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Renal development in the fetus and premature infant

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A B S T R A C T

Congenital abnormalities of the kidney and urinary tract (CAKUT) are one of the leading congenital defects to be identified on prenatal ultrasound. CAKUT represent a broad spectrum of abnormalities, from transient hydronephrosis to severe bilateral renal agenesis. CAKUT are a major contributor to chronic and end stage kidney disease (CKD/ESKD) in children. Prenatal imaging is useful to identify CAKUT, but will not detect all defects. Both genetic abnormalities and the fetal environment contribute to CAKUT. Monogenic gene mutations identified in human CAKUT have advanced our understanding of molecular mechanisms of renal development. Low nephron number and solitary kidneys are associated with increased risk of adult onset CKD and ESKD. Premature and low birth weight infants represent a high risk population for low nephron number. Additional research is needed to identify biomarkers and appropriate follow-up of premature and low birth weight infants into adulthood.

1. Introduction

Renal anomalies are a frequent form of congenital abnormality and are often diagnosed prenatally. In addition, perinatal insults and premature birth may impact renal development. Here we review mechanisms of abnormal renal development and discuss the evaluation of fetal and premature infant kidneys.

2. Normal renal development

Human kidney development begins in the first trimester [1]. There are three stages of mammalian kidney development: the pronephros, mesonephros, and metanephros. The pronephros and mesonephros form and then essentially involute [2]. The metanephros develops into the final functional mammalian kidney.

The pronephros consists of simple tubules and forms at three weeks of gestation. Just caudal to the pronephros, the mesonephros forms at four weeks. The mesonephros consists of filtering units (glomeruli with tubules) and as they degenerate the mesonephros forms the mesonephric (or Wolffian) duct. The ureteric bud is an outgrowth of the mesonephric duct that invades the surrounding metanephric mesenchyme during the fifth week of gestation. The ureteric bud undergoes branching, establishing the radial structure of the kidney and the nephron number [2,3]. Signaling from the tips of the branching ureteric bud induces nephron formation, with conversion of metanephric mesenchyme to renal epithelia (renal vesicle). In turn, reciprocal signaling from the metanephric mesenchyme to the ureteric tree stimulates radial renal branching. The ureteric tree forms the renal collecting ducts, pelvis, and ureters. The renal vesicle becomes a comma, then an S-shaped body, and ultimately forms the glomerulus, proximal tubule, loop of Henle, and distal tubules.

The first glomeruli form at 9–10 weeks of gestation [4]. During the late second and third trimester, there is an exponential increase in nephrons [1,5]. Nephron development is complete by 32 to 36 weeks of gestation [5]. Fetal urine becomes a major contributor to amniotic fluid at about 16–20 weeks of gestation, with production of up to 300 mL/kg fetal weight/day [6,7].

3. Congenital abnormalities of the kidney and urinary tract (CAKUT)

Congenital abnormalities of the kidney and urinary tract are one of the most frequent major birth defects, representing up to 20–30% of all major birth defects [8]. Whereas the prevalence of abnormalities often depends upon the setting (e.g. tertiary care centers often have a higher prevalence of anomalies), some estimates place the frequency of renal anomalies at about one in 500 live births [9,10]. There is a broad spectrum of renal defects,

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from simple hydronephrosis to bilateral renal agenesis. In one large population-based study of more than 20,000 fetuses and newborns, about one-third of renal anomalies were detected by prenatal ultrasound [9]. These anomalies were on average detected late in pregnancy, in the third trimester [9]. Time of diagnosis depended upon severity of the abnormality; for example, mean time of diagnosis of bilateral renal agenesis was 24 weeks of gestation, whereas mean time of diagnosis of hydronephrosis was 30 weeks of gestation [9]. The most frequently occurring renal anomaly diagnosed on prenatal ultrasound is hydronephrosis [11]. Fetal hydronephrosis may be transient or related to upper or lower urinary tract obstruction or vesicoureteral reflux (VUR) (discussed in detail below). The second most frequent anomaly is renal cysts (either bilateral or unilateral), followed by renal agenesis (unilateral > bilateral) [12]. Renal dysplasia may be observed, associated with hydronephrosis or cysts [12].

4. Cellular mechanisms leading to CAKUT

The most severe renal anomaly, renal aplasia (agenesis), results when the ureteric bud either fails to form or fails to reach/induce the metanephric mesenchyme leading to apoptosis (Fig. 1). Unless it receives growth factors released by the ureteric bud (e.g. glial-derived neurotrophic factor or GDNF), the metanephric mesenchyme will undergo apoptosis, leading to renal agenesis [13]. Bilateral renal agenesis results severe oligohydramnios (formerly Potter's) sequence (with severe pulmonary hypoplasia) and fetal or perinatal death [14,15].

Inhibitory signals restrict and guide the site of ureteric bud outgrowth to a single location [16]. Failure to restrict the site of outgrowth may lead to multiple ureteric buds and duplication of the kidney and/or collecting system. In the most severe cases, there is complete duplication, with an upper pole and lower pole ureter. Duplication is frequently associated with other ureteral anomalies, including VUR and ureterovesical junction (UVJ) obstruction [17]. The classic findings in complete duplications are that the upper ureter connects to the bladder in an ectopic location and is obstructed, whereas the lower pole ureter has VUR [18]. Even in the absence of duplications, defects in ureteric bud outgrowth and branching are associated with VUR, UVJ as well as ureteropelvic junction (UPJ) obstruction [19].

Experiments in fetal sheep have demonstrated that ureteral or urethral obstruction impairs fetal kidney development [20–22]. Postnatal ureteral obstruction also induces tubulointerstitial fibrosis in rodent models [23]. Whereas in humans it is not possible to eliminate the possibility that factors that affected the ureteral development independently lead to defects in renal development, it is clear that both UPJ and UVJ obstructions may result in obstructive uropathies and CKD in childhood [24]. UPJ and UVJ are rarely bilateral and thus do not typically lead to childhood ESKD unless there are associated contralateral renal anomalies [25].

In contrast, urethral obstruction during fetal development (as with posterior urethral valves) is one of the more frequent causes of ESKD in childhood [26,27]. The pathophysiology of PUV is not fully understood, and there are several competing theories on its mechanism [28]. One theory is that the “valves” (which are not truly valves) are mucosal membranes that form and fail to involute during urethral development. Alternatively, they may represent an overgrowth of normally present mucosal folds. A final theory is that they result from abnormal development of the mesonephric or Müllerian duct. A variant of this is that the mesonephric duct has an abnormal anterior insertion into the cloaca. When the rectal–urethral septum forms, the abnormal insertion prevents proper migration of the duct cranially and posteriorly and leads to obstructing anterior–lateral folds. Obstruction of the urethra during bladder development leads to permanent defects in bladder smooth musculature differentiation, with excess fibrotic tissues. PUV is frequently associated with VUR and renal dysplasia. As with urethral obstruction, it remains unclear whether the dysplasia results from obstruction/VUR or separate individual defects in renal

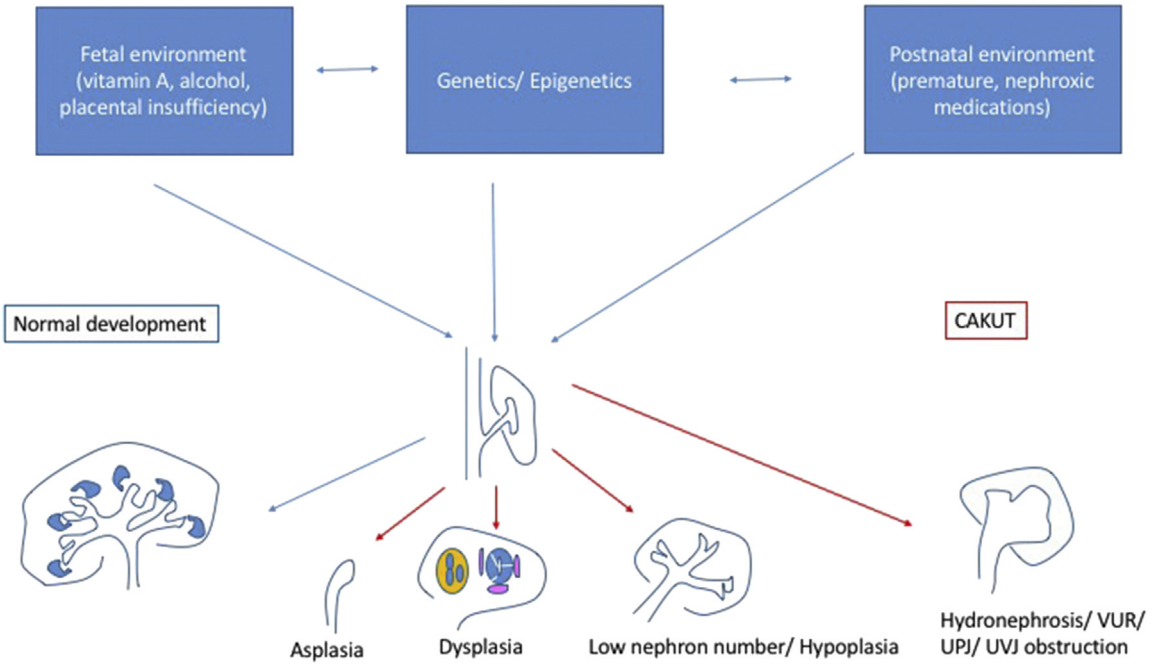

Fig. 1. Genetic, epigenetic, and environmental factors interact to modify renal developmental pathways and lead to a spectrum of congenital abnormalities of the kidney and urinary tract (CAKUT). VUR, vesicoureteral reflux; UPJ, ureteropelvic junction; UVJ, ureterovesical junction.