Kidney and Urinary Tract Diseases in the Newborn

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Preface

Physicians have always been fascinated by the complexity and intricacy of fetal organogenesis including the development of the genitourinary tract. The individual developmental stages, though complicated and still incompletely understood, usually occur without interruptions. On the other hand, newborns can face a wide variety of anomalies of the urinary tract including structural and mechanistic, spanning from acute and reversible to chronic and progressive pathology.

Advances in our understanding of pathophysiologic concepts of disease and the use of new diagnostic modalities have led to increased and early detection of a variety of conditions. In addition, increased experience and new therapeutic interventions are commonly associated with improved outcome in this particularly vulnerable patient population. This has caused a shift in certain areas to now increased interest in neonatal conditions and their possible impact on adult disease.

Care of newborns and infants with congenital kidney and urinary tract disease is complex and requires the expertise of multiple specialists, including nephrologists, urologists, neonatologists as well as other pediatric specialists depending on the condition.

This inaugural edition of "Kidney and Urinary Tract Diseases in Neonates and Infants", a first of its kind as it solely focuses on neonates and infants, attempts to provide a comprehensive overview of common medical and surgical entities that are seen in newborns and tries to be a "hands-on" resource for clinicians working with this particular patient population.

Though a first edition can never be perfect, we think to have included a variety of chapters covering the vast majority of clinical entities providers will encounter in their clinical work.

All chapters are written by experts in the field and the editors are extremely grateful for the time and effort that each contributor has provided to make this endeavor possible and, hopefully, successful.

Any task as complex as the completion of a book publication requires sets of helpful hands in the background. The editors therefore especially appreciate the constant support and guidance of Ms. Joni Fraser as without her help the publication would not have been possible.

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Development of the Kidney and Lower Urinary Tract

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Joana Rosa Pereira dos Santos and Tino D. Piscione

1.1 Introduction

Congenital abnormalities of the kidney and urinary tract (CAKUT) are the cause of 30–50 % of end-stage renal disease in young children [307]. CAKUT are represented by a heterogeneous group of renal, ureter, and bladder malformations across a wide range of clinical severity (Table 1.1). The incidence of renal and urinary tract anomalies in humans is 0.3–1.6 per 1,000 live born and stillborn infants [359]. Renal malformations account for 20–30 % of all solid-organ birth defects detected by antenatal sonography during pregnancy [273]. Thirty percent of cases occur in association with extrarenal malformations [359] and may be found as part of over 100 congenital syndromes (Table 1.2) [173].

This chapter approaches CAKUT from an embryological perspective with emphasis on morphologic, cellular, and molecular events in normal urinary tract development. The science of human embryology relates to form and process of tissue development and integrates molecular, cellular, and structural factors within a dynamic spatiotemporal framework. A clear understanding of human embryology provides a foundation for understanding structure-function relationships within a given tissue or organ. It also renders insight into the pathological basis of congenital malformation resulting from perturbations in normal organ development and leads to the recognition of associated malformations within the same organ system (e.g., genitourinary system) when developmental mechanisms are shared between tissues (e.g., kidney and ureter). Consequently, the principles of urinary tract embryology described in this chapter are fundamental to the diagnosis and clinical management of CAKUT in fetuses and newborns and crucial to understanding the long-term impact of CAKUT on overall health.

Developmental events in kidney, ureter, and bladder morphogenesis are highly conserved across vertebrate species [75]. The use of model organisms such as mice, zebrafish, and frogs has been invaluable for defining gene expression patterns in the embryonic urinary tract system and for providing a spatiotemporal framework upon which to study gene function. Understanding relationships between gene expression and function has been greatly facilitated by the creation of a molecular atlas of gene expression for the developing urinary tract, which can be accessed online through the GenitoUrinary Development Molecular Anatomy Project (GUDMAP; http://www.gudmap.org/index.html) [117]. Gene function has been largely elucidated through the anal-

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Table 1.1 Examples of renal, ureter, and bladder malformations

Renal malformations
Renal agenesis
Renal hypoplasia
Renal dysplasia
Renal duplication
Horseshoe kidney
Renal ectopia (e.g., pelvic kidney)
Cross-fused ectopia
Cystic kidney diseases
Polycystic kidney disease (autosomal dominant, autosomal recessive)
Multicystic dysplastic kidney
Medullary cystic kidney
Nephronophthisis
Ureteral malformations
Ureteral agenesis
Ureteral duplication
Ureteropelvic junction obstruction
Ureteral stricture (distal to the ureteropelvic junction)
Hydroureter (nonobstructive)
Ectopic ureter
Ureterocele
Bladder malformations
Bladder exstrophy
Bladder diverticulum
Vesicoureteral reflux

Table 1.2 Human congenital malformation syndromes associated with CAKUT

Syndromes with cystic dysplasia	
Apert	Meckel-Gruber
Bardet-Biedl	Meckel syndrome, type 7
Branchio-oto-renal	Melnick-Needles
Campomelic dysplasia	Pallister-Hall
Cornelia de Lange	Patau (trisomy 13)
Down (trisomy 21)	Senior-Loken
Edwards (trisomy 18)	Tuberous sclerosis
Jeune asphyxiating thoracic dystrophy	von Hippel-Lindau
	Zellweger
Syndromes with polycystic kidneys	
Congenital rubella	Peutz-Jeghers
Ehlers-Danlos	Pyloric stenosis
Kaufman-McKusick	Roberts
Noonan	Short rib-polydactyly, types II, III, and IV
	Zellweger
Syndromes with horseshoe kidney	
Abruzzo-Erickson	Pallister-Hall
Bowen-Conradi	Pyloric Stenosis
Cerebro-oculo-facio-skeletal (Pena-Shokeir)	Roberts
Facio-cardio-renal (Eastman-Bixler)	Trisomy 18 (Edwards)
Focal Dermal Hypoplasia (Goltz-Gorlin)	Trisomy 21 (Down)
Oral-cranial-digital (Juberg-Hayward)	Turner
Syndromes with unilateral renal agenesis	
Acro-renal-mandibular	Ivemark
Adrenogenital (21-OH-ase deficiency)	Klippel-Feil
Alagille	Lacrimo-auriculo-dento-digital
Cardiofacial	Larsen
Cat-Eye	Lenz microphthalmia
Cerebro-oculo-facio-skeletal (Pena-Shokeir)	Mayer-Rokitansky
Chondroectodermal dysplasia (Ellis-van Creveld)	Miller-Dieker, lissencephaly
Coffin-Siris	Oculo-auriculo-vertebral dysplasia (Goldenhar)
Congenital rubella	Olfactogenital dysplasia (Russell-Silver)
Fetal alcohol	Spondylocostal dysostosis

ysis of embryonic mouse mutant phenotypes generated either by targeted mutagenesis, which disrupts gene function universally, or by conditional mutagenesis, which renders in loss of gene function in a cell-specific or time-dependent manner [159]. This chapter will make reference to genetic studies in mice to gain insight into morphogenetic, molecular, and cellular mechanisms which underlie normal development of the human kidney, ureter, and bladder. By convention, text references to human genes will be noted in capitalized italics whereas mouse genes are in sentence case italics [262].

This chapter is subdivided into broad categories representing stereotypic processes in urinary tract formation. These include descriptions of the

Table 1.2 (continued)

Syndromes with renal and/or ureteral duplications	
Achondrogenesis	Congenital Rubella
Acrocephalosyndactyly (Saethre-Chotzen)	Denys-Drash
Acro-renal (Dieker-Opitz)	Fetal Alcohol
Adrenogenital (21-OH-ase deficiency)	Klippel-Feil
Bowen-Conradi	Noonan
Branchio-oto-renal	Oculo-auriculo-vertebral dysplasia (Goldenhar)
Braun-Bayer	Rubinstein-Taybi
Cerebro-oculo-facio-skeletal (Pena-Shokeir)	Trisomy 21
	Turner
Syndromes with hydroureter or hydronephrosis	
Apert	Johanson-Blizzard
Campomelic Dysplasia	Kaufman-McKusick
Chondroectodermal dysplasia (Ellis-van Creveld)	Larsen
Coffin-Siris	Menkes
Cornelia de Lange	Noonan
DiGeorge	Pyloric stenosis
Fetal Alcohol	Spondylocostal dysostosis
	Wolfram
Syndromes with renal ectopia	
Cardiofacial	Marfan
Cerebro-cost-mandibular	Mayer-Rokitansky
Craniosynostosis-radial aplasia (Baller-Gerold)	Oculo-auriculo-vertebral dysplasia (Goldenhar)
Denys-Drash	Pallister-Hall
Klippel-Feil	Seckel
	Spondylocostal dysostosis
Syndromes with renal hypoplasia	
Branchio-oto-renal	Ivemark
Campomelic Dysplasia	Poland
Cornelia de Lange	Pyloric Stenosis
Fetal Alcohol	Seckel
	Townes-Brock
Syndromes with bladder exstrophy	
Syndactyly, type IV (Haas)	

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early embryonic origins of the kidneys, ureters, and bladder, as well as descriptions of later events involved in renal collecting duct and nephron morphogenesis, ureter formation, and bladder development. Within each subdivision, attention is given to genetic or molecular control mechanisms essential for executing key developmental programs. Specific references to urinary tract morphogenesis in embryonic mice are made when orthologous events in humans have not been fully characterized. Consequently, the information in this chapter serves as a framework for understanding the breadth and complexity of anatomical and functional defects of the urinary system that present clinically in the fetus and newborn infant.

1.2 Embryonic Origins of the Urinary System

1.2.1 Overview of the Early Urinary Tract Embryology

The mammalian urinary system has embryologic cellular origins in the mesodermal and endodermal germ layers of the post-gastrulation embryo [76]. Mesodermal derivatives comprise all epithelial cell types of the mature nephron, renal pelvis, and ureter, as well as non-epithelial cell types including glomerular endothelial and mesangial cells, renal parenchymal interstitial cells (also known as stromal cells), ureteral and bladder smooth muscle cells, and adipocytes and connective tissue-producing fibrocytes of the renal capsule and ureter and bladder adventitia. Endodermal tissue, on the other hand, gives rise to the luminal epithelial cells of the bladder and urethra. Kidney and ureter development requires the initial formation of a mesoderm-derived embryonic structure known as the nephric duct (also known as the Wolffian duct or mesonephric duct). Conversely, bladder development is preceded by formation of the urogenital sinus. The following sections (Sects. 1.2.2 and 1.2.3) describe formation of the nephric duct and urogenital sinus, respectively. Table 1.3 compares the chronology of human and mouse urinary tract development.

Table 1.3 Embryonic time table for nephrogenesis: human versus mouse

	Human	Mouse
Pronephros		
First appearance	22 days	9 days
Regresses by	25 days	10 days
Mesonephros		
First appearance	24 days	10 days
Regresses by	16 weeks	14 days
Metanephros appears	28–32 days	11 days
Collecting tubules and nephrons	44 days	13 days
Glomeruli	8–9 weeks	14 days
Nephrogenesis ceases	34–36 weeks	4–7 days after birth
Length of gestation	40 weeks	19 days

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1.2.2 Nephric Duct Morphogenesis

Mesoderm-derived ancestors of the kidneys and ureters originate from within a narrow strip of tissue termed intermediate mesoderm (IM) which is located bilaterally on each side of the embryonic midline. IM is evident in human fetuses by week 4 of gestation based on the appearance of the nephric duct [139]. In mice, IM is detected by embryonic day 8.5 (E8.5) based on tissue-specific patterns of gene expression [76, 336]. IM extends bilaterally in an anteroposterior, or rostral-caudal, direction from the level of the twelfth somite at the embryonic midsection to the cloaca, which is a midline embryonic structure located in the embryonic hind region [139]. During week 4 of human fetal gestation (E9.0 in mice), IM is induced along its anteroposterior axis to form a paired set of single-cell-layered epithelial tubes which are the nephric ducts. Fully formed nephric ducts extend the full length of IM and deviate at its posterior end towards the midline to insert into the cloaca (see Sect. 1.2.3).

While the nephric duct is formed, surrounding intermediate mesoderm (referred to as mesenchyme) is induced to undergo epithelial transformation. This inductive process results in the sequential generation of three morphologically unique nephrogenic primordia – the pronephros, mesonephros, and metanephros – which connect to the anterior, mid-, and posterior sections of the nephric duct, respectively (Fig. 1.1) [75]. The pronephros is a primitive paired organ characterized by a single glomerular and tubular filtrative unit (Fig. 1.1a). In lower-order animals such as amphibians and fish, the pronephros functions as a transient embryonic excretory organ. Conversely, in higher-order mammals including humans, pronephric structures are transiently represented by nonfunctioning rudimentary tubules which degenerate by apoptosis [86, 286]. The mesonephros is a more sophisticated filtrative system characterized by several well-developed glomerular- and tubular-like structures that connect directly to the nephric duct at its midsection (Fig. 1.1b). In adult fish and amphibians, the mesonephros replaces the pronephros as the definitive filtrative organ [75]. In humans, mesonephric development begins late in the fourth week of gestation and results in the transient production of fetal urine [118, 242]. By week 5, most mesonephric tissue undergoes degeneration while the remaining tissues in males contribute to the formation of the reproductive system, including the efferent ductules of the testis, vas deferens, epididymis, and seminal vesicle. In female fetuses, the mesonephros regresses although vestigial structures may persist and are represented clinically as Gartner's duct cysts, epoophoron, and paroophoron [226]. As mesonephric degeneration takes place, IM surrounding the posterior nephric duct (termed metanephric mesenchyme) is induced to form the metanephros, which represents the nascent mammalian kidney (Fig. 1.1c). Induction of metanephric mesenchyme (MM) is dependent on outgrowth of an epithelial diverticulum from the nephric duct termed the ureteric bud (UB) which occurs at approximately week 5 of human fetal gestation (E10.5 in mice). Invasion of MM by the UB initiates a series of reciprocal inductive interactions that triggers formation of the adult mammalian kidney and ureters. Detailed descriptions of kidney and ureter morphogenesis are provided in Sects. 1.3 and 1.4.

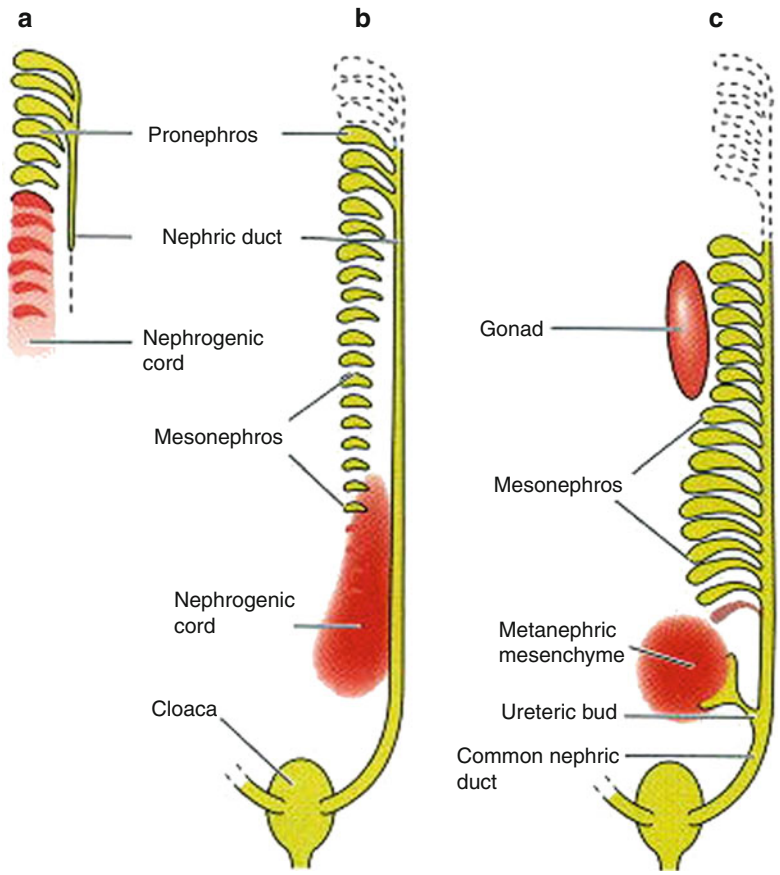

Fig. 1.1 Formation of nephrogenic primordia. (**a**) The nephrogenic cord and pronephros. (**b**) The mesonephros. (**c**) The metanephros

1.2.2.1 Molecular Pathways Involved in Nephric Duct Morphogenesis

Genetic studies in mice point to critical roles played by four transcription factor genes – *Lhx1*, *Pax2*, *Pax8*, and *Osr1* – in specifying IM for kidney and ureter development. *Lhx1* (Lim homeobox protein 1) encodes a member of the Lim family of homeodomain proteins which are essential to forming anterior embryonic structures [311]. *Pax2* and *Pax8* are paired box domain DNA-binding proteins which function as master regulators of tissue development in several organ systems, including kidney [26]. *Lhx1*, *Pax2*, and *Pax8* mRNAs are among the earliest gene transcripts detected in IM [26]. All three genes ultimately show mRNA expression in nephric duct cells, and their functions are essential to normal nephric duct formation. Mice lacking *Lhx1* function fail to form nephric ducts [336], whereas mice homozygous for a null *Pax2* mutation form posteriorly truncated nephric ducts [34, 335]. Combined inactivation of *Pax2* and *Pax8* results in complete absence of the nephric duct [26], suggesting that Pax family members have overlapping functions in anterior regions of IM. Combined *Pax2/8* function may be important for demarcating IM from lateral plate and paraxial mesoderm since *Pax2* mRNA are exclusively detected at the boundaries of these mesodermal compartments at stages prior to nephric duct formation [336]. Expression of *Pax2* and *Pax8* in this region appears to be under the positive control of bone morphogenetic protein 4 (BMP4; encoded by the *Bmp4* gene) which is secreted by cells in adjacent lateral plate mesoderm and in overlying ectoderm [142, 143, 236]. Negative control over these inductive interactions appears to be

provided by other as-yet undefined factors secreted by nearby somites [190].

Osr1 encodes an odd-skipped related zinc-finger DNA-binding protein and is required to specify IM for kidney development [141]. *Osr1* is expressed in IM surrounding the nephric duct along its entire length and is excluded from nephric duct cells. Mice lacking *Osr1* function form nephric ducts but lack kidneys, which suggest that *Osr1* plays an important role in specifying posterior IM for kidney development.

Hox genes encode a large family of homeodomain proteins and are organized into related gene subgroups or clusters sharing functions that coordinate regional expression of other genes involved in axial patterning of a wide range of embryonic tissues [71]. Two mouse hox gene clusters – *Hox4* and *Hox11* – have been implicated in establishment of anterior and posterior IM cell identity, respectively, along the early embryonic AP axis. A role for *Hox4* genes in promoting anterior IM cell fate is suggested by the mRNA expression pattern for *Hoxb4* which is detected in early mesoderm at the anterior boundary of prospective IM [9]. The notion that *Hox4* genes establish an anterior code for IM is supported by studies in cultured chick embryos which revealed an anterior shift in expression of IM-specific markers *Lhx1* and *Pax2* within chick mesoderm when the anterior limits of *Hoxb4* expression were experimentally manipulated [263]. Conversely, evidence in mice suggests that *Hox11* cluster genes (*Hoxa11*, *Hoxc11*, and *Hoxd11*) control posterior IM cell fate and promote differentiation of cells within this region along a metanephric cell lineage. In a study which involved the use of tissue-specific promoter sequences in transgenic mice to expand mesodermal expression of *Hoxd11* anteriorly into a region of IM normally fated for mesonephros development, ectopically activating *Hoxd11* in this region resulted in transformation of mesonephric tubules into a more metanephric phenotype [212]. This observation suggested that *Hox11* cluster genes are necessary for instructing IM cells to differentiate along a metanephric cell fate instead of a mesonephric cell fate. Hox11 genes also appear to be required for enabling posterior IM cells to respond appropriately to inductive cues which initiate kidney and ureter development. This is revealed in compound mutant mice when either combinations of two or all three paralogous *Hox11* genes are mutated, which results in severe kidney hypoplasia or complete agenesis of kidneys and ureters, respectively [356]. In vitro, proteins encoded by *Hox11* genes form a DNA-binding complex with proteins encoded by *Pax2* and the Eyes absent 1 (*Eya1*) proteins and directly activate the expression of key metanephric regulators, glial-derived neurotrophic factor (*Gdnf*) and sine oculis homeobox 2 (*Six2*) (see Sect. 1.3.3.1) [105]. Consequently, the complete absence of kidneys and ureters in *Hox11* triple mutant mice is likely due to a failure of *Hox11* genes to appropriately activate the expression of other genes critical for initiating urinary tract development.

1.2.3 Urogenital Sinus Morphogenesis

The urogenital sinus is an embryonic structure which originates as a sub-compartment of the cloaca. The cloaca is an endoderm-derived transient hollow structure located midline in the embryonic hind region. It connects bilaterally with the posterior ends of the paired nephric ducts (Fig. 1.2). In humans, the cloaca is formed by the third week of fetal gestation from confluence of the allantois and hindgut [267]. The allantois precedes the umbilicus as the conduit for embryonic gas and solute exchange with the placenta, while the hindgut ultimately forms distal colonic structures including the rectum and the upper part of the anal canal. Between weeks 6 and 7, the cloaca is subdivided into dorsal and ventral chambers by a fold of mesodermal tissue which projects into the cloacal cavity and creates a transverse ridge known as the cloacal septum (also known as the urorectal septum; Fig. 1.2a). The dorsal chamber generates the anorectal canal which communicates with the hindgut and ultimately develops into the rectum and anus. The ventral chamber forms the urogenital sinus which is connected at its anterior end to the allantois via