmental factors, genetic variations can be expected to influence nephron endowment as well. Within the limitation of using renal size as a marker for nephron endowment, variations in newborn renal size have been associated with single nucleotide polymorphisms in several genes that are well known to be of importance in nephrogenesis (such as *OSR1, RET, GDNF*, and *PAX2*) (Quinlan et al., 2007; Zhang et al., 2011).

Counting nephrons is currently only possible *ex vivo*, even though magnetic resonance imaging techniques are getting to the stage that *in vivo* estimations using stereology (the gold standard methodology) can be expected to become available in the next decade (Beeman et al., 2011). In the meantime, renal size is often used as a marker for nephron endowment. Unfortunately, variations in adult kidney size explain only about 10% of the variation in nephron numbers and only scarce data are available on renal numbers in children. However, a larger kidney at renal transplantation does provide a better renal survival with a lower risk of rejection and graft loss (Han et al., 2011).

Long-term implications of low nephron number, and possible role in progression of chronic kidney disease, are considered in Chapter 138.

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# CHAPTER 350

# Renal tubular dysgenesis

Michiel F. Schreuder

Renal tubular dysgenesis involves the absence or incomplete differentiation of proximal tubular nephron segments. Due to the lack of a patent nephron, it is characterized by (fetal) anuria and subsequent oligohydramnios, pulmonary hypoplasia, premature birth with severe and refractory arterial hypotension, and fetal or neonatal death (Gubler and Antignac, 2010). As the amount of amniotic fluid may be (near) normal up to 20–22 weeks of gestation, prenatal ultrasound screening may not identify the renal developmental problem. In addition to the renal abnormalities, ossification defects of the skull based on hypoplasia of the membranous bones with large fontanelles and wide cranial sutures are found.

The main cause for renal tubular dysgenesis is a genetic mutation in the renin–angiotensin system, which has shown a autosomal recessive trait (OMIM #267430). Up to 2011, around 100 patients have been described, indicating the low incidence of autosomal recessive renal tubular dysgenesis (Gubler and Antignac, 2010). Most patients have homozygous or compound heterozygous mutations in the genes encoding renin, angiotensin, angiotensin converting enzyme (ACE), or angiotensin II receptor type 1. Maternal use of ACE inhibitors or angiotensin II receptor blockers during pregnancy can have similar blocking effects on the fetal renin–angiotensin system, which may lead to renal tubular dysgenesis (Barr and Cohen, 1991).

Even though there is no actual renal function, ultrasound usually shows kidneys of normal size and architecture with an intact corticomedullary differentiation. Pathological examination of the kidneys reveals normal glomeruli, but incomplete tubular development with a reduced number of short and straight cortical convoluted proximal tubules. Other tubular segments may also be primitive, immature, or hypotrophic, and the muscular wall of arterioles are disorganized and thickened. Additional examination shows several non-specific histopathological changes, such as microcalcifications (in 66%) and medullary ray nodules (16%) consisting of tubules and stroma (Moldavsky, 2010).

Similar renal lesions are described in animals and humans that have a chronic and severe reduced perfusion of the fetal kidney, such as in major cardiac malformations, and in the donor fetus in the twin-to-twin transfusion syndrome (Genest and Lage, 1991). In addition, this may occur unilaterally when there is a local blockage of the renal blood supply (Delaney et al., 2009), for instance, due to subtotal renal artery occlusion.

Most patients with renal tubular dysgenesis do not survive beyond the neonatal period. A few patients have been described to survive with respiratory support, vasopressor treatment, and dialysis. A normal blood pressure was reached without support after 10–20 days, diuresis after a few days or as late as 5 months, and renal function recovered partially, as all patients still had chronic kidney disease at follow-up (Schreiber et al., 2010; Zingg-Schenk et al., 2008).

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# CHAPTER 351

# Congenital solitary functioning kidney

Michiel F. Schreuder

The leading causes for chronic kidney disease in children are congenital anomalies of the kidney and urinary tract (CAKUT) (Harambat et al., 2012). In addition, CAKUT can contribute to long-term health problems such as hypertension and renal dysfunction, and therefore is highly relevant for nephrologists. The distinct CAKUT category of congenital solitary functioning kidney (cSFK), for instance, due to unilateral renal agenesis/aplasia (see Chapter 346) or a multicystic dysplastic kidney, has long been considered not to pose any threats to an individual's health. These expectations were based on the absence of follow-up data on patients with a cSFK and the well-preserved renal function and health in kidney donors (Ibrahim et al., 2009).

In contrast, the hyperfiltration hypothesis described by Brenner and co-workers states that a reduction in nephron numbers leads to glomerular hyperfiltration with hypertension, proteinuria, and glomerulosclerosis in remnant nephrons over time (Brenner et al., 1996) (see Chapters 138 and 349). A solitary functioning kidney is usually enlarged due to hypertrophy when the renal mass reduction has occurred after completion of nephrogenesis. However, renal enlargement in cSFK may also be based on an increase in nephron formation. Information on nephron numbers in cSFK is lacking, but an increase in nephron numbers of 45% after fetal nephrectomy in sheep has been noted (Douglas-Denton et al., 2002). This still indicates a reduction in nephrons of 25–30% when compared to an individual with two kidneys, indicating that the hyperfiltration hypothesis is applicable to a cSFK.

Over the last years, follow-up data on patients with cSFK have become available, showing renal injury, as defined by hypertension and/or proteinuria, in up to 32% already during childhood (Westland et al., 2011). Renal function deteriorates during adolescence and during longer follow-up, renal survival of patients with a cSFK was only 60–80% at the age of 30 years (Sanna-Cherchi et al., 2009).

Within the group of cSFK, further differentiation in the renal risk can be made on the basis of the underlying diagnosis (60% renal survival in patients with unilateral renal agenesis/aplasia vs 80% in multicystic dysplastic kidney (MCDK)), and on the basis of additional urinary tract abnormalities. For instance, concomitant vesicoureteral reflux increases the risk of renal failure approximately threefold (Sanna-Cherchi et al., 2009) and blood pressure is higher in individuals with less hypertrophy of the cSFK (Dursun, et al., 2007).

These studies clearly illustrate the differences between kidney donors and cSFK patients, which may be explained by a different degree of glomerular hyperfiltration. Indeed, animal studies have shown that hyperfiltration is doubled when nephrectomy is performed during nephrogenesis when compared to nephrectomy in adulthood (Larsson et al., 1980). Furthermore, kidney donors have been screened to make sure that they are left with one optimal functioning kidney whereas the cSFK may show developmental problems as well, such as hypo (dys)plasia, with impaired functional consequences. Donor nephrectomy leads to compensatory hypertrophy, which is described in 77% of children with a MCDK (Schreuder et al., 2009), indicating some degree of hypo-(dys)plasia in the remaining 23%. This should be anticipated as many patients with a cSFK may have an underlying genetic alteration that influences renal development in general, and is not limited to one kidney (Song and Yosypiv, 2011).

Based on these findings, long-term infrequent follow-up of all patients with a cSFK seems to be indicated in order to detect signs of glomerular hyperfiltration at an early time point. Glomerular hyperfiltration with microalbuminuria is an established phenomenon in diabetes, and treatment with angiotensin type II receptor blockers or angiotensin-converting enzyme inhibitors has been shown to delay renal damage and failure (Ruggenenti et al., 2010). Even though studies showing a comparable effect in patients with cSFK are lacking, the similarities between the two situations may indicate that treatment of proteinuria or hypertension in patients with a cSFK should be based on identical drug schemes.

Having just one kidney indicates that trauma or infection with functional impairment may instantly lead to renal failure. In order to prevent this, additional measures are sometimes imposed to prevent such renal threats as much as possible, for instance, by advising individuals with a cSFK to refrain from contact/collision sports. There is no evidence to support such preventive measures, as renal loss is very rare, more likely to occur in accidents during non-contact sports/activities, and other serious injuries (e.g. to the brain or heart) are much more common (Grinsell et al., 2006). No restrictions are therefore needed, but patients should just be informed and be allowed to make an informed decision.

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# CHAPTER 352

# Duplex, ectopic, and horseshoe kidneys

Michiel F. Schreuder

Renal ectopia is a rare congenital defect where the kidney is not located in the renal fossa (Fig. 352.1B–D). During development, the kidney migrates upwards to its normal position, which can be disturbed by factors such as genetic anomalies, teratogens, and abnormal vasculature forming a physical barrier (Docimo et al., 2007). Simple renal ectopia implies that the kidney lies ipsilateral in the pelvis (Fig. 352.1B). However, in rare cases the kidney can even be located in the thorax. About 10% occur bilaterally, and in unilateral cases the left kidney is more frequently ectopic (56%).

In crossed renal ectopia, the kidney is located contralateral to the side where the ureter enters the bladder, usually below the orthotopic organ (Fig. 352.1C). Usually the orthotopic and the ectopic kidneys are fused (crossed fused ectopia, Fig. 352.1D) (Koff and Wise, 1996). Crossed renal ectopia has been speculated to result from fusion of the ureteric buds (see Chapter 343) with only one nephrogenic cord after lateral flexion of the 'tail' of the embryo. In this position, the Wolffian duct (and with it the ureteric bud) cross over the midline and fuse with the contralateral nephrogenic cord (Cook and Stephens, 1977).

In most patients, renal ectopia is asymptomatic which explains why the incidence in autopsy series (1/1000) is much higher than with clinical presentation (1/10,000) (Gleason et al., 1994). Due to prenatal ultrasound screening, most cases are detected *in utero* rather than during the evaluation of abdominal pain or a urinary tract infection. Ultrasound will also show a high rate of hydronephrosis (11–51%), either due to high-grade vesicoureteral reflux

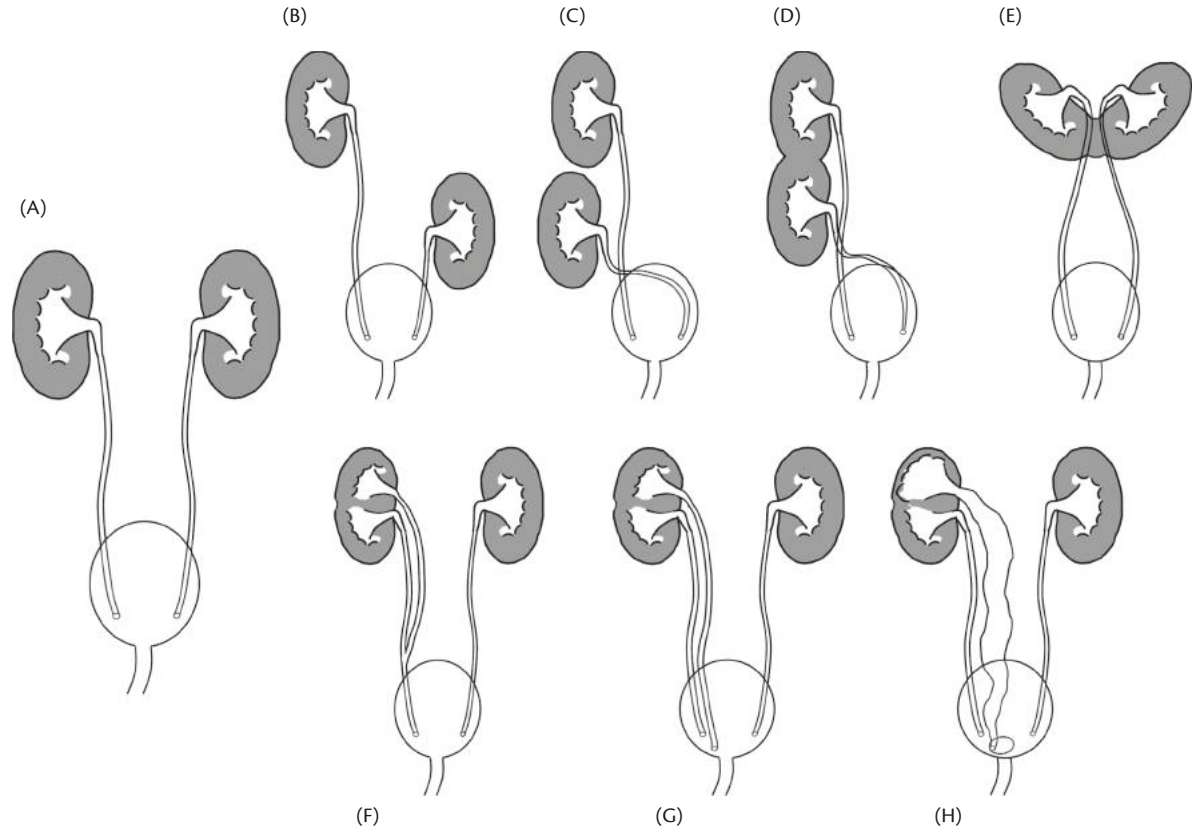


**Fig. 352.1** Various anatomical variations in renal location, fusion anomalies, and duplex urinary systems. (A) Normal anatomy. (B) Simple renal ectopia. (C) Crossed renal ectopia. (D) Crossed fused renal ectopia. (E) Horseshoe kidney. (F) Incomplete duplex urinary system. (G) Complete duplex urinary system. (H) Complete duplex urinary system with ureterocele and dilated urinary tract of the upper moiety.

(VUR) (in 2–58% of patients) or obstruction due to a high insertion of the ureter on the renal pelvis (Docimo et al., 2007; van den Bosch et al., 2010). As the contralateral kidney is abnormal in about half of the patients with renal ectopia, evaluation with ultrasound, renography, and voiding urethrocystography (VCUG) should be performed in all patients. Therapy and follow-up needs to be individualized on the basis of the evaluation, associated renal dysplasia, and extrarenal malformations.

In a horseshoe kidney, fusion of the two kidneys takes place, but the two renal moieties are still located on both sides of the midline (Fig. 352.1E). This is the most frequent renal fusion anomaly with an estimated incidence of 1/400 to 1/1800 (Docimo et al. 2007). The abnormal fusion occurs early in development, either due to abnormal migration of nephrogenic cells linking the two kidneys or the kidneys are brought closely together during a longer than normal period due to abnormal flexion or growth of the spine or pelvic organs, resulting in fusion of the adjacent metanephroi (Docimo et al., 2007; O'Brien et al., 2008). As the lower poles are fused in the midline, a horseshoe kidney is usually located lower than normal and orientation of the renal axis is shifted, which may guide diagnosis during abdominal ultrasound. Fibrous tissue is usually found at the site of the fusion (isthmus), but normal renal parenchyma may be found as well. Blood supply both to the horseshoe kidney as well as to the isthmus is highly variable. The ureters are inserted high in the renal pelvis and cross anterior to the isthmus in most cases, both contributing to the high incidence (about 1/3) of pelviureteric junction obstruction in horseshoe kidneys. Due to the stasis of urine in the pelvis, the risk of urolithiasis is also increased (up to 20%).

Diagnosis is made by ultrasound, for instance, after abnormal prenatal screening, but the isthmus may be difficult to visualize. Magnetic resonance imaging/urography, renography, and VCUG may be used to document the anomaly and its consequences for urine flow. Horseshoe kidney is frequently seen in Turner syndrome (up to 20%) and is associated with other malformations of the gastrointestinal, cardiovascular, or skeletal tract.

A duplex urinary tract, irrespective of the degree of duplication, is present in 0.8% at autopsy, of which about 20–35% is bilateral (Docimo et al., 2007). During embryogenesis, interaction between the ureteric buds and the nephrogenic cords is essential for kidney development. A duplex system forms when two separate buds arise from one side or a single bud bifurcates and reaches the metanephric mesenchyme. The majority of duplex systems are incomplete (Fig. 352.1F), indicating that the ipsilateral ureters fuse before entering the bladder. This is rarely clinically relevant, which is different from a complete duplex system (Fig. 352.1G). Such duplex systems may be categorized as anomalies of the upper moiety, with associated ureterocele or ectopic ureter, or of the lower moiety, frequently associated with VUR (Fig. 352.1H). Ureteroceles are the most frequent cause of lower urinary tract obstruction in girls, and second in boys after posterior urethral valves. Ectopic ureters can result in an uncontrollable continuous flow of urine and therefore incontinence, for example, with insertion in the vagina or bladder neck. Of note, ectopic ureters in males always insert proximal to the urinary sphincter, thereby preventing urine incontinence in most cases. A (suspected) duplex system or ureterocele after prenatal screening or a urinary tract infection warrants thorough evaluation of the anatomy and urine flow using ultrasound, VCUG, and renography.

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# CHAPTER 353

# Pelviureteric junction obstruction and megaureter in children

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Dilatation of the upper urinary tract antenatally or in infants can be due to either a urine flow obstruction, vesicoureteral reflux, a combination of obstruction and reflux, or as an anatomical variation without consequences for the urine flow (Docimo et al., 2007). This chapter focuses on obstruction as the cause of urinary tract dilatation.

Two main sites of urine flow obstruction in the upper urinary tract are located at the pelviureteric and vesicoureteric junctions. Such obstructions can be of a variable degree, ranging from (sub)total to intermittent. The urine flow obstruction leads to an increased pressure in the urinary tract that will generally lead to a dilatation. However, urinary tract dilatation is not a *condicio sine qua non* for the diagnosis of obstruction.

Nowadays, most cases are suspected on the basis of a prenatal screening ultrasound showing dilatation of the renal pelvis (hydronephrosis, incidence of 1/100 to 1/500) and/or the ureter (megaureter). In these patients, it is essential to differentiate between patients that require surgery and patients that can be monitored safely, as the underlying urinary tract abnormality may pose no threat and be self-limiting with time. In order to exclude or confirm the diagnosis of a pelviureteric junction obstruction (PUJO) or a vesicoureteric junction obstruction (VUJO), postnatal evaluation with (serial) ultrasound and diuretic renography (Gordon et al., 2011) is indicated (Nguyen et al., 2010). Unfortunately, there is no consensus on a cut-off value for the maximal dilatation of the renal pelvis that may be considered normal, which has an impact on the incidence of PUJO in neonates that are evaluated. The definition of megaureter is more straightforward (ureter diameter > 8 mm), as the lumen of the ureter is negligible under normal circumstances.

Postnatal analysis of neonates with antenatal hydronephrosis show that 10–30% is caused by PUJO, and 5–10% by VUJO/megaureter (Nguyen et al., 2010). A mild degree of hydronephrosis provides a 4.9% (95% confidence interval 2.0–11.9%) risk at PUJO, whereas a severe degree has a 54.3% (95% CI 21.7–83.6%) risk. Several other congenital anomalies are found during evaluation of prenatal hydronephrosis, but the majority of cases do show spontaneous resolution (41–88%) (Nguyen et al., 2010). PUJO occurs bilaterally in 20–40%, and about one in four patients with megaureters are found to have bilateral anomalies.

Most cases of PUJO are based on an intrinsic obstruction of the ureter around the junction with the renal pelvis, for which genetic mutations of genes involved in ureter myogenesis have been implicated (Lye et al., 2010). In contrast, PUJO can sometimes be caused by polar vessels crossing the ureter and causing an indentation, which may necessitate a different surgical approach. Furthermore, PUJO can present intermittently as a relative narrowing of the junction which may cause no relevant obstruction during normal diuresis, but may lead to stasis with capsule tension during increased volume load. In extreme cases, this may even lead to a (sub)total obstruction due to an extreme alteration in the angle between renal pelvis and ureter. Such patients may have no, or just slight, dilatation on renal ultrasound outside episodes of clinical complaints (Tsai et al., 2006).

Megaureters are classified according to the pathogenesis (primary vs secondary), and can be obstructive, refluxing, refluxing-obstructed, or non-refluxing non-obstructed. In such abnormal ureters, an abundance of collagen, produced by the smooth muscle cells, has been found as well as an abnormal response of the smooth muscle cells to certain neurotransmitters (Hodges et al., 2010). In the primary obstructive megaureter, increased levels of predominantly collagen type I have been found in the distal ureter, leading to a functional obstruction with the risk of high-urine pressure in the kidney or urine stasis with the risk of infection or stones, all of which may lead to renal damage. However, as many megaureters spontaneously resolve over time, it is essential, but equally difficult, to differentiate between cases that need intervention and patients that can safely be observed. Antibiotic prophylaxis has been shown to reduce the number of urinary tract infections by 55% (Gimpel et al., 2010), and should therefore be started directly postnatal in all patients. Unfortunately, no good parameters have been identified that dictate which approach is needed, other than increasing renal functional compromise. If surgical treatment is indicated, it involves ureteral reimplantation after resection of the distal obstructive part of the ureter, preferably after the age of 1 year to reduce the need for secondary operative repair (Docimo et al., 2007).

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# CHAPTER 354

# Posterior urethral valves

Michiel F. Schreuder

Posterior urethral valves (PUV) is the most common congenital cause of lower urinary tract obstruction in childhood in males, and a common cause (15–17%) for end-stage renal disease in childhood. PUV occur in male infants with a documented incidence of 1/5,000 to 1/8,000 (Krishnan et al., 2006; Docimo et al., 2007), which is thought to be an underestimation due to unrecognized disease in milder cases and fetal loss of severe cases.

The embryologic origin of PUV has not been definitively established. In 1919, Young et al. first described a classification of PUV into three types that has been used since, and the embryology was formulated accordingly (Young et al., 1919). However, recent studies do not support these classifications, as different types were found to represent identical entities (type I and II). Both the classification and the embryology therefore still leave room for debate. As there is no animal model known to present spontaneous PUV, such an approach cannot be used to elucidate the embryology.

During early stages of development, the urethra is formed and needs to form a continuum with the bladder, which is formed from the urogenital sinus. Persistence of (part of) this membrane will lead to a remnant rim that may obstruct urine flow (Young type III), representing 5% of all PUV. Type I represents 95% and has a different origin of the obstructive tissue. During development, the Wolffian ducts insert into the anterolateral wall of the cloaca, forming the inferior urethral crest. Remnant leaves from this crest may sweep into the urethra and fuse, thereby causing an obstruction in urine flow.

Formation of the male urethra is completed by 14 weeks of gestation, indicating that signs of obstruction can be expected from that moment of development onwards. Indeed, prenatal suspicion of PUV is possible as early as the 13th week of gestation (Maruotti et al., 2006).

Most commonly, PUV is suspected on the basis of a screening antenatal ultrasound. Ultrasound will not detect PUV itself, but recognizes the consequences of lower urinary tract obstruction with a dilated thick-walled bladder and dilation of the prostatic portion of the urethra (the so-called keyhole sign). Additional signs may be uni- or bilateral dilation of the ureter and/or the renal pelvis, and renal hyperechogenicity with loss of corticomedullary differentiation suggesting renal dysplasia. These signs are all explained by the high pressure within the urinary tract due to the urine outflow obstruction during development.

After birth, urine drainage has to be secured by placement of a bladder catheter and caution should be taken to prevent urinary tract infections. Postnatal ultrasound and voiding cystourethrogram are performed to evaluate the possible presence of PUV and its consequences for the development of the urinary tract (see Fig. 354.1). In cases where the urine pressure in the kidney was high enough to lead to destruction of normal renal development, evaluation of both glomerular (such as glomerular filtration rate estimation) and tubular (such as sodium wasting, renal tubular acidosis, and impaired urine concentrating ability) functions is essential. Definitive diagnosis can only be made during endoscopy, at which time ablation of valves can be performed.

PUV can occasionally be diagnosed in older children, especially in milder cases and children born without prenatal ultrasound screening. Such infants may present with urinary tract infections, failure to thrive, urine dribbling, a poor urine stream, or enuresis in older children.

Consequences of PUV depend on the degree of renal dysplasia and bladder dysfunction. The pathways leading to bladder dysfunction form a vicious cycle, starting with an increase in voiding pressure that secures emptying of the bladder at first. But with increasing hypertrophy of the bladder smooth muscles, incomplete emptying of the bladder reoccurs, which in itself leads to a further increase in the bladder pressure and ultimately decompensation of the detrusor muscle. The continuously high intravesical pressure leads to vesicoureteral reflux and the high pressure is transmitted back to the renal pelvis, resulting in increased apoptosis and renal fibrosis in which transforming growth factor beta is involved (Docimo et al., 2007). The resulting renal dysfunction may vary from mild to severe with the need for renal replacement therapy even in the first few days after birth. In fact, there is a continuous

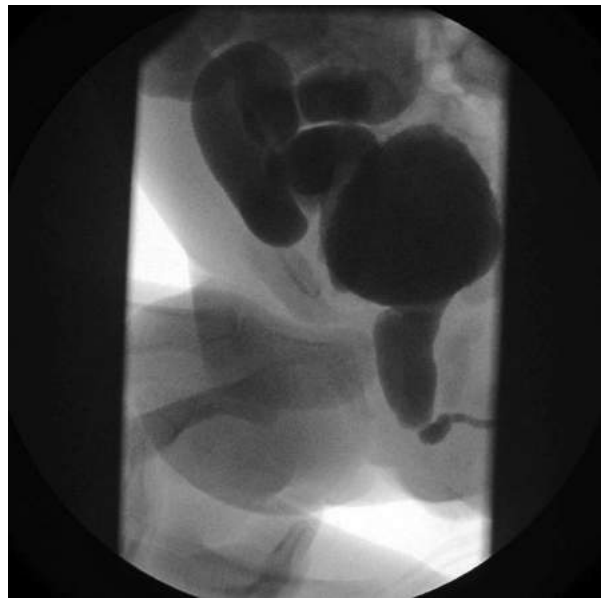

**Fig. 354.1** Classical image of a voiding cystourethrogram from a patient with posterior urethral valves and extensive vesicoureteral reflux.

increase in chronic renal failure with increasing age, and two-thirds of patients with PUV need renal replacement therapy by the age of 30 years (Sanna-Cherchi et al., 2009).

As the renal damage associated with PUV is, at least in part, explained by the urine outflow obstruction and subsequent high pressure in the urinary tract, a logical strategy is to relieve pressure during development. Indeed, animal studies support that the relief of obstruction may (partially) salvage the kidney (Sun et al., 2010). Ideally, such relief should be obtained as soon as possible after the occurrence of obstruction. Fetal vesico-amniotic shunting does abolish obstruction, but this intervention is associated with an increased chance of miscarriage (1–2%), fetal morbidity (such as bleeding or infection), and maternal morbidity (infection). As this was mainly used as a last resort, and therefore predominantly in severe cases at a relatively late time-point, no significant benefit from intervention was found. A randomized controlled trial (the PLUTO trial) was initiated to prospectively study the effectiveness of vesico-amniotic shunting (Morris and Kilby, 2009). Although recruitment was poorer than expected, neonatal survival seemed to be higher in fetuses that had undergone shunting *versus* the conservative management control group (Morris et al., 2013) Unfortunately, it is not yet clear whether the renal dysplasia associated with urethral valves is completely caused by the high urine pressure, or is just part of the congenital anomaly: if the latter holds true, prenatal relief of the high urine pressure cannot be expected to improve renal outcome.

In addition to the renal failure, a large proportion of patients with PUV continue to show lower urinary tract symptoms, such as detrusor overactivity, and high post-void urine residue, for which intermittent catheterization or a double micturition programme is needed (Caione and Nappo, 2011).

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# CHAPTER 355

# Primary vesicoureteric reflux and reflux nephropathy

Heather Lambert

## Epidemiology

The true prevalence of vesicoureteric reflux (VUR) remains uncertain because early diagnosis requires invasive radiology and most VUR spontaneously resolves. It is, however, important because views on prevalence underpin differing strategies for investigating and screening. It may be as low as 1–2% (Coulthard, 2002) but may be higher (Williams et al., 2008), depending on the population studied and selection criteria for investigation. Ransley (1978) refers to a series of screening studies in the 1950s and 1960s where only 7 of 535 healthy neonates and children were found to have VUR. Suggestions of higher prevalence (up to 30%) are based on case series of different populations including preterm babies, hospitalized children with a wide range of diagnoses, those referred with UTI in whom the reliability of that diagnosis was later analysed, and those with urogenital and other congenital anomalies (Sargent, 2000; Tullus, 2015). VUR is found in association with congenital abnormalities of the urinary tract such as ureteric duplication, contralateral multicystic dysplastic kidney, or renal agenesis. VUR occurs in 25–40% of children presenting with urinary tract infection (UTI) and in 3–19% of infants with hydronephrosis on antenatal ultrasound scan (USS) screening (Williams et al., 2008). The figures depend on the population investigated postnatally; in a review of 34 studies by the American Urological Association the rate of VUR was 16% (Skoog et al., 2010). It remains to be demonstrated whether this increased risk of VUR will necessarily be associated with an increased incidence of UTI, renal scarring, or other morbidity. Thus whilst some advocate investigation of all with antenatal hydronephrosis for VUR, others, including ourselves, opt for a more selective approach. Whilst VUR can exist in isolation, VUR may be associated with renal segmental parenchymal thinning and calyceal clubbing (Hodson and Edwards, 1960). Once called chronic pyelonephritis, the term generally now used is reflux nephropathy (RN). When a diagnosis of RN is made, it is usually not possible to distinguish the relative contribution of reflux-associated developmental dysplasia and postnatally acquired defects, unless there has been sequential parenchymal imaging. In the United Kingdom, pyelonephritis accounts for 7% of end-stage renal failure (ESRF) in adults (The Renal Association, 2014), but for children the figures are hidden in other diagnostic categories for example, dysplasia +/− VUR. RN exists in 5% of North American children receiving kidney transplants and 3.5% of paediatric dialysis patients (NAPRTCS, 2010). These may be underestimates because some RN cases may be hidden in diagnostic categories including 'tubulointerstitial disease' and 'unknown' (Neild, 2009). RN occurs in approximately of 5% of children investigated after first UTI, allowing estimation that around 0.5% of girls aged 0–16 years have RN (Coulthard et al., 1997).

## Aetiology and inheritance

VUR is usually congenital but may occasionally be acquired, for example, after urological surgery, including transplant surgery. There is good evidence that primary VUR is a genetic disorder (Murawski and Gupta, 2008). Numerous genes control ureteric morphogenesis and functional maturation of the bladder and ureter (Williams et al., 2008; Lye et al., 2010). There is a high concordance of VUR in identical twins (Kaefer etal., 2000) and kindreds with multiple affected members with apparent dominant (Chapman et al., 1985; Feather et al., 2000) or recessive (Weng et al., 2009) inheritance exist. When first-degree relatives of index cases are screened by cystography, around one-third of siblings (Hollowell and Greenfield, 2002) and up to two-thirds of offspring (Noe et al., 1992; Scott et al., 1997) have VUR. Thus, while yet-to-be defined environmental factors might predispose to primary VUR, genetics must be important. The definition of genetic factors that contribute to VUR and RN will illuminate mechanisms of normal human renal tract development. Information from such studies may also have clinical utility by giving families reasons why a malformation has occurred and may also allow the prediction of VUR status in relatives of index cases. Primary VUR can occur in the renal coloboma syndrome, caused by mutations of *PAX2* (Sanyanusin et al., 1995) encoding a transcription factor expressed in developing renal tracts (Winyard et al., 1996). Although *PAX2* mutations have not been found in non-syndromic VUR (Choi et al., 1998), defects in other genes might be relevant. VUR is less likely to be found in black children than white children after UTI (Chand et al., 2003). VUR is increased in association with duplex kidney, multicystic dysplastic kidney, and polycystic kidney disease (Atwell et al., 1977; Koslowe et al., 2003, Guarino et al., 2005; Siomou et al., 2006).

## Clinical features

VUR may be asymptomatic. There is, however, evidence of increased UTI in those with VUR and VUR is a major risk factor for progressive renal damage associated with UTI. In some cases VUR is associated with abnormal voiding patterns and with constipation

and dysfunctional elimination syndromes. Perceptions that UTI with VUR leads to RN via ascending infection stimulated an era of 'active-treatment' of VUR (Craig et al., 2000). RN can follow UTI, especially if antibiotic treatment is delayed (Coulthard, 2009). Prospective studies comparing antireflux surgery with antibiotic prophylaxis fail to show significant differences in acquisition of kidney defects (Olbing et al., 2003; Jodal et al., 2006; Hodson et al., 2007) or progression to ESRF (Smellie et al., 2001). However, not all chronic radiological kidney defects after UTIs are associated with VUR (Gordon et al., 2003) and not all RN is pyelonephritic because some individuals born with VUR have malformed kidneys (Risdon, 1993; Yeung et al., 1997). Accordingly, the rationale for active treatment of VUR has been questioned (Craig et al., 2000) and prospective trials have been initiated in children with VUR and UTI (Mathews et al., 2009). Active treatment is supported by the The Randomized Intervention for Vesicoureteral Reflux (RIVUR) trial which reported (RIVUR Trial Investigators et al., 2014) that prophylactic antibiotics reduced the risk of recurrent infection compared with placebo.

## Investigations

VUR is diagnosed by the demonstration of backflow of urine from the bladder into the upper renal tract. The main techniques used are cystography with contrast fluid (MCUG) and direct radionuclide cystography. In both of these methods, material is instilled into the bladder via a catheter. MCUG gives better demonstration of anatomy and grading but has a higher radiation dose. Ultrasound with contrast cystography is used in some centres with particular expertise but it still requires bladder catheterization. Indirect radionuclide cystography is appealing because it avoids the need for bladder catheterization, but requires cooperation and control of micturition so is not suitable for investigation of babies and toddlers.

Investigations may be initiated because of a family history of VUR, an abnormal antenatal scan or following UTI and are further discussed in Chapter 180.

### Grading of VUR

Grades of severity of VUR are recognized, designated grades I to V by the International Reflux Study Committee in 1981 (International Reflux Study Committee, 1981) and still generally accepted worldwide (Box 355.1; Fig. 355.1).

VUR is well described to be intermittent and variable in grade at different times during an examination and is not an 'all or none' phenomenon (Hellström and Jacobsson, 1999). VUR in both humans and animals can be influenced by variations in urine flow (Zinner and Paquin, 1963; Ekman et al., 1966) which may be related to changes in ureteric peristalsis. Despite that, grading of VUR remains important because higher grades of reflux are associated with increased chance of renal scarring (Smellie et al., 1992; Stokland et al., 1998; Obling et al., 2003) of reflux-associated dysplasia, and with less chance of spontaneous resolution (Elder et al., 1997; Austin and Cooper, 2010).

**Box 355.1** Grades of vesicoureteric reflux

I Into ureter only.

II Into ureter, pelvis and calyces with no dilatation.

III With mild to moderate dilatation; slight or no blunting of fornices

IV With moderate dilatation of ureter and/or renal pelvis and/or tortuosity of ureter; obliteration of sharp angle of fornices.

V Gross dilatation and tortuosity; no papillary impression visible in calyces.

### The child with a family history of VUR

This is a very important group of children, who are at high risk of developing UTI and RN, in whom there is the possibility of preventative management. Screening of asymptomatic siblings and offspring is controversial. Some advocate that early identification of children with reflux may reduce renal scarring by prevention of episodes of UTI and by early detection and treatment of UTI; but others suggest this approach has its risks and may lead to significant overtreatment of clinically insignificant VUR. However, it remains to be shown whether screening of asymptomatic relatives for VUR offers advantages over increasing awareness of parents and healthcare professionals that first-degree relatives are a high-risk group at increased risk of UTI. Moreover when asymptomatic children are found to have VUR through screening, it is not known whether treatment with prophylactic antibiotics offers any advantage over high index of suspicion and prompt treatment, nor how long antibiotics should be continued for. It has been suggested that early surgical treatment of severe VUR detected on screening may prevent renal damage but prospective studies are required to confirm this (Sweeney et al., 2001). Children who have a family history of VUR who develop a UTI warrant more intensive investigation than those without (National Institute for Health and Clinical Excellence, 2007).

Our own practice is to give education and information about the risks and uncertainties and facilitate rapid access to our assessment unit for diagnosis and treatment of UTI to all families with a history of VUR or RN, whether these families are identified via siblings, adults in nephrology clinics, or mothers attending for antenatal care or by direct referral. In addition, we offer an MCUG for babies to detect VUR, or a dimercaptosuccinic acid (DMSA) scan to detect RN for older siblings. We find parental views on intensity of investigation and management vary considerably and are much influenced by their personal experience of the condition.

## Treatment and outcome

Historically, both medical and surgical management strategies for VUR have been introduced without controlled studies documenting long-term benefit.

### Resolution of VUR with time

Resolution of VUR over time with medical treatment is related to the grade of VUR and the age of the patient (Fig. 355.2). In general, a lower grade of reflux has a better chance of spontaneous resolution. A review of studies on nearly 2000 patients suggests that for children with grade I or II reflux there is resolution in about 50% after 2 years and in about 80–90% after 5 years. For grade III reflux, increasing age at presentation and bilateral reflux decrease the probability of resolution. Bilateral grade IV and V reflux have the poorest chance, with spontaneous resolution in < 20% of patients after 5 years (Elder et al., 1997), though continued resolution of

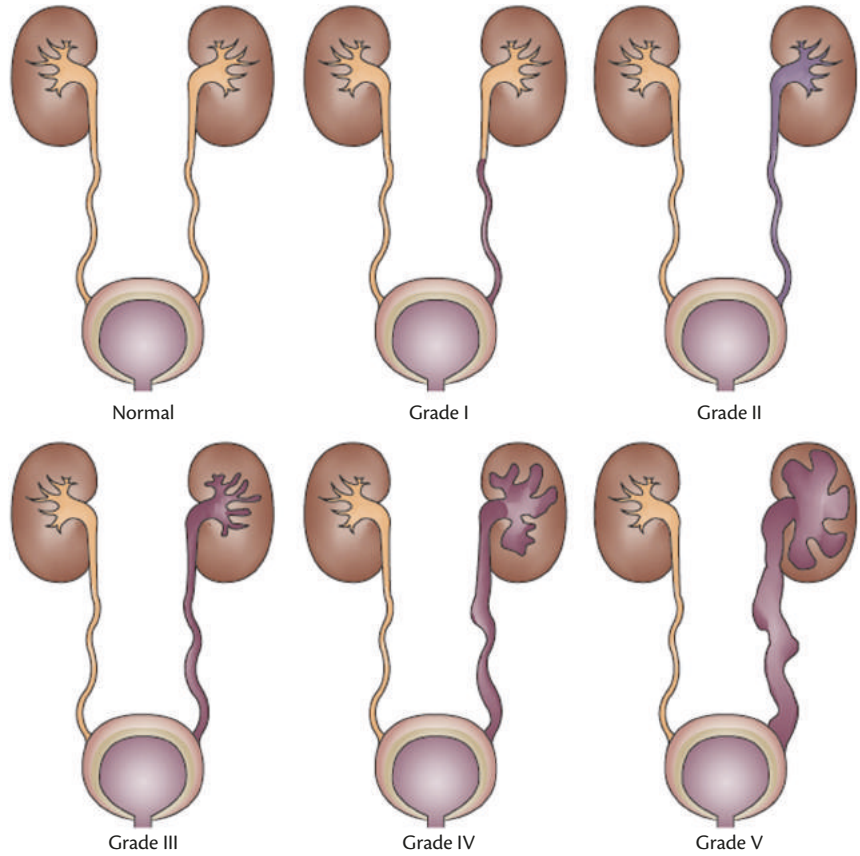


**Fig. 355.1** Grading of VUR. http://www.pediatricurologybook.com/vesicoureteral_reflux.html (Cooper et al.,).

grade III and IV reflux has been reported from 15% at 5 years to 50% at 10 years (Smellie et al., 2001). Models and nomograms have been produced using additional factors together with grade of VUR to predict resolution (Estrada et al., 2009; Austin and Cooper, 2010). It is not known whether urine infection affects resolution of VUR but in monkeys there is some evidence it may delay normal resolution (Roberts et al., 1992).

## Medical management

Since it is known that in the vast majority of cases VUR will resolve with time, the aim in medical management of VUR is twofold. The aim of using prophylactic antibiotics is to prevent or reduce frequency of UTI and pyelonephritis. The use of education, awareness, and rapid access is to enable UTIs to be diagnosed and treated very promptly. Audit of a nurse-led study working closely with GP practices showed reduction of scarring rate with rapid treatment within 3 days of onset of symptoms (Coulthard et al., 2014). Both strategies aim to reduce renal scarring, whilst waiting for resolution of VUR.

Antibiotic prophylaxis has been used for many years based on a number of older studies and case series which appeared to show that antibiotic prophylaxis provided protection against recurrent UTI (Lohr et al., 1977; Smellie, 1978; Jodal et al., 1992; Olbing et al., 1992; Weiss et al., 1992). However, there is ongoing uncertainty as to the effectiveness of prophylaxis (Williams et al., 2001). More recently the Swedish Reflux trial reported that either prophylaxis or endoscopic VUR correction reduced risks of febrile UTIs and acquisition of renal defects (Brandstom et al., 2010a, 2010b). The PREVENT study (Craig et al., 2009) provided evidence for efficacy of antibiotic prophylaxis in reducing UTI in some groups and this view is supported by the 2011 Cochrane review (Williams et al., 2011). Though others dispute this and interpret the current evidence differently. No benefit was shown in a different meta-analysis of 11 studies (Dai et al., 2010). The American Academy of Paediatrics produced a complex meta-analysis based on six studies (Garin et al., 2006; Montini et al., 2008; Pennesi et al., 2008; Roussey- Kesler et al., 2008; Craig et al., 2009; Brandström et al., 2010a, 2010b) which failed to show overall benefit. Three studies (Roussey–Kesler 2008; Craig et al., 2009; Brandström et al., 2010a, 1010b), showed moderate benefit for certain subgroups and one of these (Craig et al., 2009), was the only paper blinded and placebo controlled. In addition three papers in the meta-analysis excluded high-grade VUR (> grade 3) (American Academy of Pediatrics, 2011). Four studies (Garin et al., 2006; Montini et al., 2008; Pennesi et al., 2008; Roussey-Kesler et al., 2008;) failed to adequately account for adherence to the antibiotic treatment therapy. Poor adherence may compromise clinical trial outcomes and recommendations derived from them. Breakthrough infections may be due to non-compliance or true bacterial resistance. Compliance with antibiotic prophylaxis is recognized to be low, even in studies (Rodriguez et al., 2011) and has been variably estimated to be between one-third and two-thirds of patients (Daschner and Marget, 1975; Smyth and Judd, 1993) or even lower at 17% in a study where 58% of patients on prophylaxis had a UTI within a year (Hensle et al., 2007). Many studies quoted in meta-analyses have methodological limitations and currently the

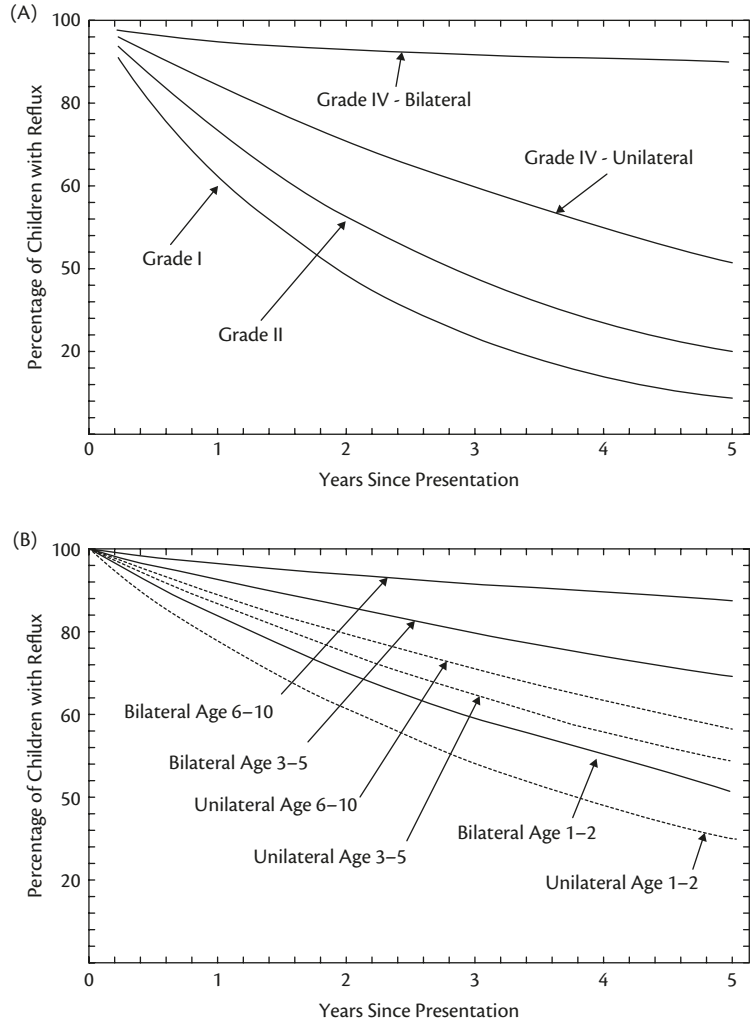


**Fig. 355.2** Resolution of VUR with time (Elder et al., 1997).

best data is from the North American RIVUR study. This 2-year, multisite, randomized, placebo-controlled trial involved 607 children with vesicoureteral reflux diagnosed after a first or second febrile or symptomatic urinary tract infection. Prophylaxis reduced the risk of recurrences by 50%. The occurrence of renal scarring did not differ significantly between the prophylaxis and placebo groups but was lower than in some other studies—perhaps related to vigilance associated with study participation. A longer-term study is required to look at effect on scarring. As expected, there was a higher incidence of trimethoprim-sufamethazole resistance when breakthrough UTI occurred in the treatment group (RIVUR Trial Investigators et al., 2014).

Trimethoprim, nitrofurantoin, or cephalexin are frequently used for prophylaxis. Non-adherence should be suspected when the infecting organism is sensitive to the prophylactic antibiotic prescribed. There is animal evidence (Slotki and Asscher, 1982) and clinical experience that very prompt treatment, within hours or a day or two of onset of symptoms, is important in preventing scarring (Coulthard, 2009). Thus it may be that education and awareness together with open hospital access for rapid diagnosis of UTI (without waiting for confirmatory culture results to commence treatment) is equally or more important than prophylaxis.

Whilst the aim of prophylaxis is to obtain high concentration of the antibiotic in the urine with minimal effect on normal body flora there is little data on the effect of long-term antibiotic prophylaxis on bowel and peri-urethral flora or on drug resistance in the community. Adverse effects of prophylaxis are not well recorded but may include gastrointestinal upset, increased risk of vaginal candidiasis, and very rarely more serious effects like rashes and bone marrow suppression (Uhari et al., 1996). Probiotics have been suggested to be as effective as antibiotic prophylaxis and warrant further study (Lee et al., 2007). Optimum duration of prophylaxis is not known; some propose a fixed time period or up to a certain age. Clinical evidence and animal studies suggest continued susceptibility of vulnerable kidneys to scarring at any age and thus logically active medical treatment, whether antibiotic prophylaxis or close urinary surveillance, should continue as long as VUR persists (Coulthard. 2002, 2009). However there is good clinical experience of antibiotic prophylaxis being successfully discontinued in some selected groups of children with persistent VUR (Cooper et al., 2000; Thompson et al., 2001; Al-Sayyad et al., 2005). There is no real evidence that helps in answering the difficult and the important question of how long to continue antibiotic prophylaxis when VUR does not resolve.

## Surgical management

There are two main forms of surgical treatment of VUR, endoscopic subureteric injection and reimplantation.

### Endoscopic subureteric injection

Injection of tissue-augmenting substances is done under general anaesthetic as a day case procedure. The term STING (initially referring to the technique when Teflon® is injected) is frequently used generically to refer to this type of procedure. The success rate in abolition of VUR varies with the centre, the material used, the timing of re-evaluation, and test used in re-examination. Overall the success rate varies with preoperative grade of VUR, ranging from 80–90% for grade I and II, to 50–60% for grades IV and V (Elder et al., 2006; Routh et al., 2010). There is a lack of controlled studies of the technique and studies have included large numbers of grade I and II VUR which tend to have spontaneous resolution of VUR. There have been concerns regarding long-term effects including migration of foreign materials. The longevity of the treatment and need for repeat are not fully known.

### Open surgical re-implantation

Surgical success in curing VUR with re-implantation is high, > 95% overall, whatever the grade of reflux (Elder et al., 1997; Barrieras et al., 2000). This is, however, a major operation requiring a stay of several days in hospital with the associated risks and costs and there remains a very small risk of obstruction following re-implantation surgery. Newer techniques such as laparoscopic re-implantation are now being reported (Marchini et al., 2011; Smith et al., 2011).

## Comparison of medical versus surgical treatment for VUR

Two large, multicentre, prospective trials of medical versus surgical treatment for children with severe VUR, now quite old, did not show superiority of either treatment (International Reflux Study Committee, 1981; Birmingham Reflux Study Group, 1987; Smellie et al., 1992; Weiss et al., 1992; Olbing et al., 2000). Neither surgical nor medical treatment appears to completely protect against progression of scarring, though apparent progression may result from contraction of a scar or a differential rate of growth of normal versus scarred kidney tissue, and although the frequency of UTI was similar there was a reduction in clinical pyelonephritis in the surgical group, though no difference in renal scarring. Surgical correction of VUR does not appear to improve the outcome for renal function in children with severe VUR and bilateral nephropathy (Smellie et al., 2001). There is little evidence regarding the optimum management in cases where severe VUR is detected by screening. Retrospective data suggests that the outcome might be better for infants with grade IV or V reflux detected without UTI and treated surgically, though there are no prospective randomized studies on this subgroup yet (Sweeney et al., 2001). In the Swedish Reflux study, prophylaxis reduced the rate of UTI recurrence and new renal damage, and endoscopic injection the rate of UTI recurrence in girls but boys were not shown to benefit from active treatment (Brandström et al., 2010a, 2010b).

A Cochrane review of 11 studies included seven papers comparing surgery plus antibiotics versus antibiotics alone and two papers comparing different materials for endoscopic treatment and two comparing antibiotics with no intervention. There was no difference in rates of UTI overall but in two studies there was a significant decrease in frequency of febrile UTI in patients surgically corrected over those treated with antibiotics alone, but in five studies there was no difference in formation of new renal scars. The conclusion was that the 'additional benefit of surgery over antibiotics was small at best' (Hodson et al., 2007). A later review in 2011 concluded that the added benefit of surgical or endoscopic correction of VUR over antibiotic treatment alone remains unclear (Nagler et al., 2011).

The choice of treatment therefore remains an individual judgement that will be based on a number of factors. Breakthrough infection, despite medical treatment or because of non-compliance, remains a commonly used factor for consideration of surgical treatment, as does deterioration of DMSA appearance. There is an understandable reluctance to continue prophylactic antibiotics indefinitely and a finality about successful surgical treatment of VUR which is appealing if VUR does not resolve spontaneously. Where there is no clear evidence of superiority of one treatment then patient and parental preference will clearly be major factors.

Recognition of the development of acquired scarring of transplanted kidneys by UTI in association with VUR has led to adoption of antireflux surgical procedures at the time of transplant in some centres (Vasdev et al., 2010) (see Chapter 179).

## VUR and altered bladder function

Bladder and bowel voiding dysfunction may predispose to infection and prolong the time for resolution of VUR. Urodynamic dysfunction, bladder instability, or high intravesical pressures are commonly found in infants, especially boys, with severe VUR (Yeung et al., 1998; Sillen, 1999; Chandra and Maddix, 2000; Willemsen and Nijman, 2000). Urodynamics in normal infants are not easily studied for comparison and the relationship of abnormal urodynamic patterns to the pathogenesis of VUR is not fully understood. Aggressive treatment of constipation and bladder training may help.

## Long-term sequelae

The long-term outcome appears to be mainly related to the development of RN rather than the reflux itself. However, VUR which does not resolve may lead to risk of recurrent UTI in adulthood and particularly during pregnancy. The terms renal scarring, RN, and chronic pyelonephritis are often used loosely and, sometimes, interchangeably which leads to confusion. Focal renal scarring is usually associated with previous UTI, and is usually inferred from investigation findings, for example, the photon-deficient areas on a radioisotope DMSA scan or the appearance of an ultrasound or intravenous urogram. RN refers to a spectrum of renal diseases associated with VUR which include renal scarring, dysplasia of various degrees, and some *in utero* renal damage. In most studies it is not clear what proportion of RN represents congenital anomalies versus defects acquired from pyelonephritis; indeed, it is debated what (non-histological) criteria can be used to distinguish these possibilities which may coexist. Pyelonephritis is perhaps strictly a histological diagnosis but is often used to describe a clinical pattern. The severity of RN increases with the grade of VUR (Silva et al., 2006; Swerkersson et al., 2007; Shaikh et al., 2010).

RN is irreversible and if severe, particularly if bilateral, is associated with a reduced glomerular filtration rate (GFR). The long-term risk of chronic renal failure or hypertension resulting from an individual episode of UTI or a minor degree of scarring in childhood is probably small but is difficult to quantify. One major problem

is timescale. Ideally, cohorts of children need following prospectively for 40 or 50 years to determine more accurate estimates of adverse outcomes in adulthood. Williams et al. (2008) estimated that for each 6000 individuals who are born with VUR, 1600 (27%) will have their clinical course complicated by UTI, 2000 (33%) will have RN, with just one (0.02%) having ESRF. But the reported incidence of RN in cohorts of patients with VUR varies (Jodal et al., 2006; Silva et al., 2006). In a UK cohort of siblings with VUR, recruited for genetics studies, who may not be representative of the whole VUR population, 55% of patients had RN and four (1%) had ESRF; those with bilateral scarring had lower GFR than those with unilateral or no RN and in 40% of sibling pairs, both had RN raising the possibility of there being a genetic influence on development of nephropathy as well as VUR itself (Lambert et al., 2011). Proteinuria is common when RN and renal insufficiency coexist (Zhang and Bailey, 1995) and, in a retrospective adult study, progressive loss of kidney excretory function positively correlated with proteinuria (Nield et al., 2004).

### Hypertension

Several retrospective and prospective studies link the development of hypertension with renal scarring (Jacobson et al., 1989, 1999; Goonasekera et al., 1996; Goonasekera and Dillon, 1998). The risk is worse for those with more severe and bilateral scarring (Smellie et al., 1998).

RN is common finding in children and young adults presenting with hypertension. Accelerated arterial hypertension may be a presenting feature when RN coexists with impaired renal function (Bailey et al., 1994). Wennerström et al. (2000), however, reported that individuals, not in renal failure, with RN had no increased risk of hypertension versus controls without RN. What appears to be a small or scarred kidney on imaging may actually represent a number of different or combined underlying pathologies, for example, dysplasia or hypoplasia. Not all of these may be associated with a greater risk of hypertension but in cases of doubt, regular long-term monitoring of blood pressure is required. We currently recommended that individuals with focal scars have their blood pressure monitored on at least a yearly basis for life in order to detect presymptomatic hypertension; the long-term outcome of which can altered by treatment.

### Renal failure

The published incidence of ESRF secondary to renal scarring varies. Pyelonephritic renal scarring was reported to be the primary renal diagnosis in 39% of children undergoing renal transplantation in Ireland from 1980 to 1990 (Thomas et al., 1992). In Wales, between 1994 and 1997, 30% of chronic renal failure (GFR less than a third of normal) in childhood has been attributed to RN (Imam et al., 1998).

In Australia and New Zealand, from 1971 to 1998, RN was the primary diagnosis in 13% of patients entering the dialysis and transplantation programme between the ages of 5 and 44 years, with no clear trend of change (Craig et al., 2000). In part of France, pyelonephritis with reflux accounted for 12% of chronic renal failure (Deleau et al., 1994). In the United Kingdom, pyelonephritis accounts for 7% of ESRF in adults (The Renal Association, 2014, and RN exists in 5% of North American children receiving kidney transplants (NAPRTCS, 2010). It is, however, difficult to distinguish from registry data between those reaching renal failure due to congenital reflux-associated dysplasia and those with scarring of normal kidneys (i.e. possibly preventable RN). Nor is it possible to discern the role of UTI in deterioration of renal function in those with dysplasia (who also have a high incidence of VUR putting them at risk of possible damage from UTI). Hopefully prospective studies will clarify issues. The most compelling data come from Sweden where the incidence of ESRF in childhood caused by non-obstructive RN has reduced from 6% in the years 1978–1985 to zero in the years 1986–1994 (Esbjorner, 1997). It has been suggested that increased awareness and improved diagnosis of UTI in young children has been important (Esbjorner, 1997; Jakobsson et al., 1999).

### Pregnancy-related complications

The outcome of pregnancy in women with RN appears to be related to renal failure and hypertension rather than the underlying disease. Pregnant women have an increased risk of cystitis and UTI if they had UTI and VUR in childhood. However, ureteric re-implantation in childhood does not necessarily protect against symptomatic UTI in pregnancy and may be associated with increased risk (Mansfield et al., 1995). There is controversy about the role of UTI in pregnancy and risk of pre-term delivery or poor fetal outcome (Davison, 2001).

The risk of hypertension (Martinell et al., 1990) and pre-eclampsia (McGladdery et al., 1992) is higher in women with renal scarring. Scarring, rather than continued presence of VUR, is related to morbidity in pregnancy (Hollowell, 2008). Fetal and maternal outcome are worse if the mother has severe renal impairment or established hypertension prior to the pregnancy, with deterioration of renal function in those with established renal failure (El-Khatib et al., 1994; Jungers et al., 1996; Lindheimer et al., 2001).

### Relationship of VUR, renal scarring, and RN

An association between VUR and scarring has been recognized since the 1960s but details of these relationships are far from clear. VUR has traditionally been thought to predispose to renal damage by facilitating passage of bacteria from the bladder to the upper urinary tract. An immunological and inflammatory reaction is caused by renal infection leading to renal injury and scarring. Extensive renal scarring causes reduced renal function, reduced renal growth, renal failure, hypertension, and increased incidence of pregnancy-related hypertension. Whilst these sequelae may occur in childhood, patients frequently do not present until many years or decades later. However, renal scarring is widely found in kidneys drained by a ureter not found to be refluxing. There are anomalies that are difficult to explain. There may be renal involvement on early DMSA (done at the time of infection) that does not go on to leave a permanent scar. However, when permanent scars do form, they do localize to the same site as the acute involvement. We do not fully understand what factors are involved in resolution of acute renal involvement as opposed to progression to permanent scarring. There may be renal involvement on acute DMSA but no evidence of VUR on imaging. However, both research and clinical evaluation and management are hampered by the nature of the techniques available to study it and by the intermittent, fluctuating nature of VUR itself and the tendency of VUR to resolve with increasing age.

Our understanding of the mechanism of focal scarring is largely based on the piglet model developed by Ransley and Risdon (1978, 1981). In their studies they found that neither VUR alone (with sterile urine), nor lower UTI alone (with no VUR) led to scarring.

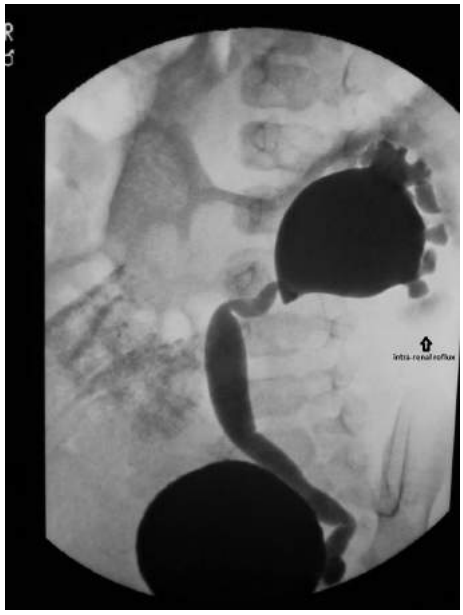


**Fig. 355.3** Micturating cystogram showing grade V reflux with intrarenal reflux.

However, scars developed in some segments of kidneys when there was VUR and UTI, leaving the adjacent segments unaffected. They found that the scarred and unscarred segments had different-shaped papillae. The scarred segments had compound papillae that were flat or concave in shape whereas the unscarred segments had simple cone-shaped papillae. Compound papillae with open gaping orifices allow intrarenal reflux whereas simple papillae with slit-like orifices do not (Ransley and Risdon, 1974).

Post-mortem examination of kidneys from young children dying of a non-renal cause reveals similar variation in papillary form, likely to lead to intrarenal reflux in about two-thirds of kidneys (Ransley and Risdon, 1975). This means that > 90% of children are likely to have at least one compound papillus capable of intrarenal reflux. This figure is higher than can be demonstrated radiologically in children with VUR (Rolleston et al., 1974; Uldall et al., 1976). A number of factors may interfere with demonstration of intrarenal reflux including timing of films, backflow of urine, or details obscured by bowel shadows. It is thus suggested that intrarenal reflux may be present more often than can be demonstrated (Ransley and Risdon, 1975). Figure 355.3 shows an example of intrerenal reflux.

There is evidence in humans that the reflux of infected urine into the kidney in the presence of compound papillae can cause acute pyelonephritis and subsequent renal parenchymal scarring (Rolleston, 1974). The presence of both types of papillae in one kidney explains why scarring is segmental and why adjacent areas can remain pristine (Ransley and Risdon, 1978). It is possible that the development of a scar can distort the intrarenal architecture to such an extent that adjacent papillae may develop intrarenal reflux leading to extension of scarring with subsequent infections. The absence of refluxing papillae may explain why some kidneys with a refluxing ureter do not scar even in the presence of infection.

Some babies born with VUR have associated dysplastic or hypoplastic renal malformations or *in utero* damage; all of which may impair renal function (Hinchliffe et al., 1992; Risdon, 1993). These abnormalities are usually associated with severe grades of VUR and sometimes with obstruction. It is not clear whether severe VUR is simply associated with renal abnormalities or whether there is a causal link. There is some evidence from animal work that fetal sterile reflux may impair GFR (Gobet et al., 1999) as well as concentrating ability (Ransley et al., 1987). Thus renal abnormalities may be found on imaging, associated with VUR *in utero* but in the absence of any history of UTI. Therefore when a child being investigated following a UTI is found to have abnormalities on DMSA scan it may be difficult to distinguish whether this is acquired scarring related to UTI or a congenital renal abnormality or both. Progressive renal impairment from dysplasia is probably not preventable and presumably results from lack of normal growth potential of abnormal renal tissue. Development of new or additional renal scarring secondary to UTI may be preventable and it is to this end that investigation and management strategies should be aimed.

### Timing of scarring

The risk of scarring following a UTI varies with age, but the precise details of this are not clear. In clinical situations it is often very difficult to know at what age an individual child acquired their scars. Young children appear to be at most risk (Berg and Johansson, 1983). In one study, children with normal DMSA scans after UTI were reinvestigated 2–11 years later. There were very few first scars found in children that had been older than 3 years at the time of their original DMSA, and none in those that had been older than 4 (Vernon et al., 1997). The reasons for this are not clear. It has been suggested, and is widely assumed, that children's kidneys may mature, or 'grow out' of their tendency to scar. It is notable that the frequency of renal scars in children presenting with their first documented UTI is not related to age (Benador et al., 1997; Coulthard et al., 1997). This apparent paradox may be explained by scarring having occurred during an earlier undiagnosed UTI.

An alternative hypothesis (Coulthard, 2002) is that children who are born with risk factors for developing focal renal scarring (that is, with VUR and compound papillae that allow intrarenal reflux) are at such high risk of developing a scar that they are overwhelmingly likely to have done so by the age of 4. Currently in the United Kingdom, UTI in young children are frequently missed or treatment delayed. According to this model, most children who reach 4 years without scarring do so only by virtue of never having possessed the risk factors; hence they have no future risk. One implication of this hypothesis is that the same proportion of children would be expected to be found to be scarred in population studies as are born with risk factors. How many infants are born at risk of scarring? The precise number of babies with VUR is unknown for obvious reasons, but a summation of past studies of normal newborns subjected to cystography suggests it is about 1% (Coulthard, 2002). Since around 90% of children have at least one compound papillus, it follows that approximately 0.9% of children are born at risk. Few studies have been designed to assess population scarring rates, but they can be estimated from some. In Newcastle, 11.3% of girls are investigated for a UTI by the age of 16 years, of whom 4.8% are found to have focal scarring (Coulthard et al., 1997). Thus, at least 0.54% of Newcastle girls have scars; the true figure is likely to be higher because diagnosis and referral rates are incomplete (Vernon et al., 1997). This figure confirms that most girls born at risk of developing a scar do acquire one. It stands as an indictment of the past management of UTI that few children, if any, are prevented from developing a scar; it is easier to identify damage than

prevent it. Another implication of this hypothesis is that kidneys that have risk factors for scarring, but which are unscarred beyond 4 years (perhaps because of prompt treatment of UTI or use of prophylactic antibiotics) will remain at risk of developing a new scar later. There is some support for this hypothesis from animal work. Normal adult pigs whose kidneys have been protected from damage by having a non-refluxing ureter have been shown to be as vulnerable to acute segmental scarring as piglets if they are exposed experimentally to VUR and UTI (Coulthard, 2002). A parallel to this animal evidence is that unscarred adult human kidneys can acquire segmental scars after being grafted into a recipient (child or adult) who has a reflux into their transplant and develops a UTI (Howie, 2002).

These observations have important implications for infants known to have VUR but no scarring, such as babies identified by screening because of a family history of VUR (Scott et al., 1997). The 90% of these children that are likely to have compound papillae would be expected to remain at risk of scarring until they outgrow their VUR.

## Summary

In summary, VUR is an inherited congenital condition associated in some cases with other anatomical abnormalities and an increased risk of UTI. VUR is a risk factor for development of RN, which, in a few individuals, may have serious sequelae, but the precise role is unclear. Investigation and management strategies are controversial and vary from centre to centre but there is consensus on the need for accurate diagnosis and prompt treatment of UTI.

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# CHAPTER 356

# The patient with urinary tract obstruction

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## Introduction

Several terms usually describe obstruction of the urinary tract and its consequences such as hydronephrosis, obstructive uropathy, and obstructive nephropathy. Obstruction can be due to anatomic or functional abnormalities of the urethra, bladder, ureter, or renal pelvis. These abnormalities can be congenital or acquired. Obstructive uropathy also can occur during the course of diseases extrinsic to the urinary tract. Although dilatation of the outflow system proximal to the site of obstruction is a characteristic finding, widening of the ureter and/or pelvicalyceal system does not necessarily indicate the presence of obstruction. Causes of such anatomical abnormalities in the absence of obstruction are (a) anatomical variants: extrarenal pelvis, megaureter (possible secondary to vesicoureteral reflux); (b) pregnancy: hormonal changes cause dilated ureters and renal pelvis; and (c) post obstruction: a 'baggy' system may remain long after relief of chronic obstruction.

Clinically obstructive nephropathy can manifest as either a sudden or insidious decline in renal function. Relief of obstruction can halt or even reverse this decline in the renal function. Thus, obstructive uropathy is a potentially curable cause of renal failure.

Obstruction may be upper (obstruction at or above the level of ureter) or lower tract (obstruction at the level of bladder or distal), partial or complete, unilateral or bilateral. Complete obstruction is the commonest cause of anuria and is often easy to diagnose because of straightforward renal imaging findings but partial obstruction is difficult to diagnose due to variable urinary output and imaging findings. Bilateral obstruction, or obstruction of a single kidney or lower tract obstruction, is a greater danger to the patient than unilateral obstruction. Obstruction associated with infection is a greater threat to kidney function and to life than obstruction in the absence of infection. Since it is common, and often reversible, obstruction of the urinary tract should be considered in every patient with unexplained uraemia, whether acute or chronic.

The incidence, prevalence, and cost of obstructive uropathy are difficult to estimate because obstruction can occur in the setting of a wide variety of diseases that may warrant hospitalization or surgical intervention. Distribution of obstructive uropathy is bimodal. It is common during childhood due mainly to congenital anomalies of the urinary tract. Its incidence then declines with age until late adulthood. At ages 60–65 years, the incidence rises particularly in men, because of the increased occurrence of prostate disease.

Urinary tract obstruction is a common cause of end-stage renal disease (ESRD) in children. Obstruction in early gestation can cause renal dysplasia; but occurring in late gestation or after birth can cause irreversible loss of renal function. New ultrasound techniques developed in the last 15 years have made possible the diagnosis of obstructive uropathy in the fetus. In the adult, obstructive nephropathy accounts for approximately 3–4% of cases of ESRD but the incidence and causes of obstructive uropathy vary with the gender and age of the patient. Calculi and pelviureteric junctional (PUJ) obstruction are common causes of unilateral obstruction, while prostatic enlargement, stone disease, and bladder and pelvic tumours account for about 75% of cases of bilateral obstruction in developed countries. Males outnumber females with ESRD due to obstructive nephropathy. In terms of racial predisposition, white people are more susceptible compared to African Americans, Asian, and Native Americans. Wide geographic variations occur in the relative incidence of some causes of obstruction, for example, schistosomiasis and genitourinary tuberculosis are more common in Africa and Asia (Klahr, 2003; Yaqoob and Juniad 2010).

## Causes of obstruction

Obstruction may be caused by lesions within the lumen or the wall of the urinary tract or by pressure from outside (Table 356.1) (Yaqoob and Chesser, 2006).

Calculi, particularly calcium oxalate stones, are the most common cause of urinary tract obstruction in the young adult male, being two to three times more common than in females. Common sites for impaction of stones are in the calyx, at the PUJ, at the pelvic brim, and at the vesicoureteric junction. Stones < 0.5 cm in diameter usually pass spontaneously. A calcified sloughed papilla in the urinary tract may mimic an opaque calculus, although the characteristic triangular shape of the opacity and the presence of relevant underlying conditions such as diabetes, sickle cell disease, and analgesic use should alert the clinician to the correct diagnosis.

Functional obstruction resulting from failure of normal peristalsis through a segment of the urinary tract usually results from an absence of smooth muscle fibres. In many cases, no gross histological abnormalities are present. Classically, obstruction is seen in childhood at the PUJ. PUJ obstruction is usually bilateral before 1 year of age. The condition may be diagnosed *in utero*, but peak incidence is at age 5 and 20% of reported cases occur in adults over the age

**Table 356.1** Causes of urinary tract obstruction

| Level of obstruction | Obstruction within the lumen | Obstruction within the wall | Extrinsic compression |
|---|---|---|---|
| Kidney | Stones<br>Sloughed papillae | Cysts<br>Tumours<br>Anatomical abnormalities, e.g. PUJ obstruction | Lower polar renal vessels crossing at PUJ |
| Ureter | Stones | Tumours<br>Stricture (malignant, post surgery or post-radiotherapy), tuberculous, schistosomiasis<br>Anatomical abnormalities, e.g. vesicoureteric junction obstruction | Tumours<br>Retroperitoneal fibrosis<br>Retrocaval right ureter (congenital)<br>Pancreatitis, inflammatory bowel disease (rare) |
| Bladder/bladder neck | Stones<br>Clot retention | Tumours<br>Functional obstruction (diabetes, neurological damage to bladder, drugs) | Pelvic tumours |
| Urethra | Stones<br>Blood clots (after catheterization or surgery) | Stricture (post infective, or post surgical)<br>Congenital urethral valves<br>Tumours | Prostate enlargement |

of 30 years. A functional defect of the vesicoureteric junction (congenital megaureter) is the second most common cause of obstruction in childhood, but is uncommon in adults. Males are more often affected than females, especially in childhood. The disease is claimed to be analogous to Hirschsprung disease of the colon but finding a reduction in the number of muscle fibres and an increase in collagen fibres, together with preservation of the nerve ganglia, makes the analogy with Hirschsprung disease invalid. Some studies have shown segmental upregulation of transforming growth factor beta (TGFβ) in the longitudinal muscle layer suggesting segmental developmental delay of the terminal ureter (Jung et al., 1997).

Diseases of the retroperitoneal space, particularly tumour invasion from cervix, prostate, bladder, colon, ovary, and uterus, commonly cause obstruction. In retroperitoneal fibrosis (see Chapter 357), it is unclear whether obstruction results from extrinsic compression or failure of peristalsis resulting from encasement of the ureter within a fibrous exoskeleton. That the latter may be the case is suggested by the fact that contrast medium injected into the lower ureter typically passes freely up to the pelvicalyceal system despite the presence of clinical, radiological, and isotopic evidence of functional urinary tract obstruction.

Functional obstruction may also occur at the bladder neck and at the level of the distal sphincter because of lack of coordination between bladder contraction and sphincter relaxation (detrusor sphincter: dyssynergia) resulting in either the bladder wall becoming non-compliant or detrusor hypertrophy. Common causes of functional outflow obstruction (neuropathic or neurogenic bladder) include diabetes mellitus, multiple sclerosis, spinal cord injuries, and meningomyelocele (in childhood). Cerebrovascular disease and advanced Parkinson disease are often associated with functional bladder outflow obstruction in the elderly population. In some patients, particularly women, a psychological component appears to exist. In some females, however, overactive external urethral sphincter is the cause of outflow obstruction (Fowler syndrome). Certain drugs, including those with antimuscarinic activity, such as tricyclic antidepressants, and calcium channel-blocking activity, have pharmacological effects on the bladder which may precipitate urinary retention.

Other causes of lower urinary tract obstruction include urethral strictures following repeated instrumentation or surgery or gonococcal infections as are urethral tumours and ureterocele. In children, urethral valves may be responsible for such obstruction. However, in men, by far the most common causes of lower tract obstruction are benign prostatic enlargement and prostatic cancer. In women, pelvic malignancy is a common cause; less common causes include uterine fibroids and complete procidentia.

It is important to realize that all causes of lower tract obstruction may also lead to upper tract obstruction. The reverse is not, of course, the case.

## Clinical presentation of obstruction and approach to investigation

It is very important to determine whether urinary tract obstruction is of recent onset (acute obstruction) or long-standing (chronic obstruction). Moreover, it is of paramount importance to determine if the obstruction is in the upper or lower urinary tract. Since the pathophysiological changes, clinical features, approach to investigation, and management differ in important respects in acute upper/lower versus chronic obstruction, they will be discussed separately.

### Acute upper tract obstruction

#### Acute ureteric obstruction

Normally urine reaches the bladder as a result of three inter-related mechanisms: glomerular filtration pressure, ureteric and pelvic peristalsis, and gravity. Coordinated smooth muscle contraction in the ureters directs urine towards the bladder, with maximum intraluminal pressures of 25 mmHg.

Acute ureteric obstruction causes delayed urinary transit, and over time, increased intratract pressures and declining blood flow to the kidneys resulting in renal impairment. Histologically, tubular dilatation initially affects mainly the collecting duct and distal tubular segments. Bowman's space may be dilated at the later stages.

## Clinical features

Acute upper tract obstruction typically gives rise to pain in the flank, which may radiate to the iliac fossa, inguinal region, testis, or labium. The pain may be dull or sharp, intermittent or persistent, though waxing and waning in intensity. It may be provoked by a high fluid intake, alcohol, or diuretics, measures which increase urinary volume and distend the collecting system: this is particularly noticeable when obstruction occurs at the PUJ. Loin tenderness may be detected and an enlarged kidney felt. Upper urinary tract infection with malaise, fever, and symptoms and signs of septicaemia may dominate the clinical picture.

Complete anuria is strongly suggestive of complete bilateral obstruction or complete obstruction of a single kidney. The differential diagnosis includes bilateral total renal cortical necrosis, acute necrotizing crescentic glomerulonephritis due to anti-glomerular basement membrane disease and vasculitides, and bilateral renal arterial occlusion. Intermittent anuria indicates the presence of intermittent complete obstruction. Partial obstruction or complete obstruction of one kidney does not usually affect urine output.

## Investigations of acute upper urinary tract obstruction

The investigation of acute obstruction must allow the site and cause to be identified rapidly, accurately, safely, and as economically as possible.

## Imaging

### *Computed tomography scanning*

Unenhanced computed tomography (CT) confers major diagnostic benefits, and is a fast, well-tolerated technique. Its accompanying higher effective radiation dose is recognized. Unenhanced spiral CT is more effective than intravenous urography (IVU) in identifying ureteric calculi and is equally effective in detecting urinary obstruction (Wong et al. 2001). CT-KUB (kidneys, ureters, and bladder) has replaced urography as the first line of investigation of the suspected acute obstruction (Fig 356.1).

### *Ultrasonography*

Ultrasound is an easy, simple, and non-invasive imaging technique in acute obstruction of the upper tract but is less accurate than CT. It can define dilatation of the intrarenal collecting system in the upper third of the ureter, but dilatation of the middle and lower thirds of the ureter is not easily visible and the dilated ureter cannot always be traced to the level of obstruction. However, colour and pulsed Doppler can sometimes detect the presence or absence of ureteral jets to diagnose ureteric obstruction (Webb, 2000).

Ultrasound may be used to investigate patients with acute obstruction if they are pregnant or have a history of contrast allergy. The risk of contrast nephrotoxicity in diabetics with moderate to severe renal impairment and in patients with myelomatosis is currently considered a relative contraindication to IVU: ultrasonography therefore has a primary role in the investigation of such patients.

### *Intravenous urography*

Emergency IVU is still a preferred method of investigating the patient with suspected acute upper tract obstruction in the developing world. It will confirm the diagnosis and will usually demonstrate the site, cause, and degree of obstruction, providing invaluable guidance for management.

### *Antegrade and retrograde pyelography and ureterography*

If the site of obstruction is not demonstrated by CT-KUB and or IVU, antegrade or retrograde examination may be helpful. Both techniques can be initiated as a method of diagnosis but then extended to provide a therapeutic role by providing drainage.

### *Magnetic resonance urography*

Magnetic resonance urography using half-Fourier acquisition single-shot turbo spin-echo (HASTE) imaging is increasingly used when the above mentioned other imaging techniques are either contraindicated or non-conclusive. It accurately and rapidly shows the level and degree of ureteric obstruction. It can be used to differentiate between acute and chronic obstruction on the basis of its ability to show perirenal fluid. Although IVU and CT scanning are likely to remain the standard procedures for imaging the upper tract, magnetic resonance urography enhanced by gadolinium and frusemide may be helpful if there is a dilated system with no excretory function, in pregnant women, in children, and in those with contrast medium allergy (Jung et al., 2000).

### *Use of radionuclides*

A technetium (Tc)-labelled mercaptoacetyltriglycine (MAG-3) radioisotope scan can be used to differentiate obstructed from unobstructed kidneys. Patients presenting with acute renal colic and positive helical CT can be differentiated into obstructed or without obstruction MAG-3 renogram with or without induced diuresis (Sfakianakis et al., 2000).

## Approach to relieve acute upper tract obstruction

### *Stones*

The majority of patients presenting with renal and ureteric colic usually have a stone in the lower third of the ureter. Such patients

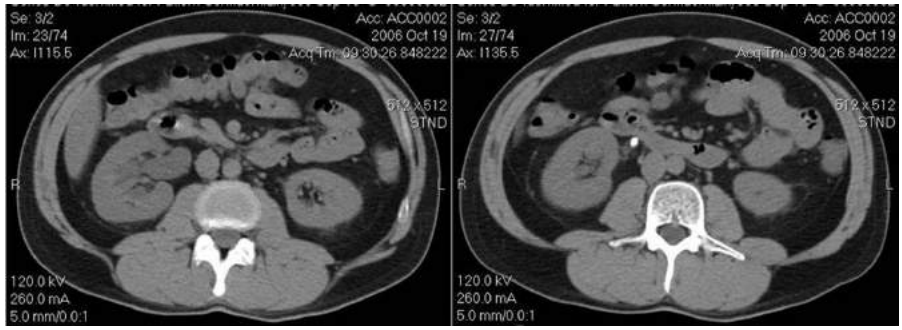


**Fig. 356.1** Two images from CT-KUB series showing calculus in the PUJ/upper ureter producing obstruction and hydronephrosis.

can be managed conservatively if the stone is ≤ 5 mm in its maximum diameter. It is unusual for acute episodes of colic to persist for > 72 hours. Patients with ureteric colic are usually admitted to hospital often unnecessarily since the only medical requirement is the provision of regular analgesia in the form of morphine, pethidine, and non-steroidal anti-inflammatory agents administered parenterally, orally or *per rectum*.

With the advent of lithotripsy there is a tendency to intervene earlier. Since most stones at that site will pass spontaneously, the extent to which lithotripsy will hasten the process is difficult to establish. Stone-free rates after *in situ* extracorporeal shock-wave lithotripsy (ESWL) have been reported to range from 81% to 96% (Danuser et al., 1993). A larger number of shock waves at a higher voltage and an increased number of repeat sessions are required when a stone is within the ureter rather than in the kidney. Some controversy remains whether upper ureteric stones should be manipulated back into the kidney before ESWL. The value of a JJ stent inserted alongside an impacted ureteric stone in both aiding fragmentation and enhancing the passage of stone fragments is unclear. Endoscopic manoeuvres, which are usually performed under general anaesthesia, are reserved for those patients with persistent colic.

#### *Drainage of an obstructed system*

If there is clinical evidence of infection above an obstruction, drainage must be established as a matter of urgency. The diagnosis is a clinical one with features of local or systemic sepsis. In most specialist centres, insertion of percutaneous nephrostomy under local anaesthetic and ultrasound/X-ray guidance is the preferred option. Such a system may be used to provide drainage for weeks or even months if necessary.

The other alternative is retrograde insertion of a JJ ureteric stent requiring general anaesthesia and X-ray image intensifier in the operating theatre. Occasionally, a retrograde catheter cannot be passed beyond the obstruction and the diagnostic role of retrograde ureterography cannot then be extended to a therapeutic one.

The two other relatively common causes of acute upper urinary tract obstruction are sloughed papillae and blood clots. The principles of management are similar to those for ureteric stones. However, greater attention is required to the underlying cause in the acute phase particularly in the patient with papillary necrosis. Surgical intervention, usually with a percutaneous needle nephrostomy, is required more often because of accompanying infection. Colic due to blood clots as in renal parenchymal tumours and transitional cell tumours of the collecting system may require ablative open surgery. An arteriovenous fistula can be embolized with high success rate. The most difficult cause of recurrent bleeding to manage is that associated with papillary necrosis in sickle cell trait or disease. Antifibrinolytic agents may be of value, but administration of such treatment during active bleeding may produce hard, rubbery clots, which fill the collecting system and require surgical removal.

## Acute obstruction in the lower urinary tract

Acute lower tract obstruction results in overstretching of smooth muscle fibres and reduced mechanical efficiency culminating in acute urinary retention. Factors such as sudden diuresis after alcohol ingestion or diuretic therapy for heart failure, urinary tract infection, and drugs with antimuscarinic and calcium channel-blocking activity may precipitate acute retention.

### Clinical features

Symptoms of bladder outflow obstruction with hesitancy, poor urinary stream, and terminal dribbling often precede acute urinary retention. Acute retention is accompanied by severe suprapubic pain, but this may be absent if acute retention is superimposed on chronic retention or if there is an underlying neuropathy. Epidural anaesthetic may precipitate painless acute retention of urine.

Acute obstruction sometimes superimposes on a chronically obstructed lower urinary tract with underlying bladder wall hypertrophy, sacculation, and diverticulum formation; these in turn predispose to chronic lower urinary tract infection and occasionally to bladder stones. Epididymo-orchitis may also be an accompanying feature.

### Investigations of acute lower urinary tract obstruction

Most patients presenting with acute urinary retention require no investigation before treatment. Suprapubic pain coexisting with a palpable bladder is sufficient evidence for immediate catheterization. If doubt about the diagnosis exists, an ultrasound examination will confirm or refute the presence of a distended bladder.

Flexible cystoscopy under local anaesthesia or a retrograde urethrogram may be performed if an attempt at urethral catheterization proves unsuccessful. This is done as an elective procedure after bladder drainage has been secured by suprapubic catheterization.

### Approach to relieve acute lower urinary tract obstruction

The bladder may be catheterized *per urethram* or suprapubically. In women catheterization *per urethram* typically presents no difficulty. A hypospadiac external urethral meatus may be difficult to locate on the anterior vaginal wall. Urethral catheterization may prove difficult in some men. Only an experienced operator should pass a urethral catheter on an introducer. If doubt or difficulty exists, the help of an urologist should be sought. After initial relief of obstruction, a comprehensive urological investigation plan should be initiated in order to determine a cause and where possible its treatment to prevent future episodes of obstruction.

## Chronic upper tract obstruction

### Chronic obstruction

Contrary to acute settings where dilatation is less marked, chronic ureteric obstruction causes dilatation of ducts of Bellini at first followed by papillary structures and compression of renal cortical tissue with thinning of the renal parenchyma. Shrinkage of the renal parenchyma with reduction in size of the kidney (obstructive atrophy) is believed to result from the effects of compression of the renal parenchyma and from prolonged renal ischaemia. Slowly progressive partial obstruction tends to result in gross dilatation of the collecting system and gross atrophy of renal parenchyma.

### Pathophysiology of kidney damage caused by chronic obstruction

The mechanisms underlying the progression of renal disease to ESRD in humans after an initial insult are not well understood. Several studies indicate that tubulointerstitial changes, not glomerular pathology, correlate better with decrements in glomerular filtration rate (GFR) in a variety of renal disease (Yaqoob et al., 1994). A number of renal diseases can cause tubulointerstitial pathology. These structural changes of the tubulointerstitial space often are considered secondary to glomerular lesions. However, certain renal diseases, notably obstructive uropathy, are characterized

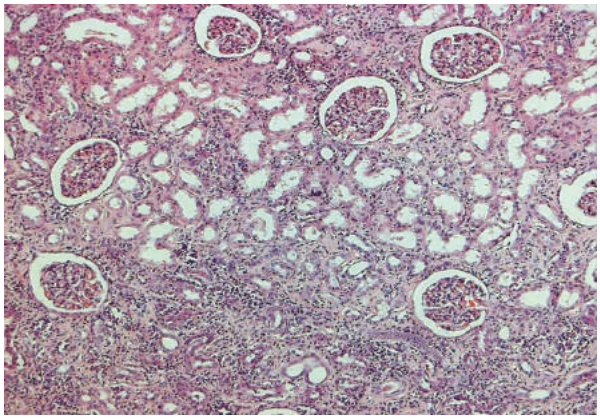

**Fig. 356.2** Histological appearances in long-standing obstruction. Note dilated tubules, interstitial fibrosis, vessel wall thickening, but preservation of glomeruli.

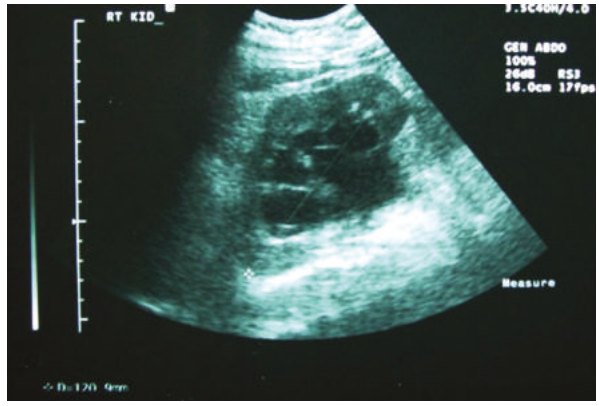


**Fig. 356.3** Ultrasound scan of obstructed right kidney, showing dilated calyces and pelvis of the kidney.

by primary tubulointerstitial pathology and subsequent involvement of glomerular structures. Obstructive uropathy can cause major changes in the tubulointerstitial compartment of the kidney (Fig. 356.2). Renal interstitial fibrosis is a common consequence of long-standing obstructive uropathy. Fibrosis likely develops due to an imbalance between extracellular matrix synthesis and matrix degradation.

Insight from experimental models of unilateral ureteral obstruction (UUO) has shed light on the molecular mechanisms of fibrosis in obstructive uropathy over the last decade which includes tubular cell hypertrophy, proliferation, apoptosis and atrophy, proliferation and activation of interstitial fibroblasts, accumulation of (myo) fibroblasts due to epithelial-to-mesenchymal transdifferentiation, inflammatory cellular infiltration, increased extracellular matrix deposition, and tubular atrophy. UUO models in genetically modified animals have provided important information about the role of specific intracellular signalling pathways for several genes in the pathogenesis of obstructive nephropathy. In addition to confirming the pivotal role for angiotensin II (Ang II) and TGFβ in obstructive nephropathy, these animals have led to the discovery of unexpected and often contradictory roles (both pro- and antifibrotic) for Ang II, matrix metalloproteinase 9 (extracellular matrix degrading enzymes), activators or inhibitors of tissue plasminogen, for the adhesion molecule osteopontin and bone morphogenic protein 7 in obstructive nephropathy. Further studies in these animals, in combination with pharmacological agents, may identify novel antifibrotic strategies in obstructive nephropathy and other progressive renal diseases (Bascands and Schanstra, 2005; Chevalier et al., 2009).

## Effects of chronic obstruction upon renal function

Obstruction causes a decline in the GFR due to both a decrease in single-nephron GFR and in the number of filtering nephrons, impaired ability to concentrate urine which is resistant to administration of antidiuretic hormone due to acquired nephrogenic diabetes insipidus, and partial distal renal tubular acidosis often with associated hyperkalaemia due to downregulation of Na-K-ATPase. These non-specific consequences of obstructive uropathy are accompanied by features of chronic kidney disease determined by severity of renal failure such as anaemia, mineral bone disorder, and both hypertension or hypotension (secondary to salt wasting).

## Clinical presentation of chronic urinary tract obstruction

Patients may present with flank or abdominal pain, renal failure, or both; the symptoms and signs of urinary tract infection and septicaemia may be superimposed. Rarely, presentation is with erythraemia or hypertension and their complications. A proportion of patients are asymptomatic, obstruction being found during investigation of some other condition such as haematuria, urinary infection, hypertension, or unexplained renal insufficiency.

Polyuria often occurs in chronic partial obstruction owing to impairment of the renal tubular concentrating capacity. Intermittent anuria and polyuria indicate intermittent complete and partial obstruction.

## Investigations of chronic urinary tract obstruction

Obstruction must be excluded early in all patients with unexplained renal failure. In patients with known renal disease, rapid deterioration in renal function unexplained by the primary renal problem also demands investigation. Relapsing urinary tract infections should also raise the possibility of an associated obstructing lesion. The diagnosis of partial obstruction should not be discounted simply because urine volume is normal or increased.

The choice of imaging depends upon the mode of presentation. Initial investigation of the patient with unexplained impairment of renal function should include ultrasonography, together with plain abdominal radiographs. Since ultrasound cannot distinguish between an obstructed distended system and a baggy, low-pressure dilated system, an abnormality on ultrasound should prompt further definitive investigation (Fig 356.3). In very long-standing obstruction, generalized thinning of the renal parenchyma (obstructive atrophy) is seen. This is typically diffuse and symmetrical and there is associated generalized calyceal dilatation.

However, on CT scan which is usually done to determine the cause of obstruction, the dilated collecting system appears as a multiloculate fluid collection of water density in the renal sinus. It is possible to distinguish the intrarenal collecting system from the extrarenal portion of the pelvis; this is important since obstruction can only be diagnosed on CT when there is dilatation of the intrarenal collecting system. A prominent extrarenal pelvis may be a normal variant. The whole dilated ureter is shown well on CT.

Scintigraphy provides functional evidence of obstruction. $^{99}Tc^{m}$-diethylaminetriaminepentaacetic acid (DTPA) and

$^{99}Tc^{m}$-methylene diphosphonate (MDP) are frequently used and are excreted purely by glomerular filtration which shows delayed parenchymal clearance of tracer and emptying of the collecting system. A dynamic renal scintigram performed during diuresis may be of value to ascertain whether prolongation of parenchymal transit time is due to retention of tracer within a large, baggy, low-pressure, unobstructed collecting system or genuine partial or complete obstruction. Partial obstruction is clinically important if it causes deterioration in kidney function. In patients with one kidney or those with bilateral partial obstruction, a decline in serial measurements of GFR attributable to obstruction may determine the need for intervention.

Antegrade (nephrostogram) and retrograde (ureterogram) studies are often necessary to define exact site of obstruction and to arrive at a definitive diagnosis.

## Differential diagnosis of non-obstructive collecting system dilatation

A number of non-obstructive conditions may cause collecting system dilatation. Ultrasound is usually unable to differentiate obstructive from non-obstructive dilatation because of its inability to show calyceal detail, differentiate an intrarenal from an extrarenal pelvis, and demonstrate the ureter. CT is also a poor indicator of whether dilatation is obstructive or non-obstructive, although it can identify cases of dilatation, which are due to an extrarenal pelvis. Scintigraphy or IVU is often of value in this situation.

Vesicoureteric reflux may be associated with dilatation of the ureters; the pelvicalyceal system may also be dilated in severe reflux. The presence of reflux on urography is suggested by the degree of dilatation varying at different times during the examination, by dilatation which is greatest from the vesicoureteric junction upwards, and by a postmicturition film which shows a large bladder residual, representing urine that has refluxed into the ureters during voiding and drained back into the bladder thereafter.

The decision of whether an operation is indicated for idiopathic PUJ obstruction may be facilitated by frusemide urography or frusemide scintigraphy. In some patients, the urographic findings are unremarkable during asymptomatic periods, while emergency IVU during an episode of pain may define the condition.

## Approach to relieve chronic urinary tract obstruction

The main goal of treatment is to relieve symptoms, improve or conserve renal function, and avoid complications such as septicaemia. Contrary to acute obstruction caused by small ureteric stones (< 5 mm) which commonly resolves spontaneously, a larger impacted stone frequently requires surgical intervention. PUJ obstruction is the second most common cause of chronic obstruction in adults. The Anderson–Hynes pyeloplasty gives very satisfactory results and provides the gold standard against which other open and endoscopic techniques (such as endopyelotomy) must be assessed.

### *Effects of relief of chronic urinary tract obstruction*

Long-term renal outcome after the relief of chronic obstructive uropathy has not been reported extensively. Even stone formers have been identified as being predisposed to chronic renal disease (Rule et al., 2011). Generally relief of obstruction results in improvement or stabilization of renal function. However, patients with irreversible damage in the kidneys manifested by moderate to severe renal insufficiency (plasma creatinine > 250 μmol/L) and significant proteinuria (> 1 g/day) may develop progressive renal failure despite relief of obstruction and be managed by usually supportive therapy for chronic kidney disease (McClelland et al., 1994). It remains to be seen whether angiotensin-converting enzyme inhibitors, $AT_1$ receptor blockers, and correction of acidosis will improve renal survival in obstructive uropathy (Yaqoob and Junaid, 2010).

## Chronic outflow obstruction

Outflow obstruction usually manifests itself clinically as urinary incontinence, hesitancy, abnormal urine flow, dribbling after urination, weak urine stream, increased urinary urgency, nocturia, sensation of incomplete bladder emptying, burning, and stinging urination. Occasionally, severe haematuria results from rupture of prostatic veins or as a consequence of bacteriuria or stone disease. Occasional patients present with severe renal failure.

The two most common causes of chronic outflow obstruction are diseases of the prostate and urothelial tumours.

### *Prostate diseases*

#### Benign prostatic hypertrophy

Men over the age of 60 years are usually affected. It is not very common in Asian individuals. The underlying cause of benign prostatic hypertrophy (BPH) is unclear. Microscopically, hyperplasia and hypertrophy of the glandular and connective tissue elements of the prostate are the main findings. Stretched and distorted urethra due to enlarged prostate glands leads to bladder outflow obstruction.

In addition to classical history and clinical presentation, an abdominal examination for enlarged, easily palapable urinary bladder together with *per rectum* examination is essential. A benign prostate feels smooth. An accurate impression of prostatic size cannot be easily obtained on rectal examination.

Patients with mild symptoms should be managed by 'watchful waiting', because symptoms following therapy are sometimes greater than those with no therapy at all. Patients with symptoms affecting quality of life can be treated medically. A number of drugs are available with variable benefits, including alpha blockers such as tamsulosin. Finasteride is a competitive and dutasteride is a non-competitive inhibitor of 5α-reductase, an enzyme involved in the conversion of testosterone to dihydrotestosterone which is primarily responsible for prostatic growth and enlargement. Finasteride and dutasteride reduce the prostatic volume with an increase in urine flow. Deterioration in renal function or the development of upper tract dilatation requires surgery.

In acute retention or retention with overflow, the first priorities are to relieve pain and to establish urethral or suprapubic catheter drainage. After the initial relief of outflow obstruction, the choice of subsequent management is dependent on the patient's co-morbidity and includes immediate prostatectomy, a period of catheter drainage followed by prostatectomy, or the acceptance of a permanent indwelling catheter (Harik and O'Toole, 2012).

#### Prostatic carcinoma

Contrary to BPH, prostatic carcinoma is a relatively serious condition and accounts for 7% of all cancers in men and is the sixth leading cancer in the world. Malignant transformation in the prostate becomes extremely common with advancing age as > 80% of men have malignant foci within the gland by the age of 80 years. However, most of these usually lie dormant. Hormonal factors play a role in the aetiology. Microscopic examination reveals adenocarcinoma-like changes.

Presentation is usually with symptoms of lower urinary tract obstruction; less common are symptoms of metastatic spread, for example, back pain, weight loss, or anaemia. The diagnosis is highly likely if a hard irregular gland on rectal examination is detected. Sometimes patients present as a result of screening for prostate cancer by measurement of prostate-specific antigen (PSA). However, on the evidence available, national programmes of screening are not justified. Treatment of well people carries a high morbidity of urinary incontinence and sexual dysfunction with no evidence as yet of increased overall survival. PSA > 4 ng/mL is abnormal but between 4 and 10 ng/mL this can be due to benign hypertrophy and cancer. If PSA is > 10 ng/mL, a prostatic biopsy will show cancer in > 50% of cases.

Transrectal ultrasound of the prostate and prostatic biopsy and histological diagnosis is mandatory before treatment. The Gleason scoring system is based on the histological appearances. If metastases are present, serum PSA levels are usually markedly elevated (> 16 ng/mL) but can be normal; it is a myth that elevated levels occur as a result of rectal examination. Ultrasonography and transrectal ultrasonography are also of value in defining the size of the gland and staging any tumour present. Endorectal coil magnetic resonance imaging (MRI) helps to detect extra-prostatic extension. Bone metastases appear as osteosclerotic lesions on X-ray and are also detected by isotopic bone scans. Management of prostatic carcinoma requires multidisciplinary approach involving medical and radiation oncologist and urologist (Damber and Aus, 2008)

### *Urothelial tumours*

Transitional cell epithelium lines the urinary tract. Transitional cell carcinoma (TCC) is common and accounts for approximately 3% of deaths from all forms of malignancy. TCC is less likely under the age of 40 years and is more common in men than women. It affects urinary bladder 50 times more frequently than the ureter or renal pelvis.

Predisposing factors include (a) cigarette smoking; (b) exposure to industrial carcinogens such as β-naphthylamine and benzidine (workers in the chemical, cable, and rubber industries are at particular risk) or ingestion of aristolochic acid found in some herbal weight-loss preparations; (c) exposure to drugs, for example, phenacetin and cyclophosphamide; and (d) chronic inflammation, for example, schistosomiasis and chronically infected bladder in paraplegics usually associated with squamous carcinoma.

In addition to outflow tract obstruction symptoms, painless haematuria is the most common presenting symptom of bladder malignancy. Sometimes pain predominates owing to clot retention. Pain may also result from local nerve involvement. Local metastases from bladder cancer may also cause symptoms depending upon the site and organs involved.

Cytological examination of urine for malignant cells and renal imaging (ultrasonography, CT, and MRI) should be performed in all patients. Cystoscopy is essential and in fact mandatory in all cases of haematuria. In a few cases where the tumour is suspected but is not clearly outlined on ultrasonography or CT, retrograde ureterography may be helpful. Relief of obstruction should be followed by specialist urological and oncological combined treatment.

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# CHAPTER 357

# Retroperitoneal fibrosis

Muhammad M. Yaqoob, Katherine Bennett-Richards, and Islam Junaid

## Introduction

Retroperitoneal fibrosis (RPF) is a rare and multifaceted disease which encompasses a range of conditions characterized by the presence of a fibro-inflammatory tissue, which usually surrounds the abdominal aorta, iliac arteries, and extends into the retroperitoneum to entrap ureters with resultant unilateral or bilateral obstruction, usually at the junction between the middle and lower thirds of the ureter. The condition is progressive: initially, the fibrous tissue is fairly cellular, later becoming relatively acellular. The mechanism by which obstruction occurs is probably due to loss of peristalsis because of the frequent observation that contrast medium injected into the lower ureter may pass freely up to the pelvicalyceal system despite the presence of clinical, radiological, and isotopic evidence of functional urinary tract obstruction. The condition was first described in the French literature and the classic description came from Ormond (1948). RPF is generally idiopathic in 66% of the cases, but can also be secondary to the use of certain drugs, malignant diseases, infections, and surgery (Box 357.1)

## Epidemiology

The only epidemiological data available about the incidence and prevalence of idiopathic RPF are from a Finnish study (Uibu et al., 2004) with an incidence of 0.1/100,000 person-years and a prevalence of 1.38/100,000 inhabitants in the study area. There is no clear ethnic predisposition. Males generally outnumber females with a ratio of 2.5:1; the mean age at presentation is 50–60 years, but few reports of children and older adults affected by the condition are described. Familial clustering is rare with anecdotal cases in twins and siblings reported (Duffy et al., 1984).

## Aetiology

The aetiology of idiopathic RPF is unclear but is probably multifactorial. It is significantly associated with human leucocyte antigen DRB1*03, an allele linked to various autoimmune diseases. Environmental factors such smoking and asbestos might play a part. The risk of RPF is significantly increased due to occupational exposure to asbestos (Uibu et al., 2004).

## Pathogenesis

Evidence has now accumulated to suggest that the condition is an autoallergic periaortitis as a result of which macrophages from atherosclerotic plaque present antigens, such as oxidized low-density lipoprotein (LDL) and ceroid, and present them to immunocompetent cells, such as B lymphocytes and T lymphocytes. These are recruited and activated in medial and adventitial aortic layers. B cells produce antibodies to ceroid (a lipoproteic polymer that results from LDL oxidation within plaque macrophages, which can also be artificially obtained by oxidation of LDL), which are found in close apposition to extracellular ceroid. The inflammatory reaction then extends into the periaortic retroperitoneum.

However, RPF has been described in the absence of atherosclerosis particularly in children. Moreover, observations over the last decade suggest idiopathic RPF is a manifestation of a systemic autoimmune disease rather than an exaggerated local reaction to atherosclerosis. It is now increasingly realized that RPF is a part of systemic disease and is initiated as a vasa vasorum vasculitis in the aortic wall which is often seen in chronic periaortitis. This inflammatory process can cause weakening of aortic wall with medial thinning and promote atherosclerosis, and also extends into surrounding retroperitoneum with fibro-inflammatory reactions typical of chronic periaortitis. Indeed, the autoimmune reaction to plaque antigens could be an epiphenomenon of this immune-mediated process.

A further potential pathogenetic mechanism may be due to activating antibodies against fibroblasts, which are detectable in about one-third of patients with idiopathic RPF. Furthermore, over the last 5 years it has been demonstrated that patients with idiopathic RPF have the presence of immunoglobulin (Ig)-G4-bearing plasma cells, a common finding in sclerosing pancreatitis, a disorder sometimes associated with idiopathic RPF as a part of a new entity called IgG4-related diseases. Moreover, several infiltrating B cells show clonal or oligoclonal immunoglobulin heavy chain rearrangement. These findings raise the possibility of RPF being a primary B-cell disorder (Vaglio et al., 2006).

## Secondary retroperitoneal fibrosis

Secondary RPF can be caused by several factors and clinical conditions with varying pathogenic mechanisms (Box 357.1). The most common cause is use of certain drugs particularly derivatives of ergot alkaloids—for example, methysergide and the other ergot derivatives that affect the retroperitoneum, and also the pericardium, the pleura, and the lungs. Their effect is probably mediated by serotonin (Moroni et al., 2005).

In malignant cases, RPF results from a florid desmoplastic response to retroperitoneal metastases or local release of mediators

**Box 357.1** Causes of retroperitoneal fibrosis

- Idiopathic retroperitoneal fibrosis (two-thirds of all cases)
- Secondary retroperitoneal fibrosis (one-third of all cases):
  - Drugs: methysergide, lysergic acid, bromocriptine, pergolide, ergotamine, methyldopa, hydralazine, beta blockers
  - Malignant diseases (8–10% of cases of RPF): carcinomas of the colon, prostate, breast, stomach, carcinoid, Hodgkin and non-Hodgkin lymphomas, sarcomas
  - Infections: tuberculosis, syphilis histoplasmosis, actinomycosis and fungal infections
  - Radiotherapy and retroperitoneal haemorrhage
  - Surgery: lymph node resection, colectomy, hysterectomy, aortic aneurysm repair
  - Others: histiocytosis, Erdheim–Chester disease, amyloidosis and as part of sclerosing peritonitis following peritoneal dialysis, IgG4 related disease.

such as serotonin in carcinoids or by the release of profibrogenic growth factors in others.

Infective RPF is probably due to local spread of an infectious focus such as tuberculosis from paraspinal abscesses. Other, rare, causes of secondary RPF include abdominal surgery, radiotherapy, and proliferative disorders, such as Erdheim–Chester disease—a rare form of non-Langerhans cell histiocytosis which is characterized by osteosclerosis, exophthalmos, and diabetes insipidus. Retroperitoneal involvement is found in approximately 20–30% of cases. It can mimic RPF but is characterized by xanthogranulomatous infiltration by foamy histiocytes nested in fibrosis (Veyssier-Belot et al., 1996).

## Clinical features

The clinical manifestations of this disorder vary with the stage of presentation. Early symptoms can consist of mild fever, weight loss, weakness, nausea, vomiting, and malaise. There is often an associated dull back, flank, and abdominal pain, with no specific radiation pattern, which generally does not respond to non-steroidal anti-inflammatory drugs. The later stage of the disease is characterized by symptoms related to the entrapment of the retroperitoneal structure, such as ureters (back and/or flank and/or abdominal pain, haematuria, polyuria, oliguria, and anuria), renal arteries (renovascular hypertension), superior and inferior mesenteric vessels (bowel ischaemia), inferior vena cava (leg oedema and deep vein thrombosis), gonadal vessels (hydrocoele) and lymphatics, aorta, and common iliac arteries (lymphoedema, claudication, and rarely gangrene). Among the possible complications caused by RPF, the most frequent is ureteral obstruction, which can lead to acute or chronic renal failure. Therefore, an early diagnosis of idiopathic RPF is necessary to prevent this severe and life-threatening complication. In up to 15% of patients, the fibrotic process can also involve structures outside the retroperitoneum, supporting the hypothesis that the disease has a systemic nature. Mediastinal fibrosis, Riedel fibrosing thyroiditis, sclerosing cholangitis, fibrotic orbital pseudotumour, fibrotic arthropathy, pleural, pericardial, and lung fibrosis have been reported usually as a part of IgG4-related disease spectrum (Stone et al., 2012). Abnormalities demonstrated by laboratory tests include some degree of renal insufficiency in up to 75% of patients. Mild normochromic normocytic anaemia, elevated erythrocyte sedimentation rate and C-reactive protein are frequent, supporting the hypothesis that the disease process has an inflammatory nature. Leucocytosis, thrombocytosis, hypergammaglobulinaemia, antinuclear antibody, rheumatoid factor and perinuclear or cytoplasmic antineutrophil cytoplasmic antibody are less common. Moreover, significant proteinuria and/or macroscopic haematuria are infrequent findings (Vaglio et al., 2006).

## Diagnosis

RPF may be more common than hitherto appreciated, if one takes into account subclinical forms of the condition. Even overt idiopathic RPF is, in all probability, much more common than is generally thought. Diagnostic delay is the rule; in one series (Baker et al., 1988), 6–12 months, or even longer, elapsed from the onset of symptoms to diagnosis. Perhaps for this reason bilateral rather than unilateral upper tract obstruction was present in the majority of patients. When taking the history, enquiry should be made about the possible presence of one of the secondary causes of RPF (Box 357.1).

Ultrasonography, isotopic methods, and the intravenous urogram will reveal findings typical of urinary tract obstruction, and the latter may show medial deviation of the ureters (Fig. 357.1). This last finding may also be present in normal subjects and is an unreliable guide to diagnosis. Computed tomography (CT) scanning will show the periaortic mass (Fig. 357.2). Magnetic resonance imaging (MRI) in RPF produces findings comparable to those with CT scanning. An advantage of MRI is the ability to display the

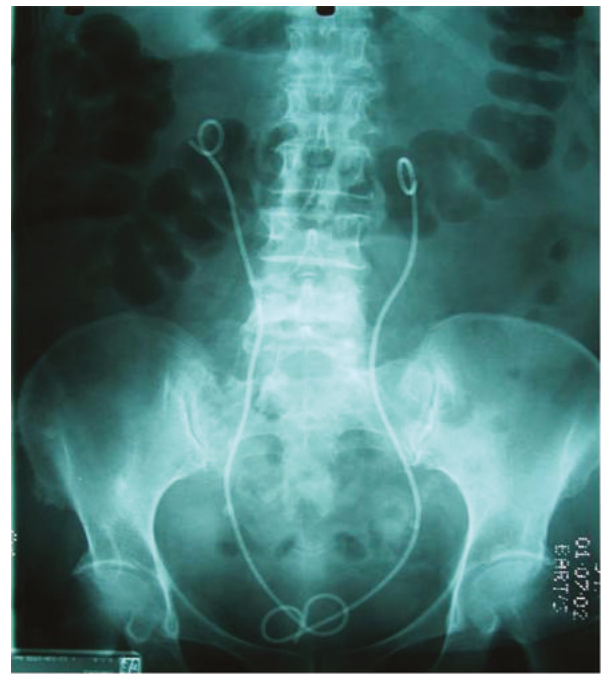

**Fig. 357.1** JJ ureteric stents in the right and left ureter in a patient with retroperitoneal fibrosis. Note the position of these stents suggesting medial deviation of the ureters.

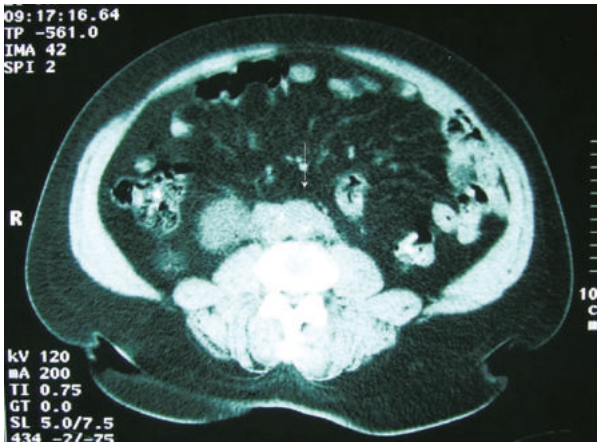


**Fig. 357.2** CT scan of a patient with retroperitoneal fibrosis. Arrow is pointing at the periaortic fibrosis.

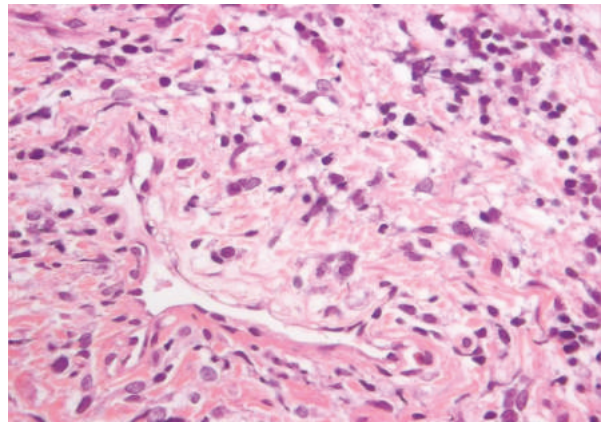

**Fig. 357.4** Histological appearance of fibrocellular tissue consistent with retroperitoneal fibrosis.

pathologic process in multiple planes (transverse, coronal, sagittal). Fluorodeoxyglucose-positron emission tomography (FDG-PET), a functional imaging modality is not useful for the diagnosis of RPF, because of its low specificity, but can be used reliably to assess the metabolic activity of the retroperitoneal mass. FDG-PET also allows whole-body imaging and can detect occult malignant or infectious foci particularly in secondary RPF. Finally, in idiopathic RPF, FDG-PET can be used to monitor the residual inflammatory component following medical therapy (Vaglio et al., 2005).

The differential diagnosis includes retroperitoneal fibromatosis a condition associated with Gardner's syndrome (a variant of familial adenomatous polyposis) and is characterized by homogenous proliferation of fibroblasts arranged in interlacing bundles. Inflammatory myofibroblastic tumour presenting as pseudotumour affects children and has distinct histological characteristics with mainly myofibroblast proliferation.

A histological diagnosis should be obtained if at all possible, and laparotomy is required in order to obtain a sufficiently large sample to exclude lymphoma and cancer with confidence. Conversely, CT-guided needle biopsy of a mass may be sufficient to diagnose lymphoma or carcinoma with confidence (Fig. 357.3).

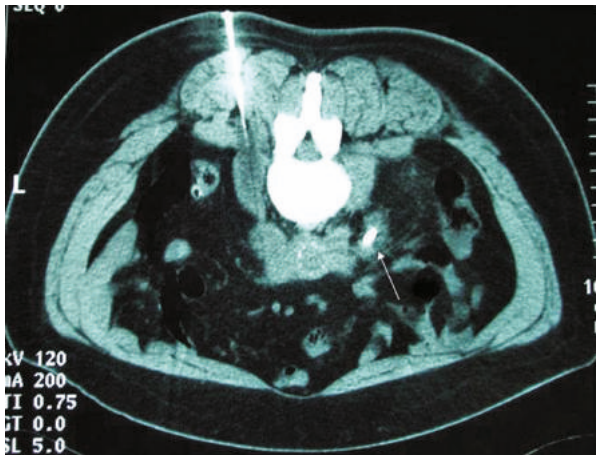


**Fig. 357.3** CT-guided needle biopsy of the retroperitoneal fibrosis showing needle and its track. Arrow is pointing at the stent which was placed in the right ureter.

The microscopic appearance of idiopathic RPF is characterized by a fibrotic tissue infiltrated by a mixture of mononuclear cells, but the relative contribution of these two elements varies with disease stage. In the early stage, the tissue is often oedematous and highly vascular with an active chronic inflammatory component comprising of large numbers of mononuclear cells (mainly CD20+ B cells,

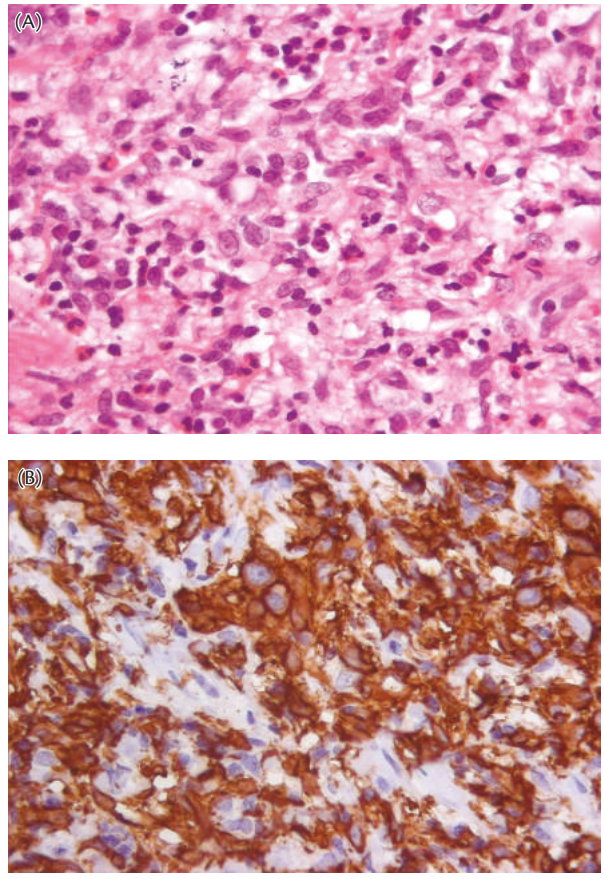


**Fig. 357.5** (A) Histological appearance of lymphoma presenting as retroperitoneal mass. (B) Histological appearance of lymphoma presenting as retroperitoneal mass which is positive for CD20, a cell surface marker for B lymphocytes.

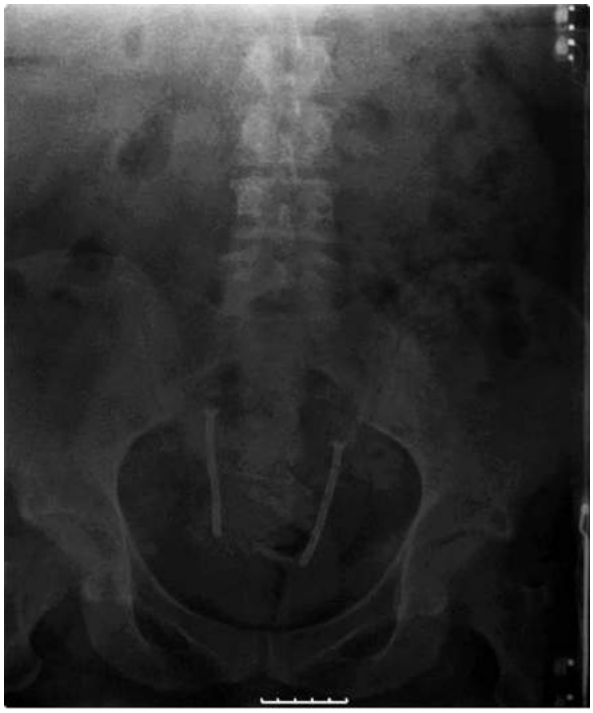

**Fig. 357.6** Memokath® metallic stents positioned in the right and left lower ureters in a patient with retroperitoneal fibrosis.

macrophages, plasma cells, eosinophils, and few CD4+ cells but absence of neutrophils) within fibroblasts and collagen bundles. In the late stages, histology shows pronounced sclerosis and scattered calcifications (see Fig. 357.4 (idiopathic RPF) and Fig 327.5 (lymphoma presenting as RPF)).

## Management of retroperitoneal fibrosis

Management is empirical and controversial since controlled trials of treatment are lacking. The objective of any therapy includes halting the progression of fibrosis, relieving ureteric obstruction, suppressing acute phase reactions, and preventing relapse. Corticosteroid therapy, with or without temporary relief of obstruction by insertion of ureteric stents, ureterolysis alone, and ureterolysis followed by steroid therapy to shrink the periaortic mass and maintain remission have all been used. Corticosteroid therapy alone may correct obstruction, but is by no means invariably effective. Ureterolysis alone may correct obstruction in the long term but is sometimes associated with recurrence of obstruction or the development of obstruction in a previously unobstructed kidney. A reasonable policy for management would seem to be to perform unilateral or bilateral ureterolysis, as appropriate, followed by corticosteroid therapy in patients fit for operation and able to take steroids safely. An attractive alternative is the use of long-term Memokath® ureteric stents (thermo-expandable metallic stent) especially in patients where open operation and long-term steroid therapy is not an option (Fig. 357.6).

Since the anti-oestrogen drug, tamoxifen, may result in the regression of desmoid tumours (which are benign fibrotic tumours), some clinicians have used and reported positive responses to this agent among patients with RPF (Bourouma et al., 1997; Ozener et al., 1997). Although differences exist in the pathobiology of RPF and desmoid tumours and the mechanism of action of tamoxifen in this disorder remains unclear. In a recent randomized controlled trial after initial induction therapy with steroids, patients randomized to tamoxifen as maintenance therapy had a higher rate of relapse compared to when steroids only were used as sole maintenance therapy (Vaglio et al., 2011).

Another possible approach is combination therapy consisting of steroids in combination with other immunosuppressive agents such as mycophenolate, cyclophosphamide, methotrexate, or ciclosporin. Few anecdotal successes have been reported with combinations with the expense and risk of increased toxicity.

Treatment of the secondary forms of RPF requires an approach to treat the underlying cause, for example, to stop the culprit drug. Unfortunately, in various types of secondary RPF (untreatable cancer, trauma, major surgery, and radiotherapy), palliative surgical approaches are the only option which involves relieving obstructive complications by the placement of ureteral stents and nephrostomies with appropriate analgesia (Yaqoob, 2009).

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# CHAPTER 358

# Branchio-oto-renal syndrome

Udo Vester and Stefanie Weber

## Epidemiology

Branchio-oto-renal syndrome (BOR syndrome, OMIM #113650) (Melnick et al., 1976) is a rare disease. Its estimated frequency is 1/40,000 children and it was described as the underlying cause of deafness in 2% of children (Fraser et al., 1980). It is one of several conditions causing renal failure with deafness (see Chapter 170).

## Aetiology and inheritance

BOR syndrome is a genetically heterogenous condition with the majority of patients (40%) bearing a dominant mutation or gene deletion of *EYA1* (Abdelhak et al., 1997). Some patients are affected by large genomic rearrangements involving the *EYA1* gene locus. A number of missense mutations have also been identified in *SIX1* and *SIX5* in a very small subset of BOR patients (Ruf et al., 2004; Hoskins et al., 2007). Mutations in *SIX5* seem to be rare (Krug et al., 2011). Members of the *EYA* and *SIX* gene families are involved in regulatory networks of organ development and *EYA1, SIX1*, and *SIX5* are all expressed in early organogenesis of the kidney and ear, explaining the phenotypic spectrum of BOR and branchio-otic syndrome (BOS). The variability of clinical symptoms is high among mutation carriers (Smith, 2009).

## Clinical features

BOR syndrome can be clinically diagnosed in the presence of typical symptoms. The diagnosis of BOR syndrome is likely in individuals with three major or two major and two minor criteria (see Table 358.1). In cases with an affected relative only one major criterion is requested.

**Table 358.1** Diagnostic criteria for BOR syndrome

| Major criteria | Minor criteria |
|---|---|
| Branchial anomalies | External ear anomalies |
| Deafness | Middle ear anomalies |
| Preauricular pits | Inner ear anomalies |
| Renal anomalies | Preauricular tags |
| | Other: facial asymmetry, palate abnormalities |

From Branchio-oto-renal syndrome: The mutation spectrum in EYA1 and its phenotypic consequences, Eugene H. Chang, Maithilee Menezes, Nicole C. Meyer, Robert A. Cucci, Virginie S. Vervoort, Charles E. Schwartz, Richard J.H. Smith, *Human Mutation*, pp. 582–589. 

Branchial anomalies include branchial cleft sinus tract or cysts and are found in every second patient. Deafness can be mild or severe and of conductive, sensorineural, or mixed origin. A hearing deficit is common and observed in > 90% of cases. BOR is one of several syndromes that may cause renal disease with hearing impairment (see Chapter 170). In BOR, hearing is usually impaired from infancy. Townes–Brocks syndrome (see Chapter 359) is associated with deafness and auricular abnormalities, but usually also other abnormalities that clearly differentiate it.

The most typical ear anomalies are preauricular pits in > 80% of cases, but a wide variety of otologic findings has been described (Smith, 2009).

Renal anomalies can be expected in two-thirds of patients (Chang et al., 2004). They range from mild (hydronephrosis, reflux) to severe affection (agenesis, dysplasia) and can be uni- or bilateral and in some cases may proceed to end-stage renal failure or even intrauterine death.

Patients with renal dysplasia without ear or branchial anomalies seem to be rare (Weber et al., 2006).

## Investigations

BOR syndrome is diagnosed in patients with branchial clefts or cysts, ear anomalies with deafness, and anomalies of the kidneys. Careful evaluation of the family history is important if typical features of BOR syndrome are present. Minor abnormalities should be searched for by thorough clinical examination.

Cervical investigations may include magnetic resonance imaging to detect typical cysts of the branchial arch. Complete assessment of hearing capability is mandatory. Renal imaging with ultrasound is requested to identify cases with renal anomalies and/or hypodysplasia (see Fig. 358.1).

Genetic testing can be helpful to confirm the diagnosis. Mutations in *EYA1* are the most frequent cause of BOR syndrome. Importantly, gene deletions and genomic rearrangements of *EYA1* are not identified by routine sequencing techniques but should be looked for in patients with typical clinical symptoms by quantitative polymerase chain reaction or comparative genome hybridization techniques. Prenatal diagnosis is feasible in families with a known mutation.

## Treatment and outcome

Branchial clefts or cysts will be treated through surgical excision. Hearing deficits should be identified early and treated as indicated. Renal or urological anomalies should be treated in a standard

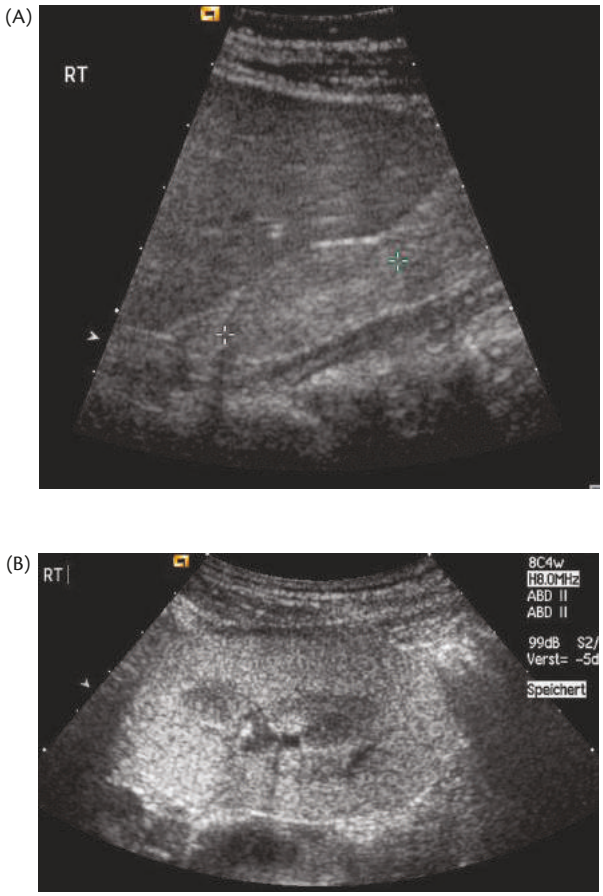


**Fig. 358.1** Ultrasonography of renal involvement in BOR syndrome: (A) Boy (2 years old) with severe renal hypoplasia and end-stage renal failure treated with peritoneal dialysis since 20 months of age. Note small and dysplastic right kidney (length 2.9 cm) (B) Boy with renal hypo/dysplasia (5 years old), renal function is preserved with a creatinine of 78 µmol/L. Right kidney is shown with increased echogenicity and reduced size (length 6.5 cm).

manner, and if end-stage renal failure develops dialysis or transplantation should be performed.

Genetic counselling of patients and families is important as the risk of BOR syndrome in the offspring is 50%.

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# CHAPTER 359

# Townes–Brocks syndrome

Udo Vester and Stefanie Weber

## Epidemiology

Townes–Brocks syndrome (TBS, OMIM #107480) (Townes and Brocks, 1972) is a rare disease with an estimated incidence of 0.42/100,000 liveborn infants (Martinez-Frias et al., 1999). However, the number of oligosymptomatic or undiagnosed cases is unknown as patients may evade the clinical diagnosis until adulthood (Faguer et al., 2009) or may be attributed to other diagnoses.

## Aetiology and inheritance

TBS is a monogenic disorder of autosomal dominant Mendelian inheritance. In 70% of cases with the classical clinical triad of TBS, mutations in *SALL1* on chromosome 16q12.1 can be identified (Kohlhase et al., 1998). The vast majority represents nonsense mutations but deletion mutations have also been reported. In 50% of patients, mutations occur *de novo*, presenting to the clinician as sporadic cases with so far uneventful family history. *SALL1* encodes for Sal-like protein 1, a transcriptional repressor with major involvement in organogenesis. Expression levels are highest in the kidney but also found in developing brain, limb, heart, and other tissues reflecting the structures affected in human TBS.

## Clinical features

The typical clinical triad in TBS consists of (1) imperforate anus, (2) dysplastic ears, and (3) thumb malformations (see Table 359.1).

Each of these symptoms is seen in > 80% of patients and the complete triad is found in two-thirds of cases (Kohlhase, 2007). Additional findings include renal involvement, congenital heart disease (Surka et al., 2001), congenital hearing loss, foot, genitourinary, or central nervous system malformations, mental retardation, hypothyroidism, and retardation of growth (Kohlhase, 2007).

**Table 359.1** Diagnostic criteria for TBS syndrome

| Main features | Additional findings |
|---|---|
| Imperforate anus | Renal involvement |
| Dysplastic ears | Congenital heart disease |
| Thumb malformation | Hearing loss |
| | Malformations of feet, genitourinary and central nervous system |
| | Other: retardation of growth, mental retardation, hypothyroidism |

Renal involvement is observed in 42% of cases, ranging from mild anomalies (including vesicoureteral reflux or horseshoe kidneys) to severe functional impairment associated with chronic or end-stage renal failure (see Fig. 359.1) (Kohlhase, 2007). Paediatric and adult nephrologists should be aware that the expressivity of TBS is highly variable. TBS should therefore be considered in all patients with any typical symptom (Kohlhase, 2007). The phenotypic variability includes oligosymptomatic cases but also isolated

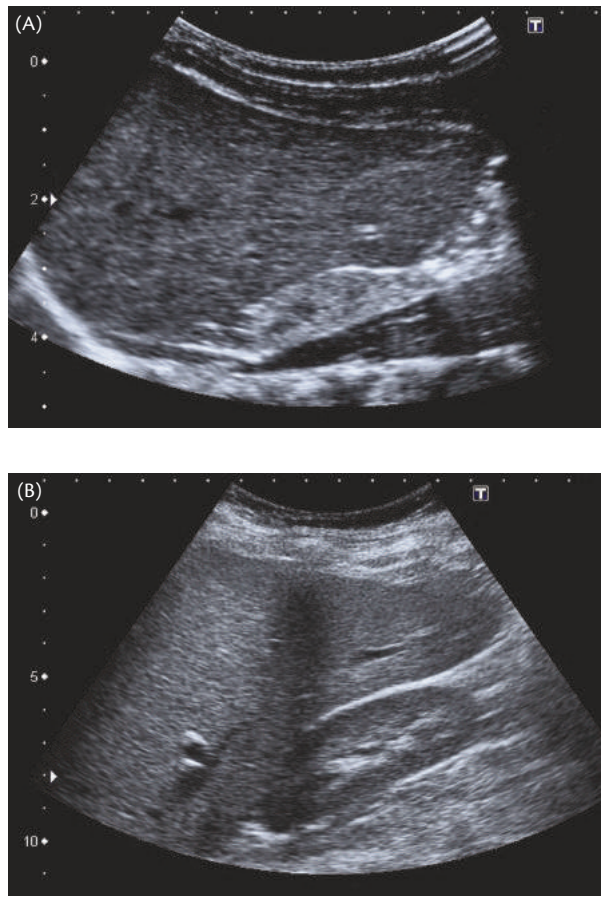


**Fig. 359.1** Ultrasonography of renal involvement in TBS: (A) Girl (3 months old) with chronic renal failure (creatinine 246 µmol/L) and severe bilateral hypodysplasia of the kidneys (length < 2 cm). Right kidney is shown with increased echogenicity and reduced corticomedullary differentiation. (B) Mother of patient in a (15 years old), renal function is well preserved (creatinin 96 µmol/L). Right kidney is shown with reduced size (kidney length 7.7 cm) but normal echogenicity.

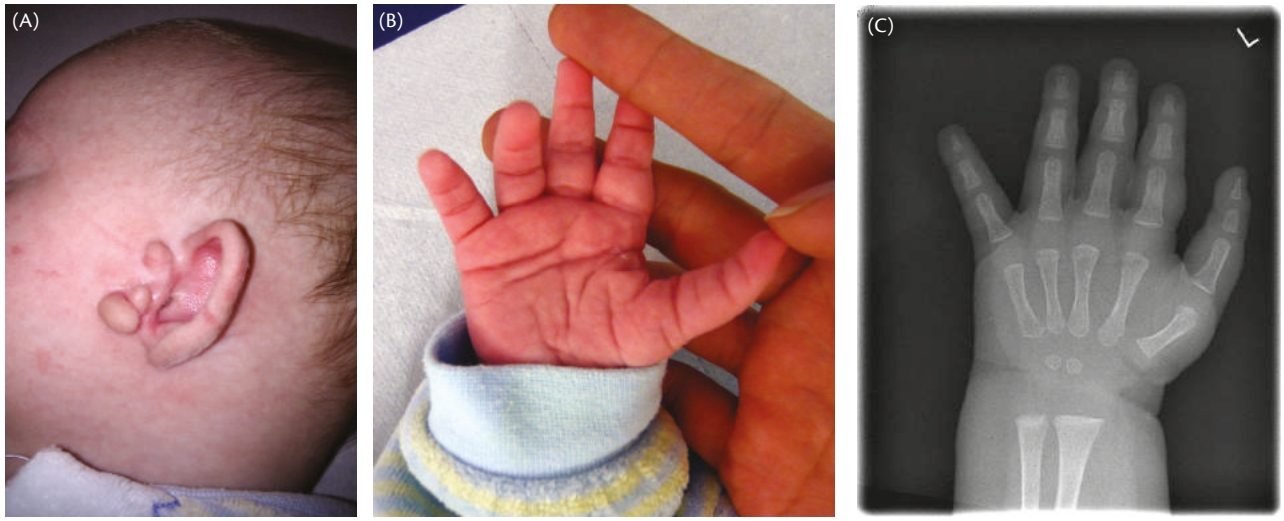


**Fig. 359.2** Extrarenal involvement in TBS (same patient as in Fig. 359.1A): (A) Dysplastic ear. (B, C) Triphalangeal thumb.

organ malformations, for example, isolated dysplasia of the kidneys (Weber et al., 2006).

A phenotypic overlap has been observed to *SALL4*-related disorders, including Okihiro, acro-renal-ocular, and Holt–Oram syndromes (Kohlhase et al., 2003). Holt–Oram syndrome, caused by mutations in *TBX5* and, more rarely, *SALL4,* is characterized by upper limb malformations including triphalangeal or absent thumbs combined with congenital defects of the heart. Importantly, renal anomalies are absent in these patients.

## Investigations

TBS is usually diagnosed in the presence of the typical triad of imperforate anus, ear anomalies, and thumb malformations (see Fig. 359.2). A thorough family history and a complete physical examination with respect to minor abnormalities are mandatory in every neonatal case. Auditory testing, echocardiography, renal imaging with ultrasound, and X-ray of bone deformities provide further information. Renal and thyroid function tests should be performed in every case as congenital hypothyroidism can be present in rare cases.

Prenatal diagnosis, based on genetic testing and ultrasound examination, is feasible, especially in families with a known mutation.

## Treatment and outcome

Treatment depends mainly upon the clinical presentation. An imperforate anus has to be operated on early after birth by an experienced paediatric surgeon, cardiac defects should be treated as recommended. Surgery of the hands may be required in some children with additional digits. A hearing deficit should be identified early and treated with hearing aids when necessary. Thyroid function has to be supplemented if indicated. Renal function should be monitored into adulthood and renal impairment has to be treated with supportive standard therapy. End-stage renal failure requires dialysis or renal transplantation which has been successfully performed in patients with TBS (Botzenhart et al., 2007; Reardon et al., 2007).

Genetic counselling of patients and families is important as the recurrence risk of TBS in families with proven mutation is 50%. All affected patients, including individuals with *de novo* mutation of *SALL1*, will statistically transmit the disease to 50% of their offspring.

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# CHAPTER 360

# Renal coloboma syndrome

Udo Vester and Stefanie Weber

## Epidemiology

Renal coloboma syndrome (RCS, papillorenal syndrome, OMIM #120330) and paired box gene 2 (*PAX2*) mutations have been reported in individuals from many regions of the world (Sanyanusin et al., 1995); however, the exact prevalence is still currently unknown. Systematic genetic studies in patients with renal malformations will be helpful to delineate the frequency of *PAX2*-related disorders.

## Aetiology and inheritance

RCS is a monogenic autosomal dominant disorder caused by mutations in *PAX2*, encoding the paired box protein PAX2. Paired box proteins are important proteins involved in early organogenesis and *PAX2* is highly expressed in the kidney, eye, and ear (Dressler et al., 1990). This pattern of expression explains the spectrum of anomalies observed in RCS patients. In approximatively 50% of patients, mutations in *PAX2* can be identified. These include missense and nonsense mutations and small intragenic deletions or duplications, most frequently affecting the paired domain of the PAX2 protein. A recurrent insertion mutation (619insG) is most probably a mutational hot spot within the *PAX2* gene (Amiel et al., 2000). Many patients of different families have been identified as carriers of this mutation. The phenotypic variability of mutation carriers is high, even among members of the same family (Weber et al., 2006).

## Clinical features

The penetrance of malformations of the eyes is very high in individuals affected by *PAX2* mutations with somewhat lower penetrance for malformations of the kidney. Disorders affecting kidney and eye are discussed in Chapter 171.

The renal (and urinary) phenotype comprises hypoplasia of the kidney, unilateral agenesis, multicystic dysplastic kidneys, and/or vesicoureteral reflux (Fig. 360.1). End-stage renal disease (ESRD) occurs in one-third of patients with proven *PAX2* mutation but in almost all individuals with *PAX2* mutation and renal hypoplasia. Age at diagnosis of RCS can be very early in the antenatal period (Martinovic-Bouriel et al., 2010) but also late in adulthood (Negrisolo et al., 2011).

The most common eye abnormalities are optic nerve dysplasia and posterior cystic dilatations of the optic nerve (Schimmenti et al., 2003). Retinal colobomas are observed in only 4% of *PAX2* mutation carriers. Visual acuity is reduced in 75% of affected individuals. Less common findings include high-frequency hearing loss, soft skin, and ligamentous laxity (Schimmenti and Eccles, 2007).

## Investigations

Careful ophthalmological examination is mandatory to detect ocular anomalies in RCS patients. If typical optic nerve anomalies are present, renal ultrasound and a hearing test should be performed in all affected individuals. Vice versa, patients with renal hypodysplasia should receive a thorough examination of the fundus of the eye and eventually a hearing test.

Mutational analysis of *PAX2* can confirm the diagnosis of RCS (Bower et al., 2012).

## Treatment and outcome

Optic nerve anomalies and hearing deficits should be identified early and treated as indicated. Chronic renal insufficiency as a consequence of hypodysplasia of the kidneys should be treated in a

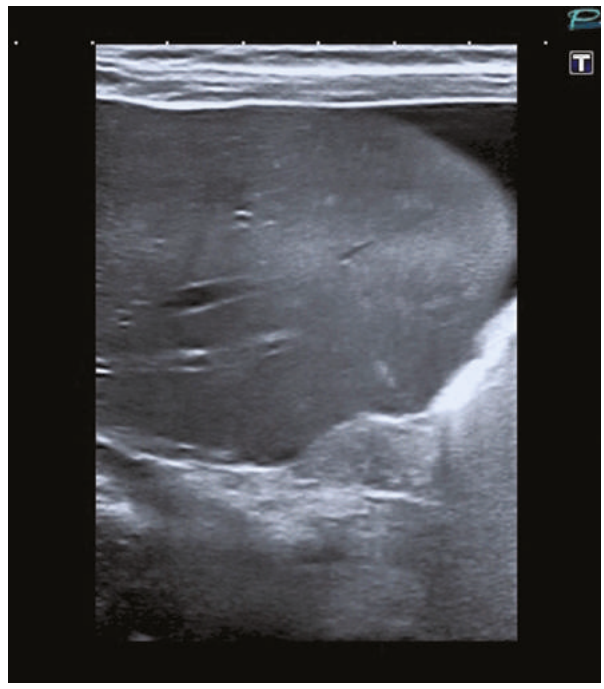

**Fig. 360.1** Ultrasonography in renal coloboma syndrome. Girl (4 months old), small solitary and dysplastic right kidney (1.7 cm in length). Pregnancy was complicated with oligohydramnios and the girl needed renal replacement therapy from the second month of life (free fluid around the liver is peritoneal dialysis).

standard manner and if ESRD develops dialysis or kidney transplantation should be performed.

Genetic counselling should be offered to a family if a mutation in *PAX2* has been identified. A germline mutation will be transmitted on average to 50% of the offspring. Careful clinical examinations of eyes, hearing capability, and kidney morphology and function should be performed in all affected individuals (siblings and off-spring).

## Differential diagnosis

Renal dysplasia and retinal/optic nerve colobomas are major findings in CHARGE syndrome (*c*oloboma, *h*eart malformations, *a*tresia choanae, *r*etardation of *g*rowth and development, *e*ar and hearing defects) due to mutations or deletions of *CHD7*. Mutations in *PAX2* have not been identified in patients with CHARGE syndrome to date. Other conditions affecting kidney and eye are discussed in Chapter 171.

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# CHAPTER 361

# Ante- and postnatal imaging to diagnose human kidney malformations

Fred E. Avni, Marie Cassart, Anne Massez, and Michèle Hall

## Imaging of the normal fetal urinary tract

### Sonographic examination

The practice of obstetrical ultrasound varies from country to country. In some European countries (Belgium, France), three sonographic examinations are performed during the pregnancy, one during each trimester. In other countries, one single examination is proposed during the mid trimester (United Kingdom, Scandinavian countries) while in others an obstetrical sonogram is only performed in case of a clinical problem (e.g. in many states of the United States). These variable approaches are due to the controversy that has been raised by some authors about the clinical yield of obstetrical ultrasound in general (Sylvan et al., 2005; Salomon et al., 2011).

The examination (ultrasound) is performed using (mainly) transabdominal or transvaginal transducers (usually during the first trimester). The settings must be optimized to the maternal size.

#### Bladder

At the embryonic stage, around the 9th week, the urine is collected in the bladder that can be visualized as a fluid-filled structure within the fetal pelvis. It will be an essential landmark. During the second and third trimester, the bladder empties and refills continuously every 25–30 minutes and the cycle can be monitored during the sonographic examination. At the end of the pregnancy, this cycle somewhat slows especially in female fetuses. The bladder is limited by the umbilical arteries that can be identified turning on colour Doppler (Chamberlain et al., 1984; Rosati and Guariglia, 1996) (Fig. 361.1A).

#### Kidneys

The fetal kidneys can be demonstrated around 11 weeks (using endovaginal probes) or somewhat later around 12 weeks (with transabdominal probes). During the first trimester, the kidneys appear as hyperechoic oval structures at both sides of the spine. This hyperechogenicity will progressively decrease and around 32 weeks, the cortical echogenicity should always be less than that of the liver or spleen. A corticomedullary differentiation (CMD) appears around 15 weeks (hyperechoic cortex and hypoechoic medulla). It should always be demonstrated in fetuses older than 18 weeks (Fig. 361.1B). Thanks to this CMD, the kidneys are easily demonstrated; some urine distending the renal pelvis may help for their identification. The kidney growth can be evaluated throughout pregnancy by measuring its length and comparing it to normal charts (as a simple rule, renal growth is 1.1 mm/gestational week). These measurements will contribute to characterize (small) dysplastic kidneys or (large) polycystic kidneys (see 'Abnormal kidney size') (Rosati and Guariglia, 1996; Chitty and Altman, 2003). Under normal conditions, the fetal ureters are not visible

#### Sonographic evidence of normally functioning urinary tract

A normal functioning urinary tract is confirmed through by the visualization of a fluid filled bladder and normal kidneys as well as normal amniotic fluid volume.

### Magnetic resonance imaging of the fetal urinary tract

For more than 20 years, fetal magnetic resonance imaging (MRI) has been introduced as a complementary examination to ultrasound for the visualization of normal and abnormal fetal development. The technique has been widely used for the characterization of central nervous system and chest anomalies. Its use for the evaluation of the fetal abdomen is more recent. As the urinary tract is concerned, fetal MRI is able to provide additional information compared to ultrasound in selected indications such as difficult fetal lie or maternal obesity with poor visualization of the fetal structures especially in case of high suspicion of renal anomalies. Furthermore, fetal MRI has the advantage of better tissue characterization (to demonstrate very small cysts) and a larger field of view (to evaluate large complex malformations). The technique is also helpful in differentiating urinary from digestive tract malformations or on the contrary confirming the association of both. It also defines large abdominal cystic masses. T2-weighted sequences are mainly used for the visualization of abnormalities of the urinary tract. T1-weighted sequences are helpful whenever digestive tract malformations are suspected (Cassart et al., 2004a).

The limited availability of MRI equipment renders its use difficult in some countries; nevertheless, its indications are widening and one could expect more utilization of the technique in the future.

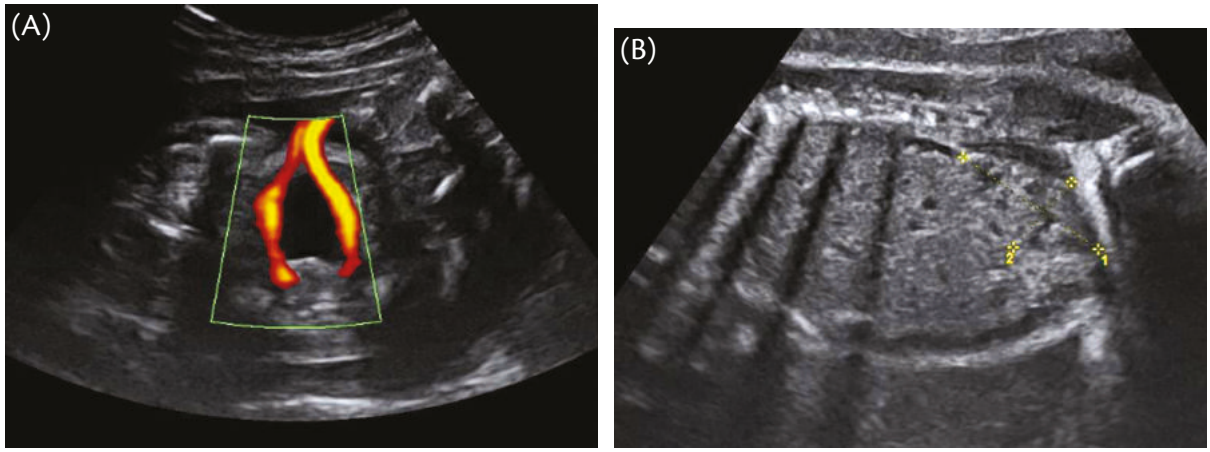


**Fig. 361.1** (A) Fetal bladder in the second trimester. Transverse scan of the fetal pelvis. Power Doppler of the umbilical arteries visible at both sides of the bladder. (B) Normal kidney (third trimester)—the kidney is limited by the crosses. A corticomedullary differentiation is visible.

## The abnormal fetal urinary tract

Anomalies involving the urinary tract are numerous and encompass a wide number of malformations, most minor and amenable to postnatal treatment but some life-threatening. These anomalies can be isolated, limited to the urinary tract, or in association with malformations in other systems. Therefore, the sonographic examination should be as meticulous as possible in order to visualize the associated malformations and assess the prognosis (Zhou et al., 1999; Wellesley and Howe, 2001; Richmond and Atkins, 2005; Wiesel et al., 2005). Abnormalities of the urinary tract can be found at any time during the pregnancy. Therefore, in order to screen all potentially abnormal cases, one sonographic examination should be performed during each trimester.

### Abnormal renal number

#### Renal agenesis

*Bilateral* renal agenesis is incompatible with extrauterine life. The condition is part of the Potter syndrome. The diagnosis is based on the discovery of an anamnios after 15 weeks of gestation and on the absent renal structures. The bladder is empty.

In unilateral agenesis, sonography shows, a normal kidney will not be identified in one of the lumbar areas. Whenever no other complication or malformation is present, the prognosis for postnatal life is excellent. Whenever one or both lumbar fossa is empty, the kidneys should be searched in an ectopic location. In doubtful conditions, MRI could provide additional information regarding the location and appearance of the two kidneys (Mandell et al., 1994; Latini et al., 1998; Cassart et al., 2004a).

#### Renal duplication

When no complication occurs, renal duplication is a benign condition and should be considered as normal variant. On ultrasound, two separate renal pelvis are identified.

### Abnormal kidney location and fusion anomalies

There are various ectopic locations possible for the kidney. The ectopic kidney is recognizable thanks to the characteristic CMD. One or both kidneys can be ectopic. The pelvic location is the commonest (Fig. 361.2). Other ectopic/fusion anomalies detected *in utero* include horseshoe kidney, crossed fused ectopia (both kidneys lie on the same side), or intrathoracic ectopia. In horseshoe kidneys, a bridge of renal tissue can be visualized in front of the spine. Crossed ectopia should be differentiated from duplex kidneys. In crossed (fused) ectopia, there is an angulation between the two kidneys whereas in duplication the two renal moieties lie in the same continuous plane (Meizner and Barnhardt, 1995). An ectopic kidney is usually smaller and can be malrotated. Complications such as dilatation or dysplasia may occur as well.

### Abnormal kidney size

Measurements of the kidneys must be systematic whenever their echogenicity is abnormal or whenever the amniotic fluid volume is reduced (Chitty and Altmann, 2003).

*Small kidneys* (below −2 standard deviations (SD)) are usually in relation with hypoplasia or dysplasia (or both) resulting from an embryological maldevelopment, secondary to reflux (reflux nephropathy), obstruction, or to an ischaemic phenomenon. The prognosis of small kidneys will depend upon the remaining renal function. Cases with oligohydramnios have the poorest prognosis (Oliveira et al., 1999). Dysplastic parenchyma appears hyperechoic possibly with cysts (Fig. 361.3).

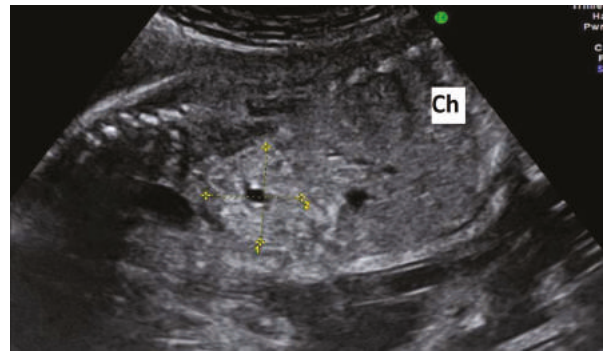


**Fig. 361.2** Ectopic pelvic kidney—third trimester. Sagittal view of the fetal abdomen. The pelvic kidney (limited by crosses) lies above the bladder. Ch = fetal chest.

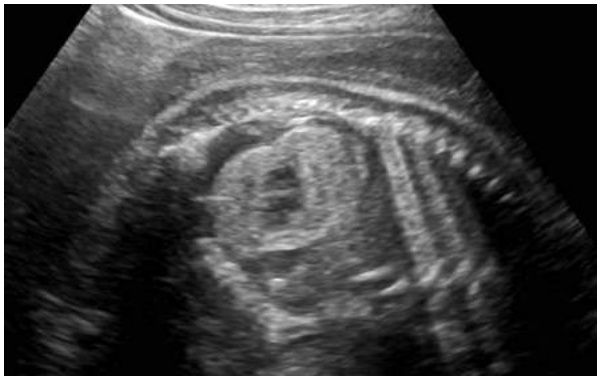

**Fig. 361.3** Renal dysplasia—third trimester. Sagittal scan of the right kidney (associated with marked hydronephrosis—not shown) appearing hyperechoic without CMD.

The differential diagnosis of *enlarged kidneys* (above +2 SD) includes renal dilatation, cystic kidneys, syndromes with organomegaly (i.e. Beckwith–Wiedemann syndrome) and renal tumours (see below).

## Urinary tract dilatation

Dilatation of the renal pelvis is a common finding on obstetrical ultrasound. Its frequency is evaluated around 1–4% of all pregnancies. Yet, all dilatations do not have the same clinical relevance; furthermore, their antenatal and postnatal evolution is variable (Ismaili et al., 2003, 2004).

### Definition

Various criteria are used in order to objectivate renal dilatation. The best criterion is the measurement of the anterior–posterior diameter of the renal pelvis on a transverse scan of the fetal abdomen. Many authors agree that the upper limit should be 4 mm during the second and 7 mm during the third trimester of the pregnancy (Fig. 361.4A). These limits are set in order to detect not only patients that will need corrective surgery (in case of obstructive dilatation) but also the majority of fetuses and neonates presenting with vesicoureteric reflux (VUR). The latter being at risk for developing complications and eventually worsen their renal function (Ismaili et al., 2003; John et al., 2004; Hubert et al., 2007; Nguyen et al., 2010).

A pyelectasis refers to a visible renal pelvis below the significant threshold. During the second trimester, it is considered as a minor sign of chromosomal anomaly.

Other sonographic evidence of an abnormality of the urinary tract include the visibility of the fetal ureter at any moment of the pregnancy (Fig. 361.4B) and the demonstration of an enlarged bladder (> 3 cm length on a sagittal scan during the second and 5 cm during the third trimester) (Fig. 361.4C).

### Evaluation of the dilatation during fetal life

Once a dilatation has been detected *in utero*, the subsequent evaluation should answer three questions: the origin of the dilatation, the coexistence of associated anomalies, and finally the prognosis of the malformation. The most common cause for urinary tract dilatation is ureteropelvic obstruction (UPJ). Other causes include ureterovesical junction obstruction (UVJ), VUR, complicated duplex kidneys, and bladder outlet obstruction (BOO).

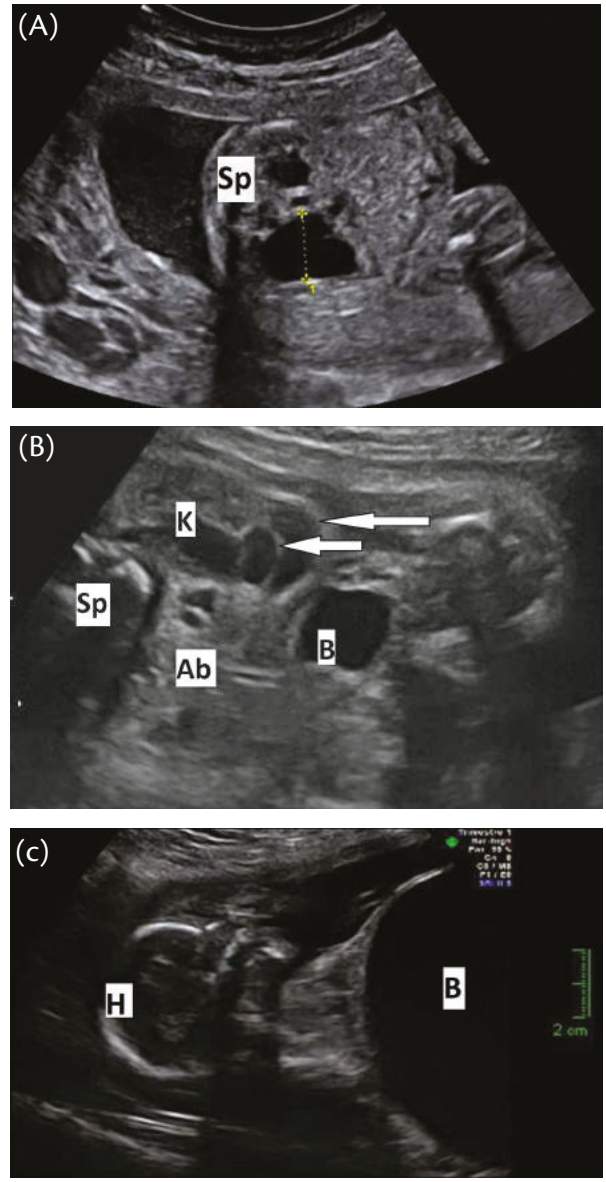


**Fig. 361.4** (A) Bilateral asymmetrical dilatation—third trimester. Transverse scan through fetal abdomen. Marked left (14 mm between crosses) and moderate right (6 mm) dilatation. Sp = spine (B) Ureteral dilatation (case of UVJ obstruction). Transverse scan of the fetal abdomen through the dilated convoluted ureter (arrows). Ab = abdomen; B = bladder; K = dilated kidney; Sp = spine. (C) Megabladder—Early second trimester (case of urethral atresia). Sagittal view through the fetal head and abdomen. The abdomen is filled by the distended bladder (B). H = fetal head

In case of *UPJ obstruction*, the renal pelvis is dilated (Fig. 361.5A). As mentioned, the threshold measurement on a transverse scan of the kidney is 7 mm for a mild dilatation, between 7 and 15 mm moderate, and above 15 mm a system is considered markedly dilated. The more dilated the system, the more probable a decrease in renal function after birth. Furthermore, thinned, echogenic cortex with cysts corresponds most likely to obstructive dysplasia with impaired function. Yet, there is no direct correlation between the renal aspect and postnatal function (Kaefer et al., 1997).

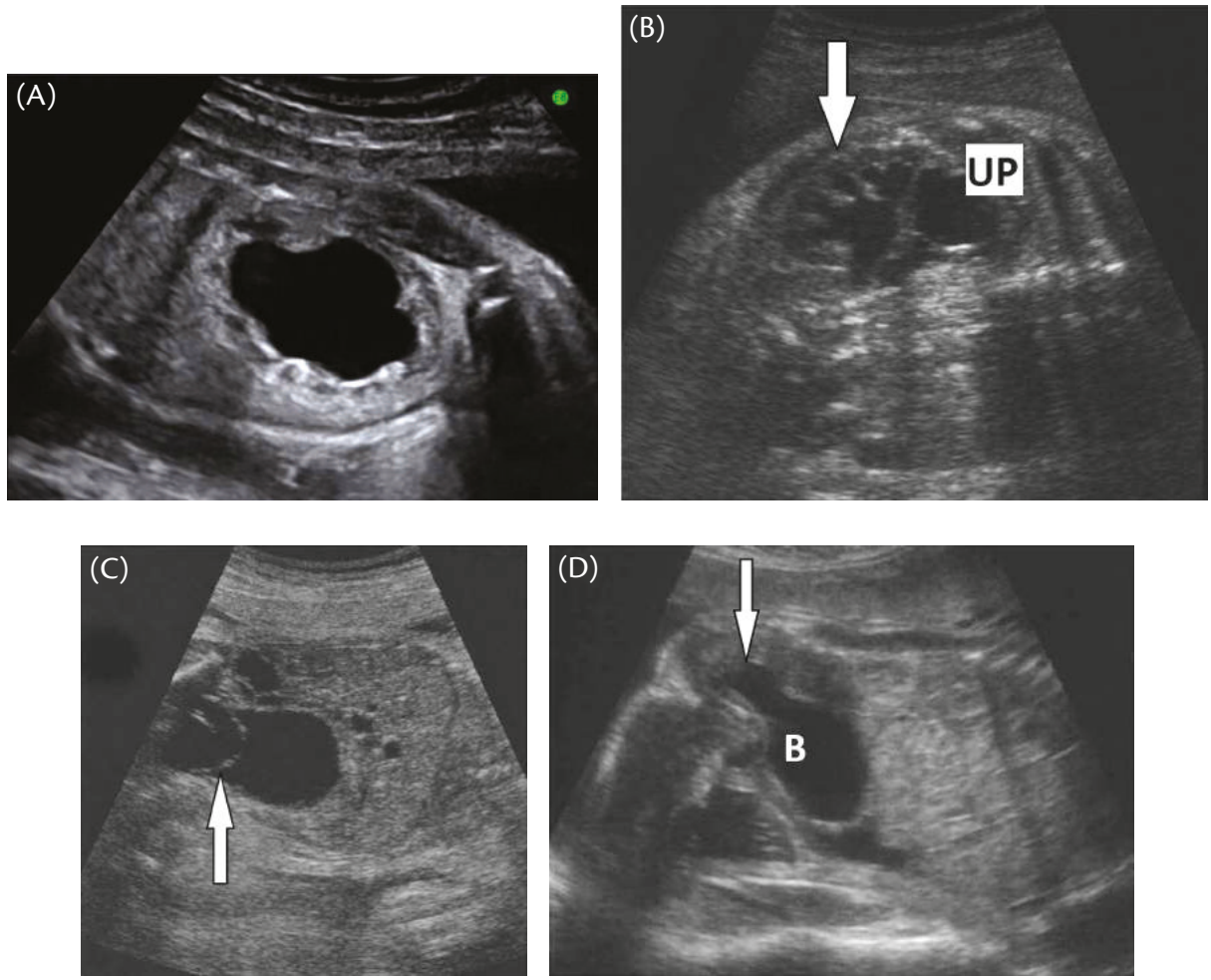


**Fig. 361.5** (A) UPJ obstruction—third trimester—sagittal scan of the left kidney. A marked dilatation is demonstrated. (B) Renal duplication—obstructed upper pole and ectopic ureterocoele (third trimester). Sagittal scan through the left kidney demonstrating the dilated upper (UP) and lower poles (arrow). (C) Sagittal scan through the bladder displaying the ureterocele (arrow). (D) Posterior urethral valves—third trimester. Sagittal scan showing the distended bladder (B) and dilated posterior urethra (arrow).

It is noteworthy that obstruction may lead to leakage (rupture of a renal calyx or even bladder), and to urinary extravasation either as a perirenal urinoma or as ascites. The functional significance of the leakage is not straightforward. In some instances it may protect the renal parenchyma while in others renal growth is impaired (Kaefer et al., 1995).

The main differential diagnosis of UPJ obstruction is *non-obstructive dilatation* (which is a postnatal diagnosis), multicystic dysplastic kidney (MCDK) (part of cystic renal diseases, see below), and UVJ obstruction. The diagnosis of *UVJ obstruction* is based on the demonstration of a dilated ureter (Zhou et al., 1999) (Fig. 361.4B). The dilatation may increase *in utero* but usually decreases, at least after birth. In most instances, it is not possible to differentiate between dilatation secondary to UVJ obstruction from dilatation secondary to high-grade VUR. A hint for the differential diagnosis is the variability of the diameter of the renal pelvis during one single examination suggesting VUR.

*Complicated renal duplication* is usually easy to demonstrate, once dilatation develops in either moiety (Fig 361.5B. Various complications may occur at the level of each moiety of the duplication; obstruction, MCDK, or reflux. The upper pole may end into an ureterocele or into an ectopic extravesical insertion. The ureterocele is seen as a septum within the bladder (Fig. 361.5C). The parenchyma related to obstruction may be thinned and dysplastic. The ectopic extravesical insertion may be more difficult to diagnose in utero (Whitten et al., 2003).

Finally, the UT obstruction can be located below the bladder. The commonest cause in males fetuses are posterior urethral valves (PUV) (Fig. 361.5D). The condition may or not induce dilatation of the upper UT. The dilatation can be uni- or bilateral, related to obstruction or to VUR (Harvie et al., 2009). The degree of associated dysplasia is also variable. There seems to be a correlation between cortical echogenicity and the degree of obstructive dysplasia.

Bladder enlargement due to obstruction secondary to PUV must be differentiated from other causes of BOO and from other causes of large bladder without obstruction (Box 361.1) (Carlsson et al., 1992; Mandell et al., 1992).

### Prognosis—*in utero* treatment

Whenever a renal anomaly (mainly dilatation) is detected, a complete survey of the fetal anatomy should be performed in order to detect associated malformations that would indicate the need for

**Box 361.1** Causes of enlarged bladder (> 3 cm second trimester and > 6 cm third trimester)

- Urethral atresia ('prune belly' sequence)
- Megalourethra
- Posterior urethral valves
- Anterior urethral valves
- Prolapse of ureterocele
- Pseudo-megabladder megaureter syndrome (< vesicoureteric reflux)
- Megabladder microcolon hypoperistalsis syndrome
- 'Normal variant' in female fetuses.

chromosomal analysis or the possibility of polymalformative syndromes; both worsen the prognosis (Wellesley and Howe, 2001; Staebler et al., 2005). In selected cases, fetal MRI (such as complex uropathy, lack of visibilities due to fetal positioning or maternal obesity, bilateral diseases, etc.) could be useful and provide additional information on the association of malformations or the status of the renal parenchyma. T2-weighted sequences are usually sufficient (Cassart et al., 2004) (Fig. 361.6).

In case of dilatation, the prognosis will depend upon the type and extent of anomalies; features of poor prognosis include early diagnosis, bilateral marked dilatation, persistently obstructed bladder, oligohydramnios, and secondary lung hypoplasia. Bilateral renal dilatation and BOO have an increased risk of associated chromosomal anomalies and therefore in such cases an evaluation of fetal chromosomes may be warranted. The finding of associated echogenic and/or cystic renal parenchyma is frequently but is only partially informative about renal function. Conversely, normal cortical echogenicity does not exclude dysplasia.

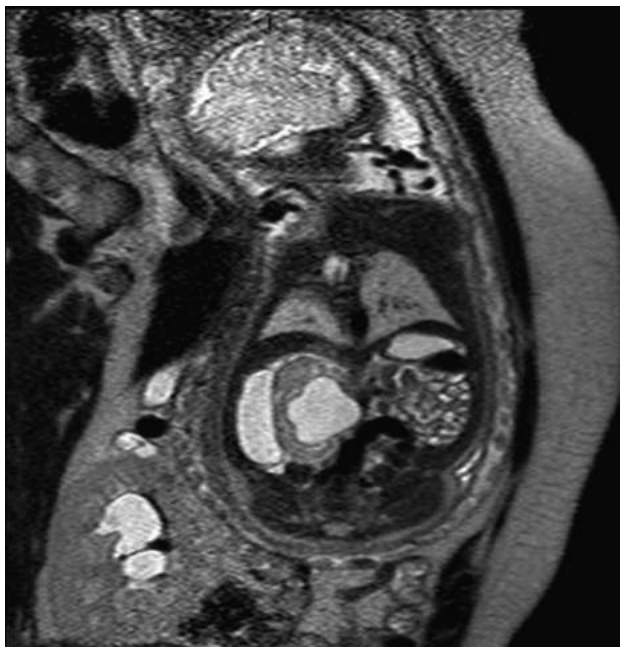

**Fig. 361.6** Fetal MRI. Case of UPJ obstruction with perirenal urinoma—third trimester. T2-weighted sequence.

The role of measuring urinary electrolytes in the fetal urine obtained through transabdominal puncture is controversial. There are discrepancies in the predictive values of urine biochemistry due to small sample size, variations in cut-off values, gestational age, and sampling frequency. Fetuses with renal damage show increased urinary concentrating especially of sodium and calcium without clear convincing confirmation.

Measurements of $B_2$-immunoglobulin or C cystatin in the fetal urines allow a better accuracy. The outcome of vesico-amniotic shunting is also controversial. Although technically relatively easy, the long-term results have not been established (Ciardelli et al., 1996; McLorie et al., 2001).

## Management of fetal pelvis dilatation after birth

Any information relevant for the proper postnatal management should be transmitted to the postnatal team in charge of the newly born.

After birth, some conditions require an immediate confirmation and therapeutic manoeuvres. For instance, obstructive posterior urethral valves or prolapsed ectopic ureterocele into the urethra leading to oligo-anuria necessitates an immediate treatment. In case of such suspicions, ultrasound and voiding cystourethrogram (VCUG) should be performed immediately after birth in order to confirm the anomaly (Ismaili et al., 2002; Hubert and Palmer, 2007; Riccabona et al., 2009; Nguyen et al., 2010; Skoog et al., 2010).

In all other cases, the workup should be planned without emergency. A large debate arose regarding the respective role of ultrasound and VCUG in the postnatal workup. Some authors advocate the systematic use of a VCUG in every case of antenatal detection of urinary tract dilatation; for others only patients with persistent dilatation should undergo a VCUG (Skoog et al., 2010). Whatever the choice, all patients are put under prophylactic chemotherapy up to the final diagnosis and a final therapeutic decision.

Practically, an algorithm based on ultrasound examinations is applied (Fig. 361.7). A first ultrasound examination should be performed during the first week of life in order to verify the urinary tract including the kidneys, bladder, and ureters. The sonographic analysis should be as detailed as possible and any significant anomaly should lead to the performance of a VCUG (Box 361.2). If the examination is negative, a control sonographic examination should be performed at the age of 1 month. Again if any abnormality is found, a VCUG should be performed, but if no anomaly is demonstrated no further evaluation is needed. At this stage, prophylactic antibiotherapy should be stopped (Riccabona et al., 2009).

The role of VCUG is clearly to detect VUR that will render long-term follow-up and persistent prophylaxis necessary (Fig. 361.8A). This attitude is intended to reduce unnecessary complications that are associated with high grades of VUR. It might also demonstrate anomalies of the urethra and potentially abnormal ureteral findings. Follow-up studies include ultrasound (every 6 months for the first year, yearly during the following 8 years) in order to verify renal growth, VCUG every year to monitor the reflux and mercaptoacetyltriglycine (MAG3) isotopic studies in order to verify renal function (Upadhyay et al., 2003; Cheng et al., 2004).

If no reflux is present, complementary imaging will be necessary in order to precisely identify the origin of the dilatation. Renal function will be assessed through isotopic studies; the morphology of complex or complicated urinary tract malformations will best be evaluated by magnetic resonance urography (Fig. 361.8B). The

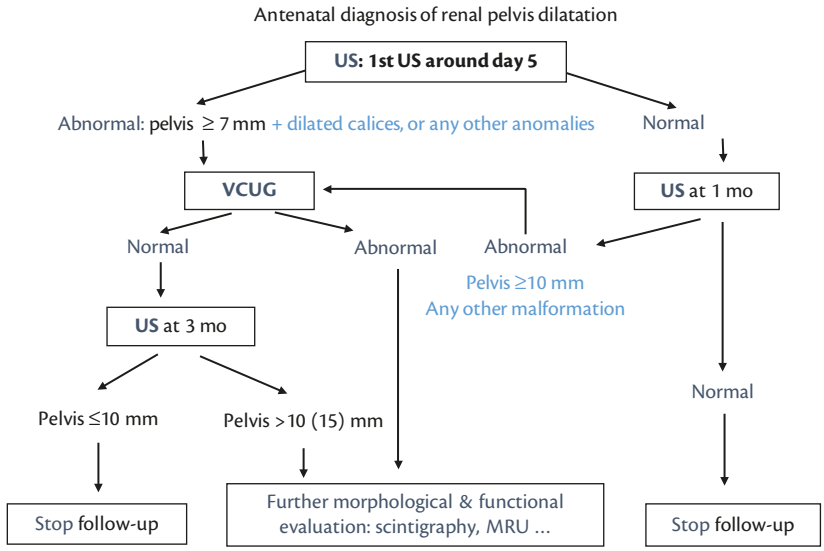


**Fig. 361.7** Postnatal imaging strategy in infants with mild to moderate fetal renal pelvis dilatation.

technique is particularly helpful for the assessment of very dilated urinary tract and complicated duplex systems with dilatation of the upper- and/or lower moieties. Also, the technique is able to provide information on the functional status of the kidney. It will help the surgeon in optimizing treatment (Avni et al., 2002; Onen et al., 2002). After this evaluation and if a conservative attitude is elected, a sonographic follow-up is advised in order to follow renal growth and dilatation. The length of follow-up must be adapted to the type of anomaly. It has been shown that a large proportion of urinary tract dilatation will resolve spontaneously (Upadhyay et al., 2003; John et al., 2004; Riccabona et al., 2009; Skoog et al., 2010).

Using this algorithm, very few abnormal cases escape the workup and the risk of complications is very low.

## Cystic renal diseases in the fetus and in the perinatal period

In the fetus, cystic renal disease should be suspected whenever bilateral hyperechoic kidneys or cysts (uni- or bilateral) are discovered during an obstetrical ultrasound examination (Avni et al., 2006; Bisceglia et al., 2006).

**Box 361.2** Characteristics suggesting an abnormality of the urinary tract on neonatal ultrasound

- Pelvic dilatation > 7 mm
- Calyceal dilatation
- Parenchymal thinning
- Lack of corticomedullary differentiation
- Small size kidney
- Thickening of the pelvic wall
- Thickening of the ureteral wall
- Ureteral dilatation > 3 mm
- Enlarged bladder.

The imaging approach for the diagnosis should be based on a detailed sonographic analysis that includes the measurement of renal length (Chitty and Altmann, 2003), the presence or absence of CMD, and the presence, number, size, and location of the cysts. This evaluation should be completed through the analysis of the entire fetus looking for associated anomalies.

The timing of detection is important as well as the amount of amniotic fluid. Both are important features for the final diagnosis and prognosis.

A pre-existing familial history of any renal cystic disease or of any syndrome with renal involvement in a fetus in which abnormal kidneys have been detected signifies recurrence of the disease (Avni et al., 2006; Bisceglia et al., 2006; Avni and Hall, 2010).

### Hyperechoic kidneys in the perinatal period

This group includes many diseases genetically transmitted or acquired during fetal life.

They have to be approached step by step. Most will be discovered during the second and third trimester (Avni et al., 2006; Chaumoitre et al., 2006).

#### *Sonographic criteria*

Renal cortical hyperechogenicity is determined by comparing the renal cortex to the adjacent liver or to the spleen. While hyperechogenicity is usually obvious on the screen, an objective criteria is that the renal cortex should not be hyperechoic compared to the liver or to the spleen during the first trimester.

A second important criterion for the differential diagnosis is the appearance of the CMD that can be normal, increased, absent, or reversed due to hyperechoic medulla.

A third sonographic criterion will be renal size: markedly increased (= above +4 SD); moderately increased (= above +2 SD); normal or small (= less than −2 SD).

A fourth ultrasound criterion will be the presence of renal cysts (Fig. 361.9A).

#### *Differential diagnosis*

In case of markedly enlarged (> +4 SD) hyperechoic kidneys diagnosed during late first and early second trimester, a Meckel–Gruber

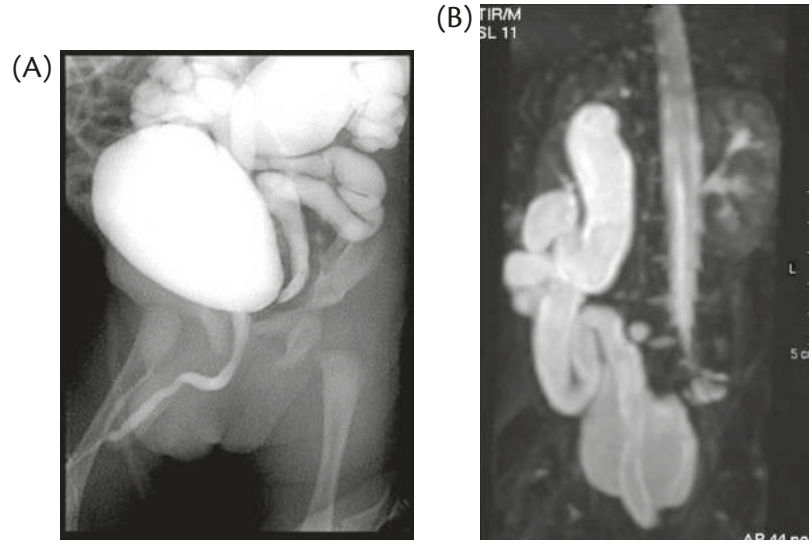


**Fig. 361.8** (A) Postnatal reflux neonatal VCUG. Bilateral grades IV/V reflux. No urethral anomaly. (B) Neonatal MRI. Right duplication with dilated upper and lower ureters—normal left kidney.

syndrome should be considered first especially if the medulla appears enlarged and hypoechoic and if polydactyly and cerebral anomalies are associated. If diagnosed during the second and third trimester, the main diagnosis to be added to the differential would be autosomal recessive polycystic kidney disease (ARPKD) and the Bardet–Biedl syndrome (BBS).

In ARPKD, the CMD can be partially absent, completely absent, or even reversed (Fig. 361.9B). A few visible cysts are rare but possible *in utero*. Oligohydramnios is a frequent finding and is associated with pulmonary hypoplasia. The prognosis is very poor (Tsatsaris et al., 2002; Chaumoitre et al., 2006). BBS is a syndrome that associates enlarged hyperechoic kidneys and post-axial polydactyly. The other symptoms of the disease will develop after birth (Cassart and Eurin 2004).

In case of moderately enlarged hyperechoic kidneys (+2 SD), three diagnoses have to be considered: *TCF2* gene mutation-associated nephropathy (Fig. 361.9C), ARPKD and autosomal dominant polycystic kidney disease (ADPKD) (Brun et al., 2004; Decramer et al., 2007).

An anomaly of the *TCF2* gene (transcription factor gene) (leading to hepatocyte nuclear factor-1B (HNF1B)-related morphological anomalies) has been shown to represent the main cause of fetal hyperechoic kidneys (Decramer et al., 2007). This mutation is associated with a wide spectrum of renal morphological and structural anomalies that includes on histology glomerulocystic type changes, cystic dysplasia, or renal agenesis (Fig. 361.9C). In such kidneys, beside renal hyperechogenicity, the CMD may or not be visible. Cysts may be visible already *in utero* but are visualized more often after birth located in the subcapsular area. A familial history of diabetes is a frequent finding.

The involvement and extension of lesions related to ARPKD can vary from 10% to 90% of the kidneys. This determines varying ultrasound appearances. In cases with mild involvement, the kidneys can be just moderately enlarged with hyperechoic cortex and a few small cysts mainly within the pyramids. After birth, cysts may also develop throughout the medulla first, within the cortex thereafter. Fetuses with mildly enlarged kidneys have a better prognosis for survival than cases with massive enlargement.

An ADPKD can be suspected already *in utero* based on a striking hyperechoic renal cortex that increases the CMD. The kidneys are usually normal in size or slightly enlarged. Such findings should prompt familial inquiry. Cysts may be observed *in utero* but usually develop after birth (Fig. 361.9D).

Once these three diagnoses are excluded, there is a wide spectrum of other diseases that can lead to hyperechoic kidneys; clinical inquiry may help to progress to the diagnosis. Complementary examinations such as chromosomal analysis, search for infection, toxic, maternal diseases, or ischaemia will help to approach the diagnosis (Table 361.1) (Slovis et al., 1993; Brun et al., 2004).

### Renal cyst(s) discovered in the perinatal period

An unilocular *single renal cyst*, occurring in the otherwise normal appearing kidneys can be detected *in utero* or after birth. It should be differentiated, especially if the cyst is septated, from a cystic tumour, a segmental cystic dysplasia, a dysplastic upper pole of a duplex kidney, or an urinoma (McHugh et al., 1991).

Whenever *multiple cysts* are detected, the first criteria for the differential diagnosis would be uni- or bilateral involvement:

- Multiple cysts detected in one kidney only correspond most often to a MCDK. MCDK, a non-functioning kidney, usually has a straightforward ultrasound appearance: multiple cysts of various sizes without connection between them, no recognizable normal renal parenchyma, and no central renal pelvis (Fig. 361.9E). It should be differentiated from obstructive dysplasia (associated with a urinary tract obstructive malformation) in which the dilated urinary tract is recognizable. MDK can occur in the upper pole of a duplex kidney. MCDK will evolve and usually shrink after diagnosis. This can be followed by ultrasound (Kuwertz-Broeking et al., 2004; Aslam and Watson 2006).
- Bilateral multiple renal cysts can be visualized in a large number of isolated renal or syndromic diseases (Box 361.3). It may or

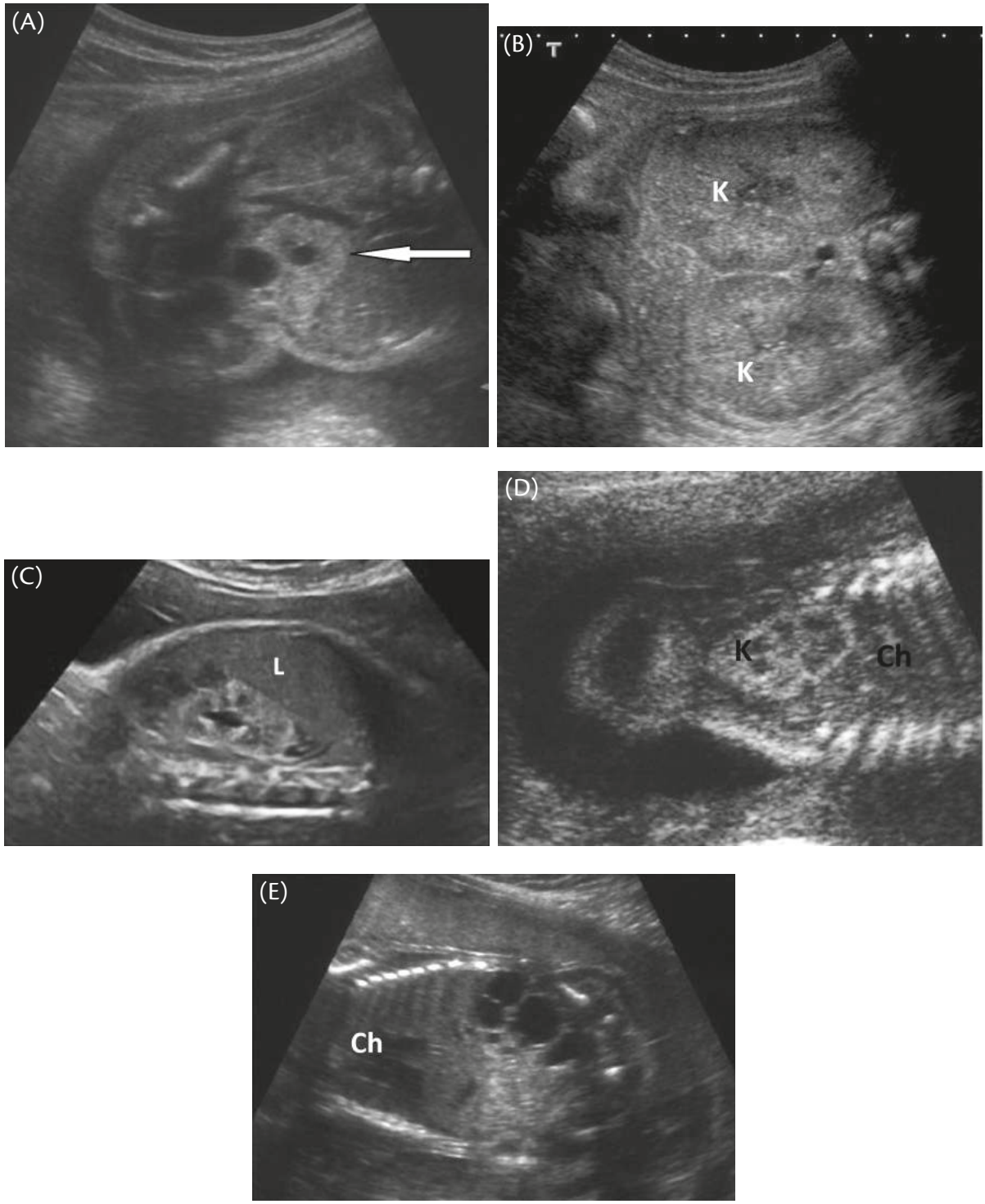


**Fig. 361.9** (A) Unilateral hyperechoic kidney—case of a pelvic cystic dysplasia. Third trimester. Sagittal scan through the pelvic kidney (arrow). The renal parenchyma is hyperechoic and contains cysts. (B) ARPKD—third trimester. View of the fetal abdomen. Markedly enlarged hyperechoic kidneys (K) with somewhat hyperechoic medulla (reversed CMD). (C) *TCF2* (HNF1B) mutation—third trimester, sagittal scan of the right kidney. It appears hyperechoic compared to the liver with partial CMD (left kidney had the same appearance). L = fetal liver. (D) ADPKD—third trimester. Sagittal scan of the kidney. The cortex is hyperechoic and CMD preserved even increased. Size was normal for gestational age. Ch = fetal chest. (E) Multicystic dysplastic kidney—third trimester. Sagittal scan of the fetal trunk; the kidney contains cysts of variable sizes without connection between them. Ch = fetal chest.

Courtesy of C. Garel, MD.

**Table 361.1** Bilateral hyperechoic kidneys

| Previous familial history | No previous history | |
|---|---|---|
| Recurrence | Urinary tract dilatation | No dilatation: |
| | Obstructive dysplasia | Renal cystic diseases |
| | | Syndromes with kidney involvement |
| | | Acquired renal lesions (ischaemia, infection, toxic) |
| | | Chromosomal anomalies |
| | | Congenital nephrotic syndrome |
| | | Nephroblastomatosis |
| | | Metabolic diseases |
| | | Normal variant |

not be associated with global renal hyperechogenicity (see above) (Glazier et al., 1996).

A step-by-step approach, including detailed ultrasound analysis, familial history, and complementary examinations will lead in many cases to the diagnosis. Amniotic fluid volume and associated morphological or chromosomal anomalies are mandatory for the prognosis. It is of note that many renal cystic diseases present some type of hepatic ductular anomalies. These are not detected by perinatal ultrasound.

## Renal tumours

More than half of all congenital abdominal masses found in the neonate originate in the kidney. In the fetus, the most common renal tumour is the mesoblastic nephroma (Fig. 361.10). It appears as a solid-type tumour that is sometimes difficult to delineate from the adjacent renal parenchyma. The tumour can appear as partially cystic. *In utero*, polyhydramnios is typically associated and hypertension develops after birth. Cases of fetal renal Wilms tumour have been reported. The main differential diagnosis of a cystic renal tumour includes MCDK. The prognosis is good. Bilateral involvement suggests nephroblastomatosis.

**Box 361.3** Bilateral multiple cysts

- Bilateral MDKD (oligohydramnios)
- Bilateral obstructive dysplasia (urinary tract dilatation)
- ADPKD
- ARPKD
- Subcortical cysts (glomerulocystic kidneys)
- Syndromes with cystic dysplasia
- (Meckel–Gruber medullary cysts)
- Tuberous sclerosis (macrocysts)
- Ivemark II syndrome
- Bardet–Biedl syndrome (cortical cysts)

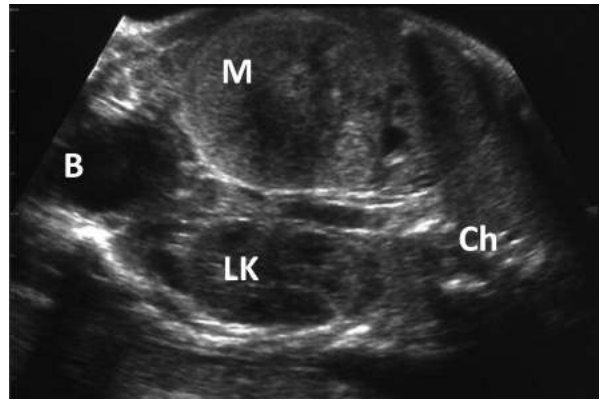


**Fig. 361.10** Mesoblastic nephroma—third trimester. Sagittal scan of the fetal trunk. A large round solid mass (M) has developed in the lower pole of the right kidney. B = bladder; Ch = chest; LK = left kidney.

Patients with Beckwith–Wiedemann syndrome, congenital aniridia, Perlman syndrome, and Denys–Drash syndrome are at risk of developing malignant renal tumours rarely *in utero*, usually these form after birth (Bove 1999; Irsutti et al., 2000; Leclair et al., 2005).

## Acquired renal pathologies

Renal anomalies can occur during pregnancy because of a maternal disease or because of ischaemic damage (or both). For instance, maternal diabetes or twin pregnancies increase the risk for renal vein thrombosis in the fetus.

Sonographically, at the acute stage of the thrombosis, the volume of the affected kidney and its echogenicity increases. Doppler analysis may in some cases confirm the thrombosis. Rapidly, collateral vessels develop and the renal vascularization resumes to almost normal. Some vascular calcifications in the interlobar areas may remain as sequelae. A thrombus within the inferior vena cava and adrenal haemorrhage may be associated findings (Wright et al., 1996).

Maternal deficit in neuropeptidase may induce an acute transient glomerulonephritis in the fetus which will determine increased volume and echogenicity. Transient renal failure may occur at birth (Debiec et al., 2002).

Materno-fetal infection may involve the kidneys and determine increased echogenicity as demonstrated in some cases with cytomegalovirus.

## Other congenital renal disorders

### Congenital nephrotic syndrome

Congenital nephrotic syndrome may rarely affect the fetus. The kidneys appear diffusely hyperechoic usually without CMD. The placenta is thick and polyhydramnios is present. The proteinuria can be detected in the amniotic fluid. A particular association is the Denys–Drash syndrome that includes pseudo-hermaphrodism and a particular nephrotic syndrome (mesangial sclerosis). Patients affected by the syndrome carry an increased risk for Wilms tumour (Hofstaetter et al., 1996).

## Bladder, urethra, and urachus

As mentioned earlier, the bladder is the first structure of the urinary tract to be seen in the fetal pelvis around 9–10 weeks that

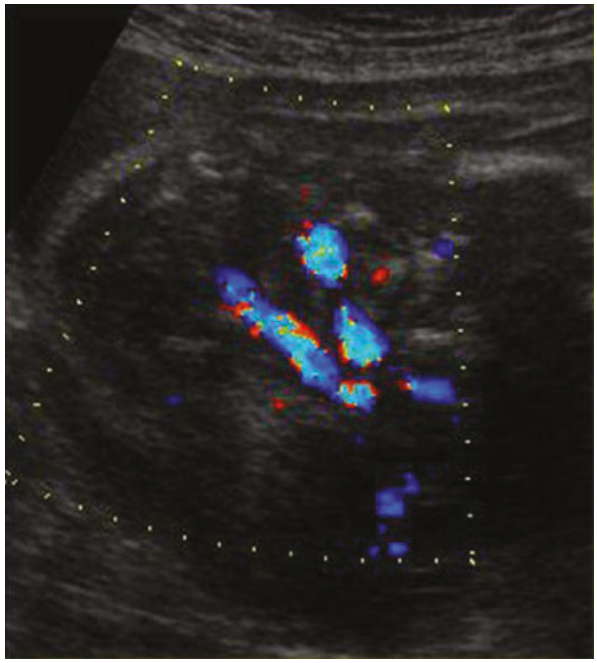

**Fig. 361.11** Bladder exstrophy—late second trimester. No urine fluid bladder can be recognized between the umbilical arteries (compare with Fig. 361.1).

indicates the production of urine. Its demonstration is an important part of the obstetrical ultrasound assessment of the normal fetal development.

Anomalies of the bladder can be suspected whenever it is > 3 cm length in the second trimester, > 6 cm in the third trimester of the pregnancy, or not visible during an entire examination.

Whenever an *enlarged bladder* is demonstrated, BOO should be suspected first. During the first and early second trimester, it could result from a urethral atresia and a 'prune belly' syndrome. The kidneys may appear hyperechoic due to obstructive dysplasia. The prognosis is poor (McHugo and Whittle, 2001; Anumba et al., 2005) (Box 361.1).

In the second and third trimester in male fetuses, an enlarged bladder usually results from posterior urethral valves (PUV) (Fig. 361.5D). The bladder wall can be thickened. The upper urinary tract may or not be dilated with hyperechoic renal parenchyma corresponding to obstructive dysplasia. The condition can also be associated with perirenal urinoma due to extravasation.

The differential diagnosis of enlarged bladder should include massive VUR and megacystis microcolon hypoperistalsis syndrome. Finally, one should not forget to consider a pseudo-enlarged bladder in the third trimester female fetus.

When the *bladder is not visible*, the amount of amniotic fluid helps to differentiate cases secondary to lack of urine production from bladder malformation.

In case of oligohydramnios, absent or non-functioning kidneys should be suspected (e.g. bilateral renal agenesis, bilateral multicystic kidneys, etc.).

When the amount of amniotic fluid is just slightly reduced, intrauterine growth retardation and/or materno-fetal infection should be considered (Wilcox and Chitty, 2001).

If the amount of amniotic fluid is normal, a bladder malformation should be considered. In case of bladder exstrophy, no bladder is seen between the umbilical arteries (Fig. 361.11). Instead, a soft tissue mass is seen just below the umbilicus corresponding to the open bladder (mucosa). In the male, the penis is shortened and widened and the gender ambiguous.

The condition has to be differentiated from the OEIS complex (omphalocele-exstrophy-imperforate anus complex) in which an omphalocele is present as well (Goldstein et al., 2001; Warne et al., 2002).

An abnormal bladder can also be observed in case of cloacal malformation sequence (persistence of the urogenital signs). In such a condition there is a single opening draining the bladder, the vagina, and eventually the colon. It may be difficult to differentiate by ultrasound alone between these different structures.

In the male fetus, the main malformation involving the urethra is PUV (see above). This condition determines BOO at variable degrees. On ultrasound, the distended posterior urethra can sometimes be clearly demonstrated (Fig. 361.5D). The prognosis is also variable depending on the degree of obstruction and renal dysplasia. Anterior valves are very rarely demonstrated *in utero*.

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