

Chapter 2

Anatomy, Applied Embryology, and Pathogenesis of Congenital Anomalies of the Kidney and Urinary Tract

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Abbreviations

CAKUT	Congenital anomalies of the kidney and urinary tract
CKD	Chronic kidney disease
MCDK	Multicystic dysplastic kidney
PKD	Polycystic kidney disease
RCAD	Renal cysts and diabetes syndrome
UPJ	Ureteropelvic junction
UVJ	Ureterovesical junction

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT spectrum) affect up to 3 % of human fetuses, accounting for one third of malformations detected antenatally [1, 2]. Thankfully, only a small proportion lead to chronic kidney disease (CKD) in childhood but they still present diagnostic and management challenges for fetal medicine and pediatric practitioners. It is critical to understand normal development

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of the kidney and urinary tract in order to frame the clinical implications of CAKUT. Many accounts focus predominantly on genetic causes of CAKUT, but it is also important to consider other contributors such as lower urinary tract obstruction, teratogens, and maternal diet. Ultimately, renal function in CAKUT is determined by the number of functioning nephrons formed during development in the first instance then the degree of ongoing disruption of this reduced nephron complement by factors such as obstruction or infections over the long term. Our role as physicians is to understand the former and take steps to correct or minimize the latter.

There are a wide spectrum of intrinsic kidney defects within CAKUT including aplasia, hypoplasia, dysplasia (with or without cysts), and multicystic dysplastic kidneys. Extrarenal parts of the spectrum encompass ureteric anomalies such as mega-ureter, ureteropelvic junction obstruction, ureterovesical junction (UVJ) obstruction or incompetence, and anomalies of the bladder and urethra [3]. Falling between these are conditions such as ectopic and horseshoe kidneys and duplex kidneys/ureters, where there are both renal and lower urinary tract issues. Around 50 % of the CAKUT cases associated with pediatric CKD5 have normal urinary tracts, whereas the rest have some degree of dysfunction ranging from significant flow impairment in boys with posterior urethral valves through varying degrees of vesicoureteric reflux [4]. It is important to detect the latter groups since further renal impairment can occur with undetected/suboptimally treated obstruction or urinary tract infections.

Anatomy and Embryology of Normal Renal Development

The human kidney develops from a few hundred cells at its inception into a mature organ with many hundreds of thousands of nephrons. Early reports estimated around one million nephrons per kidney, although definitive quantification was hampered by lack of material and differences in ascertainment techniques. More recent systematic studies demonstrate a normal range between 740,000 and 1,400,000 [5] with interesting links between renal size and a lower nephron complement, predisposing to hypertension and CKD in some populations [6, 7].

There are three phases of kidney development in humans with consecutive paired organs developing from intermediate mesoderm on the dorsal body wall (Fig. 2.1). The first two stages, the pronephros and mesonephros, degenerate during fetal life in mammals, whereas the metanephros develops into the mature kidney. This is a potential example of ontogeny recapitulating phylogeny because hagfish and some amphibians only have the pronephros for a kidney, while lampreys, other fishes, and amphibians stop at the mesonephros.

The pronephros develops around day 22–23 after fertilization; it starts as a small group of primitive epithelial structures called nephrotomes from the second through sixth somites in the neck/upper thorax, and then new tubules develop in subsequent somites. The pronephric duct is generated as the nephrotomes form at the level of the ninth somite, but it has nowhere to empty so none of these tubules are thought to be functional. The duct elongates rapidly in a caudal direction, reaching the cloaca by day 26, being rechristened the mesonephric, or Wolffian duct, as mesoneph-

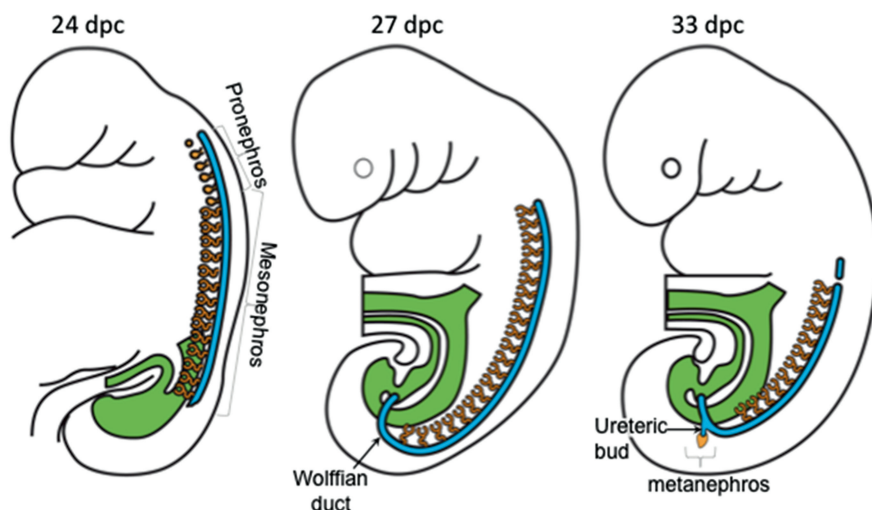


Fig. 2.1 Three phases of human kidney development between 24 and 33 days postconception (dpc). The pronephros, which develops in the upper thorax, consists of simple tubules connected to the pronephric duct which elongates caudally stimulating mesonephric glomeruli and tubules. This area is renamed the mesonephros and the duct becomes the mesonephric or Wolffian duct. Ongoing duct migration reaches the cloaca and the ureteric bud then branches from it into metanephric mesenchyme to form the metanephros. The latter will generate the definitive adult kidney, while more proximal pro- and mesonephric segments degenerate completely (aside from small contributions to the male urogenital system)

ric tubules develop alongside it. Caudal extension is accompanied by complete degeneration of nephrotomes and the pronephric part of the duct by day 25.

The mesonephros develops from around 24 days of gestation, comprising the craniocaudal duct and tubule-like structures. The mesonephric duct initially lacks a lumen, but this forms in a reverse caudocranial direction after fusion with the cloaca. Mesonephric tubules develop from intermediate mesoderm by 'mesenchymal to epithelial' transformation, a process which is subsequently reiterated in metanephric development. Approximately 40 mesonephric tubules are produced (several per somite), but synchronous cranial regression and caudal development means that there are never more than 30 pairs at any one time. The tubules contain segments analogous to those in the mature kidney including a vascularized glomerulus and proximal and distal tubules and are believed to produce small quantities of urine between weeks 6 and 10 (based on analogy with other large mammals). The mesonephros involutes during the third month of gestation, although caudal segments contribute to male urogenital structures including the epididymis, seminal vesicle, and ejaculatory duct.

The metanephros, the precursor to the mature human kidney, develops from around day 28. It consists of only two cell types at its inception: the epithelial cells of the ureteric bud and the mesenchyme cells of the metanephric mesenchyme. A series of reciprocal interactions between these tissues cause the ureteric bud to branch sequentially to form the ureter, renal pelvis, calyces, and collecting tubules, while mesenchymal cells either (1) undergo epithelial conversion to form the nephrons from glomerulus

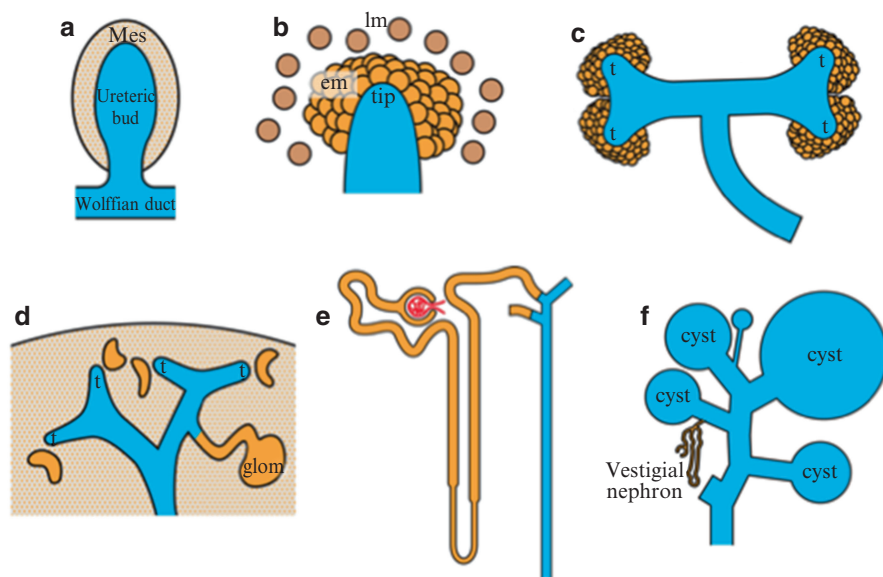


Fig. 2.2 Schematic of critical steps in metanephric development. (a) The first phase involves ingrowth of the epithelial ureteric bud (in blue) into the metanephric mesenchyme (in white/orange). (b, c) Mutual induction between the tip(s) of the ureteric bud and mesenchyme stimulates the bud to branch serially and the latter to delineate into two populations—the loose mesenchyme (lm) retains its phenotype and will form the stroma of the adult kidney, while cells adjacent to the bud tips compact and condense (cm) then undergo epithelial conversion. (d, e) These newly formed epithelia progress through vesicle, comma, and S-shaped stages as the nephron is formed. This includes glomerulus (glom) through distal tubule, which fuses with collecting ducts generated from repeated branching of the ureteric bud. (f) Dysplastic kidneys arise when induction fails or is incomplete; in the extreme case of multicystic dysplastic kidneys (MCDK), there are multiple cysts arising from ureteric structures and a few primitive, vestigial nephrons without any normal functioning renal tissue

to distal tubule or (2) give rise to interstitial cells (Fig. 2.2). Some mesenchymal cells also contribute to the renal vasculature.

The first phase of metanephric development occurs when the ureteric bud sprouts from the distal part of the mesonephric/Wolffian duct, and this penetrates the metanephric blastema, a specialized area of sacral intermediate mesenchyme (Fig. 2.2). The first glomeruli form by 8–9 weeks and nephrogenesis continues in the outer rim of the cortex until 34 weeks [8]. Nephrons elongate and continue to differentiate postnatally, but new nephrons are not formed. Similarly, nephrogenesis is completed before birth in most large mammals, but it must be noted that new nephrons are still formed for at least 7 days after birth in mice and rats which may confound some experimental analysis of kidney development.

Differentiation of the Ureteric Bud

The ureteric bud starts as a pseudostratified projection which grows into the metanephric blastema, becomes invested with mesenchyme, and begins to proliferate, extend, and branch, rapidly forming a polarized one-cell-thick epithelial tube. This

process is contingent on mutual induction with the mesenchyme, and defects in either cell lineage can impair development. Branching occurs repeatedly, including exponential phases during nephrogenesis, hence generating a complex three-dimensional treelike collecting duct system. It is estimated that 18–20 rounds of branching occur in humans, but, in a similar fashion to pronephric and mesonephric structures, many of the early generations do not persist long term: it is difficult to be precise because of the scarcity of human fetal material, but Potter estimated that the first three to five generations are remodeled to form the renal pelvis while the next three to five give rise to the minor calyces and papillae [8].

Epithelial Differentiation of Parts of the Mesenchyme

Each nephron develops from the subpopulations of mesenchymal cells induced to condense around the ampullary tip of each ureteric bud branch. The mesenchyme is initially loosely arranged, but those cells destined to become nephrons condense around the bud tips and undergo 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. The proximal S-shape develops into the glomerulus, while distal parts generate the remaining nephron from proximal convoluted tubule to distal segments. These latter parts fuse with the collecting ducts thus generating the first part of the functional urinary tract.

Stromal Differentiation of the Mesenchyme

Much of the original work on nephrogenesis disregarded stromal cells, viewing them as unimportant supporting tissues. Recent mice studies have shown that stromal signaling is essential for normal ureteric bud and nephron formation as well as renal patterning; indeed one study linked aberrant stroma to both intrinsic dysplasia and fused horseshoe kidneys [9]. Stroma also contributes to the renal microvasculature which is increasingly highlighted in renal diseases [10].

The Spectrum of Maldevelopment in CAKUT

The wide spectrum of malformations within CAKUT is well covered in pathology textbooks [11], but we will highlight the most important ones here. As nephrologists, we tend to divide these into malformations with an intrinsic defect in the kidney such as agenesis, dysplasia, or polycystic kidney disease (PKD) versus extrarenal pathologies such as posterior urethral valves or vesicoureteric reflux. This simplifies understanding, but we must recognize that this is an artificial distinction since there is often combined maldevelopment of the kidney and urinary tract at the same time leading to a synergistic impairment of renal function [12].

Based on the renal embryology outlined above, there are several key phases that should be considered in CAKUT including:

1. Initial 'setup' of the renal field via pronephric and mesonephric stages.
2. Outgrowth of the ureteric bud into the correct area of prespecified metanephric mesenchyme.
3. Mutual induction between epithelial cells in the bud and mesenchyme that:
 - Cause the bud to branch repeatedly with each tip inducing new mesenchymal condensates
 - Induce mesenchyme to epithelial conversion which generates nephrons
 - Promote stromal patterning and microvasculature

Later stages include differentiation of segment specific cells and elongation and growth of tubules and the collecting systems. These may also be affected in CAKUT, but they are unlikely to have such a large impact on renal function in childhood because they affect nephron structure rather than nephron number.

Absent Kidneys: Agenesis or Aplasia

These result in the same thing, a missing kidney, but they have a different etiology—agenesis is a primary defect with aberrant initiation of the pronephros-mesonephros sequence and/or failure of ureteric bud outgrowth. In contrast, renal aplasia occurs when kidneys were initially induced but failed to progress through nephrogenesis and then involuted. Aplasia includes multicystic dysplastic kidneys (MCDK), since at least two thirds of these involute eventually; hence, there may be no trace of cysts if assessed after that point. Absence of both kidneys is rare at 1:7,000 to 1:10,000 births with a slight male bias. These babies usually die at birth with the Potter Sequence of anhydramnios-defective lung maturation-respiratory insufficiency, along with limb and face deformities. Lack of one kidney is commoner, affecting 1:1,000 individuals and affects both genders equally. Intriguingly, the left kidney is more often missing; no one knows why but there is slightly different timing of nephrogenesis on each side which may be important. Uncomplicated unilateral agenesis is increasingly detected on antenatal ultrasound; otherwise it may be silent because the other kidney can compensate if normal. Around half of cases have an associated urogenital anomaly when investigated. The commonest is vesicoureteric reflux (VUR), but others include contralateral renal dysplasia, absence of vas deference (perhaps indicating aberrant mesonephric development), absent adrenals, and pelvic renal ectopy. Bilateral or unilateral renal agenesis accompanies many syndromes such as the branchio-oto-renal syndrome, renal cysts and diabetes syndrome (RCAD) and the hypoparathyroidism, hypoparathyroidism, sensorineural deafness and renal disease syndrome (HDR), Fanconi's anemia, and Fraser, Kallmann, Di George, and Smith-Lemli-Opitz syndromes.

Dysplasia

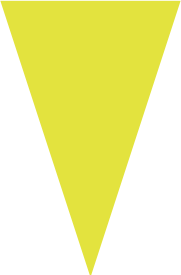
Dysplastic kidneys fail to undergo normal differentiation; they usually accomplish phases 1 and 2 above, but there is disruption of the critical third phase (see genetics, obstructions, and teratogen section for causes). The dysplastic kidney can be either larger or smaller than normal and diffusely or partly cystic [2]. Diagnosis is routinely assigned on the basis of renal ultrasound although, in the strictest terms, it can only be made definitively by histology. Characteristic features include disrupted organization of normal nephrons, abundance of undifferentiated cells, thick vessels, metaplastic cartilage, and primitive, poorly branched ducts with smooth muscle collars. Cartilage is pathognomic but only present in around a third of cases. The extreme case is a multicystic dysplastic kidney (MCDK) where all of the renal parenchyma is replaced by cysts and poorly differentiated interstitial tissues, i.e., there is no functioning renal tissue. Such kidneys are often attached to an atretic ureter, raising the possibility of early pathology at the time of bud outgrowth and ureteric development. Dysplasia can occur as an isolated anomaly or in a multiorgan syndrome, such as RCAD.

Unilateral dysplasia is more common than bilateral, and coexisting abnormalities of the urinary tract occur in 50–75 % of patients, particularly renal ectopias such as horseshoe kidney, ureteral duplication, hydroureters, UPJ and UVJ obstruction, and vesicoureteric reflux. Prognosis is poor for bilateral dysplasias because they have an intrinsic nephron deficit, with severity ranging from the lethal Potter's sequence, through neonatal renal failure to later CKD. Conversely, children with unilateral dysplasia generally do well, with prognosis dependent on severity of coexisting anomalies. Historically, dysplastic kidneys were removed surgically because of case reports linking them to hypertension and Wilms' tumors. However, over 70 % of MCDK will eventually involute and disappear without intervention, as will a significant proportion of non-cystic dysplastic kidneys, and the systematic reviews conducted thus far do not substantiate these risks [13].

Hypoplasia

Hypoplastic kidneys are defined as (1) weighing less than 50 % of the normal mean for age and (2) lacking any primary histological abnormality—they may contain significantly fewer nephrons, but the formed nephrons appear normal and there are no undifferentiated tissues. In one variant, oligomeganephronia, both glomeruli and tubules are significantly enlarged [14]. Hypoplasia may be isolated or part of a wider malformation syndrome such as the renal coloboma syndrome. In theory, one should have detailed histologic examination of the kidney to exclude evidence of dysplasia before labeling as hypoplasia, but this is often not done if renal architecture looks normal (albeit in a small kidney) on ultrasound because of worries about the morbidity of biopsying a small kidney.

Table 2.1 Initial nephron number in CAKUT and renal diseases

Intrinsic renal conditions	Initial nephron number (100–0 %)	Range within extrarenal CAKUT spectrum			
ADPKD					Vesicoureteric reflux
ARPKD				Horseshoe kidneys	
Nephronophthisis			Duplex kidneys		
RCAD		Posterior urethral valves			
Bardet-Biedl					
(Cystic) dysplastic					
MCDK					
Agenesis					

Variants on hypoplasia include the small kidneys associated with low birth weight and prematurity, which are linked to low nephron number and increased risk of hypertension, proteinuria, and kidney disease in later life (Table 2.1) [15]. One component here may be the antenatal steroids given to stimulate lung development before premature birth—these are necessary to save the baby’s life, but there is experimental animal evidence that high-dose corticosteroids halt or seriously retard nephrogenesis too. Bilateral small kidneys are occasionally seen in children with multiple congenital malformations, Down’s syndrome, or long-standing disease or anomalies of the central nervous system. These may represent a failure of renal growth, rather than an intrinsic defect in early nephrogenesis.

Cystic Kidney Diseases and Ciliopathies

Renal cysts can develop at any stage of life, ranging from in utero through late adulthood. A key distinction between different conditions relating to CAKUT, however, is whether the cysts arise during kidney development or after the full nephron complement has been reached. Multicystic dysplastic kidneys clearly combine cysts

and severe perturbation of early nephrogenesis (see panel f in Fig. 2.2). In contrast, most polycystic kidney disease (PKD) and the new group of diseases called ciliopathies (including Bardet-Biedl syndromes and nephronophthisis which have molecular defects in components of the primary cilium [16]) have relatively normal early development, then cysts develop later, i.e., there is a secondary, induced nephron defect so we will not consider them as CAKUT here.

Other CAKUT

There are many other parts of the spectrum including structural and functional lower urinary tract flow disruption (such as obstruction and reflux), ectopia, and renal fusion. To avoid repetition, these are considered in other parts of the book.

Intrinsic Nephron Number: A Key Concept in CAKUT

Functional renal mass is lost as all renal conditions progress through the CKD stages, but there is a fundamental difference at onset between CAKUT and diseases of the more mature kidney—the former start with the handicap of a reduced nephron number, particularly with intrinsic renal maldevelopment. Therefore, these children have less functional reserve and will show signs of CKD at earlier disease stages. The extreme examples are MCDK which have very low or zero functional nephrons versus conditions such as PKD and nephronophthisis where initial nephron count may be normal; nephrons are then lost as a secondary effect when cysts, inflammation, and fibrosis destroy normal functioning tissues.

The same principles apply to the extrarenal CAKUT spectrum, but these conditions tend to be more variable. The best example here is boys with posterior urethral valves where some have major disruption with very few functioning nephrons leading to renal failure from birth, while others have minimal initial perturbation. It is likely that all of these conditions have some deficit in nephron number, even when initial examination and blood tests are normal. Measurement of “functional” renal size may help predict how quickly CKD will progress [7], but it would be prudent to arrange lifelong renal follow-up in all of these cases.

Underlying Pathogenesis of CAKUT: Known Unknowns

There have been major advances in understanding the genetic and molecular pathogenesis of CAKUT over the last 20 years, with new causes being reported almost weekly [17]. It is striking that even with this increased knowledge, however, that less than a third of cases have been linked to gene mutations, which points to either

inadequacies in current technologies or an (as yet) unfathomably complex interaction between genes, environment, and stochastic factors that we may never understand. We will briefly consider some of the most important molecular pathways identified thus far, along with the importance of obstruction and maternal dietary factors.

Important Genetic Factors in CAKUT

1. Regulating ureteric outgrowth and bud branching—The GDNF/RET system. Precise temporospatial control of ureteric bud outgrowth involves a large number of factors, but most function by regulating glial cell line-derived neurotrophic factor (GDNF) and its receptor Ret [18]. Both are expressed in the developing urogenital tract, genetic ablation abrogates metanephric development completely or causes severe dysplasia, and dysregulation can cause multiple ureters. One of the negative regulators is the SLIT2-ROBO pathway, and human mutations in this system have recently been implicated in cystic dysplastic kidneys, unilateral renal agenesis, and duplicated collecting system [19].
2. Mesenchymal-epithelial conversion—The PAX–EYA–SIX transcription cascade. PAX genes are well preserved from *Drosophila*, through zebrafish to human. Controlled expression of PAX2 is mandatory for normal kidney development and there is a direct correlation between expression and kidney phenotype [20]. PAX2 mutations cause the ‘renal-coloboma’ syndrome with optic nerve colobomas, renal anomalies, and vesicoureteric reflux [21], while polymorphisms with reduced PAX2 expression are associated with smaller kidneys inferred as having fewer nephrons [22]. PAX genes work in a functional cascade with SIX and EYA genes, and several of these have been linked to renal malformations including EYA1 in the branchio-oto-renal syndrome and SIX1 and SIX2 in familial CAKUT [23, 24].
3. Defective maturation and cysts—Hepatocyte nuclear factor (HNF) 1 β . Mutations of the TCF2 gene, encoding the transcription factor hepatocyte nuclear factor 1 β , cause the renal cysts and diabetes (RCAD) syndrome which is probably the major single cause of human congenital kidney malformations, accounting for up to a third of several antenatal presentations with ‘bright’ kidneys and 10 % of CAKUT overall [25]. Diverse renal malformations occur in RCAD, ranging from grossly cystic dysplastic kidneys, through hypoplasia with oligomeganephronia to apparent unilateral agenesis. Females may also have uterine abnormalities. An important issue is that cysts and diabetes can present at different times; hence, it is always worth asking at every appointment whether there have been any new diagnoses of diabetes since this may engender analysis for these mutations and gene deletions. We had one case of unexplained dysplasia where diabetes was not uncovered until the child was given steroids after renal transplantation.

Importance of Urinary Tract Obstruction in CAKUT

The second commonest cause of CKD5 in infancy is dysplasia brought on by urinary tract obstruction, particularly posterior urethral valves [4, 26]. Moreover, the most severely perturbed nephrogenesis seen in MCDK are classically reported to be connected to ‘atretic’ (i.e. obstructed) ureters. Experimental obstruction of the developing urinary tract has been known to generate typical morphology of renal malformations for over 40 years, and molecular analyses confirm similarities with human CAKUT [27].

Lower urinary tract issues are considered in detail elsewhere in this book, but it is worth noting that the pathology in human CAKUT contains a mixture of primary and secondary effects with a direct reduction in nephron number and later bladder dysfunction, which contributes to ongoing injury via ischemia and oxidative stress which promote proximal tubular cell death and interstitial fibrosis [28]. There are also conflicting data on whether correcting the obstruction is effective, with good results in large animals but poorer outcomes in mice and rats. The latter data are consistent with the generally poor results for in utero intervention to relieve obstruction in humans where shunting may improve perinatal survival but does not significantly improve the poor renal function [29].

Teratogens and Maternal Diet may Contribute to CAKUT

Many drugs and chemicals are teratogenic to the developing kidney [30]. They can be divided into two broad categories: exogenous factors such as drugs versus endogenous factors which become teratogenic when present in abnormal quantities. An example of the former is the renin-angiotensin system: angiotensin-converting enzyme inhibitors and receptor blockers are prescribed to treat hypertension, but, when used during pregnancy, these can cause neonatal renal failure from a combination of hemodynamic compromise and renal tubular dysgenesis (along with skull malformations termed hypocalvaria). An example of the latter is retinoic acid, a natural metabolite of vitamin A, which perturbs nephrogenesis if depleted or in excess [31].

High glucose levels in diabetic mothers are associated with an increased incidence of kidney and lower urinary tract malformations, plus abnormalities in the nervous, cardiovascular, and skeletal systems [32]. This may not be a direct effect on the kidney, however, since diabetes is associated with caudal regression syndrome in the fetus which might clearly affect the lower urinary tract. It is also possible that some CAKUT cases ascribed to maternal diabetes had HNF1 β mutations as reported in the RCAD syndrome above.

Maternal diet may have a more subtle effect on nephrogenesis, affecting nephron number without gross changes. This forms part of the ‘Barker hypothesis’ based on epidemiological data suggesting that fetal life programs the child for later diseases: individuals born to mothers with poor diets are much more likely to develop hypertension,

cardiovascular disease, and diabetes in adulthood, and this has been ascribed to reduced nephron number [6, 33]. Clearly, dietary effects may be multiplied in CAKUT where there is already a nephron deficit.

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