

Anatomy and ontogeny of kidney development

^{1,2}Carmen Micu, ²Bogdan Micu, ¹Ana-Nadia Schmidt, ³Nicolae Miu

¹ Department of Anatomy and Embryology, “Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca, România; ² Vth Surgical Clinic, “Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca, România; ³ Department of Pediatrics, IInd Pediatric Clinic, “Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca, România.

Abstract. Understanding the significant events in the development of the urinary system has great importance in both early diagnosis of congenital anomalies before the onset of irreversible complications and in the correlational relationship between various diseases found in one single patient.

Key Words: intermediate mesenchyme, metanephros, ontogeny

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Corresponding Author: C. Micu, carmenmmicu@yahoo.com

Introduction

Concerns about prenatal diagnosis of congenital renal disease (Morcel *et al* 2011; Gérard-Blanluet *et al* 2011; Amsalem *et al* 2011) and changes in the deterministic background, accounting new risk factors (Sun *et al* 2010; Harewood *et al* 2010; Martinovic-Bouriel *et al* 2010; Dührsen *et al* 2011, Demirel *et al* 2011), justify the normal development of the kidneys.

Fetal ultrasound examination should be performed based on a rigorous “checklist” program (Syngelaki *et al* 2011) for a careful fetal anatomy scan (Stoll *et al* 2010; Abdelazim *et al* 2010; Taori *et al* 2010).

In the UK, NICE (National Institute for Clinical Excellence) recommends to perform two ultrasound examinations on pregnant women (National Collaborating Centre for Women’s and Children’s Health 2008).

According to this program, the second examination performed at 20 weeks of pregnancy is aimed at identifying fetal structural abnormalities.

Detection rate (Harewood *et al* 2010) of some anomalies (including renal anomalies) was compared with data reported by “European Network for Surveillance of Congenital Anomalies”, including figures provided by medical records from 20 countries, figures covering 28% of all births in the European Union. (Garn *et al* 2000; Harewood *et al* 2010).

Renal agenesis or dysgenesis are potentially fatal birth defects affecting 2 to 5 children per 10,000 live births annually in the United States (Davis *et al* 2010).

According to the National Center on Birth Defects and Developmental Disabilities (2006), 3 to 5 children are born to diabetic mothers in the United States every year.

Maternal diabetes, known as a risk factor for other birth defects, is also increasingly recognized for renal agenesis/dysgenesis. The prevalence of all types of congenital malformations in children born to mothers with pregestational diabetes (type 1 and

type 2) is estimated between 5.0 and 6.1% compared to a 1.3 to 2.8% prevalence in the general population (Moore *et al* 2000; Sheffield *et al* 2002; Jeansen *et al* 2004; Davis *et al* 2010).

Development of the urinary system

The urinary system develops from intermediate mesenchyme and it is intimately associated with the reproductive system in early stages but it precedes it (Lermann *et al* 2007; Strandring 2008). Intermediate mesenchyme (IM) is disposed longitudinally in the trunk, subjacent to the somites, adjacent to the splanchnopleuric mesoderm (medially) and to the somatopleuric mesoderm (laterally).

In lower vertebrates, intermediate mesenchyme typically develops serial, segmented epithelial diverticuli called nephrotomes (Larsen *et al* 1997).

Each nephrotome encloses a cavity (the nephrocele), which communicates with the coelom through a peritoneal funnel called the nephrostome. The dorsal wall of the nephrostome evaginates as a nephric tubule. The dorsal tips of the cranial nephric tubules bend caudally and fuse to form a longitudinal primary excretory duct, which grows caudally and curves ventrally to open into the cloaca. The more caudally placed, and therefore chronologically later, tubules open secondarily into this duct or into tubular outgrowths from it (Keeling 2001).

Glomeruli, specific arrangements of capillaries and overlying coelomic epithelium, arise from the ventral wall of the nephrocele (internal glomeruli) or the roof of the coelom adjacent to the peritoneal funnel (coelomic or external glomeruli), or from both (Schmidt 2002).

It has been customary to describe the urinary system as three organs, the pronephros, mesonephros and metanephros, succeeding each other in time and space, so that the last to develop is retained as the permanent kidney (Keeling 2001; Schmidt 2002; Deprest *et al* 2010).

Pronephros

The intermediate mesenchyme becomes visible in stage 10 embryos and can be distinguished as a nephrogenic cord when 10 somites are present. The pronephros appears in human embryos as clusters of cells in the most cranial parts of the nephrogenic cord. More caudally, similar groups of cells appear and become vesicular. Their central ends are connected with the coelomic epithelium by cellular strands, which probably represent rudimentary peritoneal funnels. Glomeruli do not develop in association with these cranially situated nephric tubules, which ultimately disappear. It is doubtful whether external glomeruli develop in human embryos (Keeling 2001; Schmidt, 2002).

Primary excretory duct

In stage 11 (embryos with 14 somites), the primary excretory duct can be seen as a solid cell cord in the dorsal part of the nephrogenic cord. Its cranial end is about the level of the ninth pair of somites and its caudal tip merges with the undifferentiated mesenchyme of the cord (Larsen 1997; Standring 2008). It differentiates before any nephric tubules, and when the latter appear it is at first unconnected with them. In older embryos, the duct has lengthened and its caudal end becomes detached from the nephrogenic cord to lie immediately beneath the ectoderm. From this level it grows caudally, independent of the nephrogenic mesenchyme, and then curves ventrally to reach the cloaca. It becomes canalized progressively from its caudal end to form a true duct, which opens into the embryonic cloaca in stage 12 (Standring 2005).

Mesonephros

From stage 12, mesonephric tubules which develop from the intermediate mesenchyme between somite levels 8-20, begin to connect to the primary excretory duct, which now becomes the mesonephric duct. More caudally, a continuous ridge of intermediate mesenchyme extends to the level of somite 24. The mesonephric tubules (nephrons) are not metameric - there may be two or more mesonephric tubules corresponding to each somite.

Within the mesonephros, each mesonephric tubule first appears as a condensation of cells, which epithelialize and form a vesicle. One end of the vesicle grows and opens into the mesonephric duct, while the other dilates and invaginates. The outer layer forms the glomerular capsule, while the inner cells differentiate into mesonephric podocytes, which clothe the invaginating capillaries to form a glomerulus (Larsen 1997).

The capillaries are supplied with blood through lateral branches of the aorta. It has been estimated that 70-80 mesonephric tubules and a corresponding number of glomeruli develop.

Glomeruli are not all present at the same time, it is rare to find more than 30-40 in an individual embryo, because the glomeruli and the cranial tubules develop and atrophy before the development of those situated more caudally (Standring 2005).

By the end of the sixth week, each mesonephros is an elongated, spindle-shaped organ that projects into the coelomic cavity, on both sides of the dorsal mesentery, from the level of the septum transversum to the third lumbar segment. This whole projection is called the mesonephric ridge, mesonephros, or Wolffian

body. It develops subregions, and a gonad develops on its medial surface (Larsen 1997).

There are striking similarities in structure between the mesonephros and the permanent kidney or metanephros, but the mesonephric nephrons lack a segment that corresponds to the descending limb of the loop of Henle. The mesonephros is believed to produce urine by stage 17 (Keeling 2001; Schmidt 2002).

A detailed comparison of the development and function of the mesonephros and metanephros in staged human embryos is not available.

Mesonephric duct

Once mesonephric nephrons connect to the primary excretory duct it becomes the mesonephric duct. This runs caudally in the lateral part of the nephric ridge, and at the caudal end of the ridge it projects into the cavity of the coelom in the substance of a mesonephric fold. As the mesonephric ducts approach the urogenital sinus the two mesonephric folds fuse between the bladder (ventrally) and the rectum (dorsally).

In the male, the mesonephric duct forms (Mizuno 2010; Hofkamp *et al* 2010): epididymal duct, deferent duct and ejaculatory duct.

There is a well known close connection in development between the urinary and the genital system.

The mesonephros derived from intermediate mesoderm gives birth to the mesonephric duct (MD) or Wolffian duct, as a result of the epithelial-mesenchymal interactions. Mesonephric duct develops cranially (from the pronephros) to the cloaca (caudally) along the urogenital ridge and it is the common origin for male reproductive system and urine collection tubes.

Ureteric bud

The ureteric bud, also known as the metanephrogenic diverticulum, emerged as a diverticulum of the distal portion of the MD. It is oriented - increasing caudally - towards the metanephric blastema and interacts with it, and then branches off creating the urinary collecting tubes system. Ureteric bud branching also induces nephrogenesis inside the metanephric blastema (Larsen 1997).

Later, the mesonephric duct develops under the influence of growth factors and testosterone in males (regresses in females), resulting in male genital tract.

Thus, a possible disruptive mesonephric duct (MD) development would cause renal abnormalities (agenesis, hypoplasia and dysgenesis) of the urinary and/or genital tract in male (Mizuno 2010). In both urinary and genital systems in males, the pathogenetic mechanism (suggested by animal experiments) would involve homeobox genes, adhesion molecules, growth factors and their receptors (Hofkamp *et al* 2010).

Metanephros

The pronephros and mesonephros are linear structures. They both contain stacks of tubules distributed along the craniocaudal axis of the embryo. This display results in the production of hypotonic urine.

In contrast, the metanephric tubules are arranged concentrically, and the loops of Henle are directed towards the renal pelvis. This arrangement allows different concentration gradients to develop within the kidney and results in the production of

hypertonic urine. Metanephric nephrons do not join with the existing mesonephric duct but with an evagination of that duct, which branches dichotomously to produce a characteristic pattern of collecting ducts.

The metanephric kidney develops from three sources:

1. an evagination of the mesonephric duct – the ureteric bud,
2. a local condensation of mesenchyme – the metanephric blastema,
3. the angiogenic mesenchyme migrates into the metanephric blastema only later to produce the glomeruli and vasa recta.

An intact nerve supply may also be needed for metanephric kidney induction.

An epithelial/mesenchymal interaction between the duct system and the surrounding mesenchyme occurs in both mesonephric and metanephric systems. In the mesonephric kidney, development proceeds in a craniocaudal progression, and cranial nephrons degenerate before caudal ones are produced. In the metanephric kidney a part of the mesenchyme remains as stem cells that continue to divide and enter the nephrogenic pathway later, when the individual collecting ducts lengthen (Brancati *et al* 2010).

Experimental studies on mutant mice demonstrated that a defective mechanism in the apoptosis in the undifferentiated mesenchyme induces an abnormal interaction between the ureteric bud and the metanephric blastema (Suresh *et al* 2011). These changes would cause preexisting intrinsic abnormalities of the kidneys that would validate early, and the role of certain genes and biochemical modulators is undoubtedly.

Angiotensin II receptor type 1 (AT1 receptor) plays an important role in the final stage of nephrogenesis, participating in nephron maturation and ureter formation process. Angiotensin II stimulates the branching of the ureteric bud and this sequentially induces metanephric blastema (metanephric mesenchyme) in both glomeruli and proximal and distal renal tubules.

In Germany, the use of ARBs (hypotensive) led to the emergence of a drug-induced fetopathy: altered - dysgenic proximal and distal renal tubules with oliguria and renal hypoplasia (Hünseler *et al* 2011).

The temporal development of the metanephric kidney is patterned radially (Hünseler *et al* 2011), so that the outer cortex is the last part to be formed. The following interactions occur in the development of the metanephric kidney. The ureteric bud undergoes a series of bifurcations within the surrounding metanephric mesenchyme and forms smaller ureteric ducts. At the same time, the metanephric mesenchyme condenses around the dividing ducts to form S-shaped clusters, which transform into epithelial structures and fuse with the smaller ureteric ducts at their distal ends. Blood vessels invade the proximal ends of the epithelial structure to form vascularized glomeruli.

The ureteric bud bifurcates when it comes into contact with the metanephric blastema in response to extracellular matrix molecules synthesized by the mesenchyme. Both chondroitin sulphate proteoglycan synthesis and chondroitin sulphate glycosaminoglycan processing are necessary for the dichotomous branching of the ureteric bud.

In metanephric culture, incubation of fetal kidneys in β -D-xyloside, an inhibitor of chondroitin sulphate synthesis, dramatically inhibits ureteric bud branching (Standring 2005).

Subsequent divisions of the ureteric bud and associated mesenchyme define the gross structure of the kidney and the major

and minor calyces, as well as the distal branches of the ureteric ducts that will form the collecting ducts of the kidney. As the collecting ducts elongate the metanephric mesenchyme condenses around them.

Each epithelial group elongates, and forms first a comma-shaped, then an S-shaped, body, which continues to elongate and subsequently fuses with a branch of the ureteric duct at its distal end, while expanding as a dilated sac at its proximal end. The latter involutes, and cells differentiate locally such that the outer cells become the parietal glomerular cells, while the inner ones become visceral epithelial cells (podocytes). The podocytes develop in close proximity to invade capillaries derived from angiogenic mesenchyme outside the nephrogenic mesenchyme. This third source of mesenchyme produces the endothelial and mesangial cells within the glomerulus. The metanephric-derived podocytes and the angiogenic mesenchyme produce fibronectin and other components of the glomerular basal lamina. The isoforms of type-IV collagen within this layer follow a specific programme of maturation if the filtration of macromolecules from the plasma becomes restricted (Standring 2005).

Platelet derived growth factor (PDGF) β -chain and the PDGF receptor β -subunit (PDGFR β) have been detected in developing human glomeruli between 54 and 109 days of pregnancy (Standring 2005).

PDGF β -chain is located in the differentiating epithelium of glomerular vesicles during its comma and S-shaped stages, while PDGFR β is expressed in undifferentiated metanephric blastema, vascular structures and interstitial cells.

Both PDGF β -chain and PDGFR β are expressed in mesangial cells, which may promote further mesangial cell proliferation (Standring 2005, 2008).

Metanephric mesenchyme will develop successfully in vitro, which makes experimental perturbation of kidney development comparatively easy to evaluate. Early experimental studies demonstrated that other mesenchymal populations and spinal cord were able to induce ureteric bud division and metanephric development. Nerves “enter” the developing kidney very early, travelling along the ureter (Keeling 2001).

If developing kidney rudiments are incubated with antisense oligonucleotides, which neutralize nerve growth factor receptor (NGF-R) mRNA, nephrogenesis is completely blocked. It is thus suggested that metanephric mesenchyme induction is a response to innervation, the inductive being accomplished by the nerves.

The powerful inductive effect of the spinal cord on metanephric mesenchyme may be a further expression of this phenomenon. All stages of nephron differentiation are present concurrently in the developing metanephric kidney.

Antigens for the brush border of the renal tubule appear when the S-shaped body has formed. They appear first in the inner cortical area. The metanephric kidney is lobulated throughout its fetal life, but this condition usually disappears during the first year after birth. Varying degrees of lobulation may persist through-out life.

The growth of left and right kidneys is well matched during development.

Fetal kidney volume increases most during the second trimester of pregnancy (in both sexes). For reasons that are not understood, male fetuses show greater values for renal volume than

female fetuses from the third trimester onwards. Steroid hormones induce fetal kidney growth restriction and cystogenesis the developing kidney (Chan *et al* 2010).

Tumor mass such as sacrococcygeal teratomas may interfere in both development and growth of the kidney and urinary tract, and therefore urological problems seem to be common in patients with sacrococcygeal teratomas (Le *et al* 2011).

Fetal kidney develops during the first trimester of pregnancy and becomes functional between 6-10 weeks of pregnancy, producing urine at 11 weeks.

If maternal pregestational diabetes type 1 and type 2 are both present before pregnancy, the disease will have a negative impact on kidney development during the critical period.

Results based on animal studies leading to the association between renal agenesis/dysgenesis and hyperglycaemic uterine environment caused by uncontrolled diabetes. It has also been shown that kidney structure is disorganized on a hyperglycemic background (Al-Haggar *et al* 2010). Hyperglycemia leads to ureteral bud dysmorphogenesis and therefore, to disruptions in nephrogenesis (Davis *et al* 2010).

On the other hand, in pregnant women between 24-28 weeks of pregnancy after the critical period of renal development, controlled gestational diabetes is considered to affect fetal growth rather than organogenesis (Davis *et al* 2010).

Endocrine development of the kidney

The kidney functions not only as an excretory organ, but also as an endocrine organ, secreting hormones that are concerned with renal haemodynamics. Before birth homeostasis is controlled by the placenta. The fetal kidney produces amniotic fluid (Larsen 1997).

The kidneys of new-borns of less than 36 weeks are immature. They contain incompletely differentiated cortical nephrons, which compromise their ability to maintain homeostasis. Problems of immaturity are further emphasized by the effects of hypoxia and asphyxia, which modify renal hormones (Keeling 2001).

Renal hormones include the renin-angiotensin system, renal prostaglandins, the kallikrein-kinin system, and renal dopamine. Renin is found in the smooth muscle cells of arterioles, interlobular arteries and branches of the renal artery, and has also been described in the distal convoluted tubule cells.

Kallikrein has been found in rat fetal kidney, and prostaglandins in the renal medulla and renal tubules.

Renal dopamine is produced mainly by the enzymatic conversion of l-dopa to dopamine in the early segments of the proximal convoluted tubule, being also sourced locally from dopaminergic nerves (Chan *et al* 2010).

Other renal hormones include antihypertensive lipid, which is produced in the interstitial cells of the renal medulla, and, possibly, histamine and serotonin.

Growth factors produced by human embryonic kidney cells include erythropoietin and interleukin β (which stimulate megakaryocyte maturation) and transforming growth factor- β (Keeling 2001).

Ascent of the kidney

The metanephric kidney is initially sacral. As the ureteric mug lengthens, it gets a cranial position. The metanephric pelvis lies

on a level with the second lumbar vertebra when the embryo reaches a length of c.13 mm.

During its ascent, the metanephric kidney receives its blood supply sequentially from arteries in its close vicinity, i.e. the median sacral and common iliac arteries (Standring 2005).

The definitive renal artery is not recognizable until the beginning of the third month. It arises from the most caudal of the three suprarenal arteries, all of which represent persistent mesonephric or lateral splanchnic arteries (Schmidt 2002).

Additional renal arteries are relatively common, and may enter the kidney through the hilum or the upper or lower pole of the gland. They also represent persistent mesonephric arteries. Disruption of normal migration of the kidney before the eighth week determines its malposition during embryogenesis (organogenesis). Frequently, the ectopic kidney is located in the pelvic or lower back region. (Standring 2005, 2008; Schmidt, 2002, 2005).

Pelvic kidney is often considered to be a normal variant but with a different prognosis (Batukan *et al* 2011).

Generally speaking, renal abnormalities would be more common in ectopic kidneys, which can be complicated by hydro-nephrosis, recurrent urinary infections and then kidney stones (Batukan *et al* 2011).

Pelvic kidney is defined as one located inside from the fetal pelvis bones and in close proximity to the bladder.

In a study on 26,464 pregnant women, Batukan & Yuksel (2011) diagnosed 36 cases of pelvic kidney confirmed postnatally. Of these, 22.2% were isolated renal abnormalities, in 50% of them associated abnormalities of the urogenital apparatus were detected prenatally or postnatally, the others showing associated malformations outside the urinary system.

Thoracic kidney is extremely rare, this high position could be caused by a different pathogenetic mechanism. In adults, thoracic kidneys are rare cases reported after severe trauma.

There are 4 groups of thoracic kidney according to Guessen, 1984 and Liddell 1989 (Batukan *et al* 2011):

- thoracic kidney with closed diaphragm
- thoracic kidney with eventration of the diaphragm
- thoracic kidney with congenital or acquired diaphragmatic hernia
- thoracic kidney with traumatic rupture of the diaphragm

Thoracic kidney is accompanied by abnormal high origin of the ipsilateral renal artery. Unlike other types of renal ectopia, thoracic kidney is accompanied by a normal renal function and apparently, the surgical indication would not necessarily be strong in the neonatal period (Deprest *et al* 2010; Athanasiadis *et al* 2011).

Conclusion

This paper is a review of the literature. Kidney development occurs in overlapping stages which have a well-established genetic determinism. The action of a teratogenic factor or mutant genes' expression can influence the embryogenesis of one or more organs, depending on the time they occurred.

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Authors

- Carmen Micu, Department of Anatomy and Embryology, "Iuliu Hațieganu" University of Medicine and Pharmacy, 1-3rd Clinicilor Street, 400006, Cluj-Napoca, Cluj, România, EU, email: carmenmmicu@yahoo.com
- Bogdan Micu, 5th Surgical Clinic, "Iuliu Hațieganu" University of Medicine and Pharmacy, 11th Tăbăcarilor Street, 400139, Cluj-Napoca, Romania, EU, e-mail: micubogdan@yahoo.com
- Ana-Nadia Schmidt, Department of Anatomy and Embryology, "Iuliu Hațieganu" University of Medicine and Pharmacy, 1-3rd Clinicilor Street, 400006, Cluj-Napoca, Cluj, România, EU, email: dr_nadia_schmidt@yahoo.com
- Nicolae Miu, Department of Pediatrics, 2nd Pediatric Clinic, "Iuliu Hațieganu" University of Medicine and Pharmacy, 3-5th Crisan Street, 400177, Cluj-Napoca, Cluj, România, EU, email: e-mail:pediatrie2@spitcocluj.ro

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