INTRODUCTION

Urinary tract infection (UTI) is common in pediatric population, which merits special attention as it has been considered a risk factor for the development of renal insufficiency and end stage renal disease. The risk of having a UTI before the age of 14 y is approximately 1-3 % in boys and 3-10 % in girls ***(NICE, 2007 and Chang et al., 2006)*.**

The incidence varies with age. During the first year of life, the male to female ratio is 3-5:1. Beyond 1-2 y, there is a female dominance with ratio 1: 10 ***(Elder et al., 2001)*.**

The risk of recurrent UTI varies between 12 % and 30 % in first 6-12 months after initial episode ***(Dai B et al., 2010)*.**

A high index of suspicion is required for the diagnosis as signs and symptoms in younger age group are not localised. Therefore, early detection and therapy are needed to prevent scarring and further renal damage ***(Saadeh and Mattoo, 2011)*.**

Children presenting with features of UTI are requiring further testing to demonstrate presence of pathogens like bacteria, viruses and fungi. However, symptoms alone are not sufficient for the diagnosis. Similarly pyuria alone is also not suggestive of infection unless culture is positive, as the former may be found in other situations such as fever, acute glomerulonephritis and urolithiasis ***(Bell and Mattoo, 2009)*.**

Certain risk factors have been identified for recurrence of UTI and most recurrences occur within 12 months of the primary infection. The risks include age of <6 months during first UTI, presence of VUR, neurogenic bladder, incomplete bladder emptying, constipation and underlying structural abnormalities of kidney, ureter and bladder ***(Elder et al., 2011)*.**

The prevention of recurrent UTI and detection of congenital anomalies of kidney and urinary tract are major objectives in the management. Use of ultrasound is required to detect underlying congenital abnormalities, whereas voiding cystourethrogram and dimercaptosuccinic acid (DMSA) scan are useful in the diagnosis of obstructive uropathy and vesicoureteric reflux and renal scar, respectively.Early diagnosis of neurogenic bladder by urodynamic studies is helpful in prevention of recurrence ***(Williams and Craig, 2008)*.**

The children requiring surgical interventions are to be recognised early to prevent recurrent UTI. The treatment of vesicoureteric reflux by chemoprophylaxis in lower grades and surgical treatment in higher grades are important consideration in prevention of recurrent UTI. This is required to prevent renal parenchymal damage and scarring that can cause hypertension and progressive renal insufficiency in later life ***(Om Prakash et al., 2013)*.**

AIM OF THE WORK

Early diagnosis and treatment of UTI in infants and children for the optimal clinical outcome and the prevention of long-term morbidity and sequelae.

Chapter 1
EMBRYOLOGICAL AND ANATOMICAL CONSIDERATIONS

Introduction

The urinary and reproductive organs are developed for the most part from intermediate mesoderma and they are preceded by a set of structures, which disappear almost entirely before the end of fetal life, except the ducts. These embryonic structures are the pronephros, the mesonephros and the metanephros for the development of the urinary system, and the Wolffian and Müllerian ducts for the development of the reproductive organs. Concerning the genital system, initially there is the indifferent stage, where the two sexes develop in an identical fashion. Subsequent to six weeks, the two sexes develop differently.

Development of the kidneys

In the embryo there are three different kidneys (pronephros, mesonephros metanephros) that are developed in a sequence with only the last one persisting and being the permanent and definitive kidney of the adult. In the outer part of the intermediate mesoderm, immediately under the ectoderm, in the region from the fifth cervical segment to the third thoracic segment, a series of short evaginations from each segment grows dorsally and extends caudally, fusing

successively from before backward to form the pronephric duct. This continues to grow caudally until it opens into the ventral part of the cloaca; beyond the pronephros it is termed the Wolffian duct. Thus, the Wolffian duct is what remains of the pronephric duct after the atrophy of the pronephros. In humans, the pronephros begins to regress around the end of the fourth week. It develops a duct system and in the course of each duct a glomerulus also is developed, but it never becomes functional. It undergoes rapid atrophy and it disappears ***(Larson, 1997)***.

As the pronephros is regressing, the mesonephros is developed and arises caudal to the pronephros at 4 weeks. The mesonephric vesicle, a collection of mesoderm, elongates to become a tubule. The medial end receives an invagination of capillaries, creating a Bowman's capsule while the lateral end of the tubule drains into the mesonephric duct. This maturation of the mesonephric vesicles progresses in a cranio-caudal fashion. The caudal end of the mesonephric duct is connected with the urogenital sinus. This junction will be important later in the developing male genital structures ***(Moore and Persaud, 1998)***.

The mesonephric duct is also known as the Wolfian duct. The mesonephros atrophies and for the most part, it disappears rapidly as the metanephros develops beginning during the 6th or 7th week, so that by the beginning of the 5th month, only the ducts and a few of the tubules of the mesonephros remain. The metanephros is the definitive and permanent but immature

kidney. It arises from two closely related structures, the ureteric bud and the metanephrogenic blastema ***(Gray and Skandalakis, 1993)***.

The ureteric bud starts close to where the Wolffian duct opens into the cloaca, invades the center of the metanephros and grows along the posterior abdominal wall. The ureteric bud forms the collecting ducts and tubules of the pyramids, the calyces, the renal pelvis and the ureter. The renal tubules, on the other hand, are developed from the metanephrogenic blastema and rapidly elongate to form the parts of the nephron: the proximal tubules, the loops of Henle and the distal convoluted tubules. These last join and establish communications with the collecting duct system derived from the ultimate ramifications of the ureteric bud. In the other end, the renal tubules give rise to Bowman's capsules and glomeruli ***(Larson, 1997)***.

The ureteric bud and the nephrogenic blastema having joined, the future kidney begins its ascent and rotation. As the kidney move into the lumbar region, it takes new arterial supply from the aorta and new venous drainage into the vena cava and it undergoes a rotation of 90 degrees during the 7^{th} and 8^{th} week, so that the renal parenchyma lies lateral to the pelvis, as the kidney face ventrally at first **Fig 1** ***(England, 1997)***.

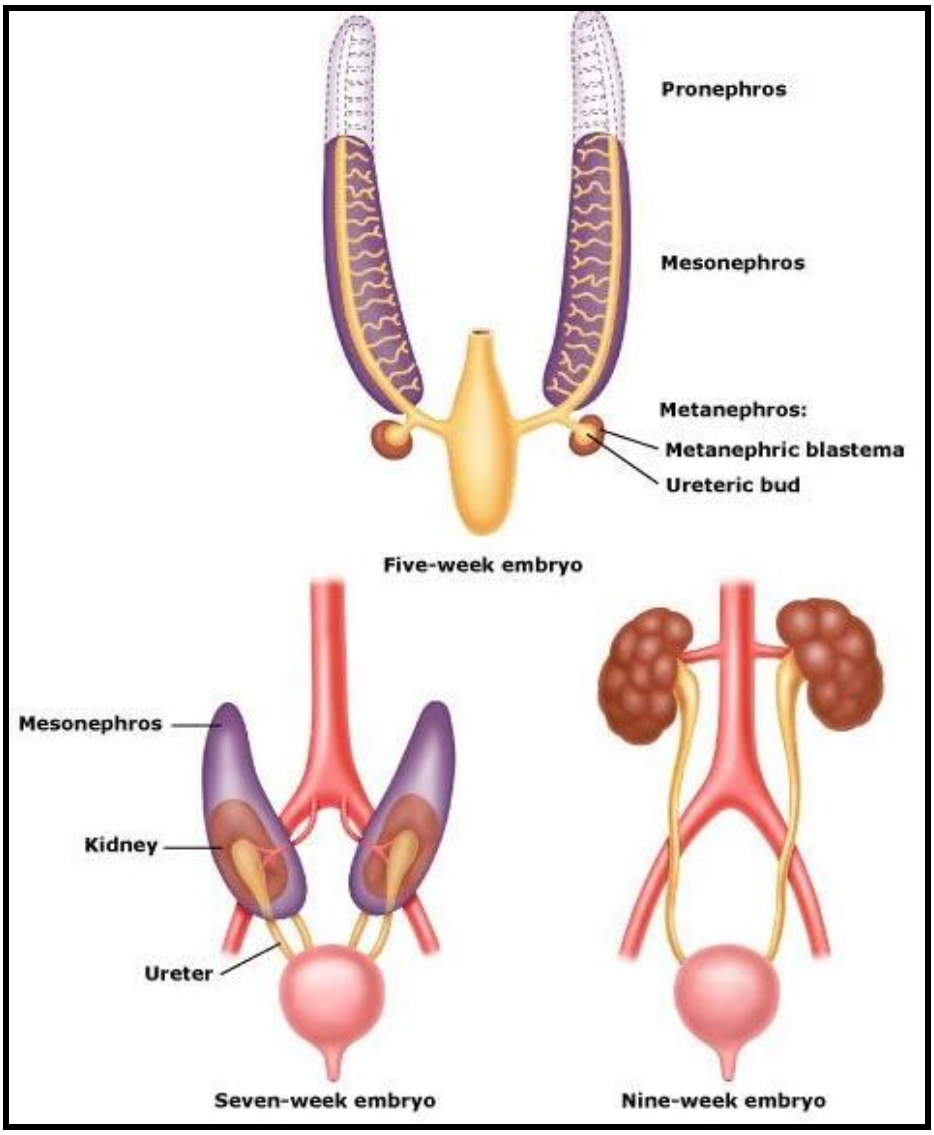

Figure (1): Embryology of kidney

Development of the urinary bladder and the urethra:

In contrast to the kidneys and the ureter, which are of mesodermal origin, the structures of the lower urinary tract are formed from endoderm. During the 6th week, the ventral cloaca

elongates and forms four segments: an expanded distal portion, the urogenital sinus; a tubular portion, the primitive urethra; an upper dilation, the future bladder; and a tubular portion, the urachus, which is continuous with the extraembryonic allantoic stalk ***(Chochard, 2012)***.

The urinary bladder is formed partly from the entodermal cloaca and partly from the ends of the Wolffian ducts. In other words, the allantois takes no share in its formation. When the urorectal septum is separated, it gives the anal canal and the urogenital sinus. The upper part of the urogenital sinus becomes the urinary bladder. The allantois is connected here and degenerates to give the urachus, the median umbiligal ligament of the adult. The middle part of the urogenital sinus gives males their prostatic and membranous urethra, and the lower, phallic part gives some urethra ***(O'Rahilly and Müller, 1996)***.

The mesonephric ducts and ureters enter the bladder. As the metanephric kidney ascends, the ureters migrate superiorly on the bladder. The mesonephric ducts migrate inferiorly and become the ejaculatory ducts in males. The trigone is the triangle located between the entrances of the mesonephric ducts and the ureters. Its mucosa is of mesodermal origin. The rest is endoderm. Eventually the mesoderm of the trigone is replaced by endoderm ***(Moore and Persaud, 1998)***.

In the male, the prostatic and membranous part of the urethra are formed by the pelvic or the tubular part of the urogenital sinus. In the female, the entire urethra and the paraurethral glands are formed by the cranial part (vesicourethral part) of the endodermal origin. However, in the female, the caudal ends of the mesonephric ducts disappear, whereas in the male, each seminal vesicle is formed from a lateral outgrowth of the caudal end of the mesonephric duct. Each ejaculatory duct is also of mesonephric origin and it is formed by the part which is located between the urethra and the duct. Muscular layer is mesodermal in origin. The distal part of the male urethra is ectoderm from the gland penis. The mucosa of the urethra is endoderm in the female and in the proximal part of the males. By 13 weeks, the urethra is almost complete ***(Moore and Persaud, 1998)***.

Chapter 2

CONGENITAL ANOMALIES ASSOCIATED WITH URINARY TRACT INFECTION

Anatomic abnormalities of the urinary tract predispose children to UTI because of inadequate clearance of uropathogens. Infections associated with urinary tract malformation generally appear in children younger than 5 years of age. It is essential to identify these abnormalities early because if uncorrected they may serve as a reservoir for bacterial persistence and result in recurrent UTI. Surgical intervention may be required to correct the anatomic abnormality. In contrast, congenital anatomic anomalies, such as posterior urethralvalves and vesicoureteral reflux (VUR), do not predispose children to colonization but perhaps increase the likelihood of inadequate washout in the routine ways. These urinary tract malformations increase the likelihood that infections of the lower urinary tract (ie, bladder and urethra) will ascend to the upper tracts with possible pyelonephritis and potential renal deterioration ***(Shortliffe, 2002)***. Importantly, children with known urinary malformation may be on chronic antimicrobial prophylaxis. Consequently, this patient population is associated with a higher incidence of multidrug-resistant uropathogens ***(ladhani and gransden, 2003)*** and non–E coli uropathogens, particularly Pseudomonas ***(Ashkenazi et al., 1991)*** and Enterococcus ***(Bitsori et al., 2005)***.

Congenital Causes of UTI

Vesicoureteral Reflux

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder into the ureter and, often, into the renal collecting system. Approximately 40% of children with UTI are subsequently diagnosed with VUR ***(Wein et al., 2012)***. Primary VUR results from a congenital abnormality of the ureterovesical junction, whereas secondary VUR is caused by high pressure voiding due to neuropathic bladder, bladder outlet obstruction or dysfunctional elimination syndrome. VUR is also a risk factor for pyelonephritis, with potential for renal injury ***(Dillon and Goonasekera, 1998)***.The radiographic diagnosis of VUR is primarily made based on upper tract urinary reflux observed on VCUG **Fig 2** ***(Martin and Peters, 2013)***.

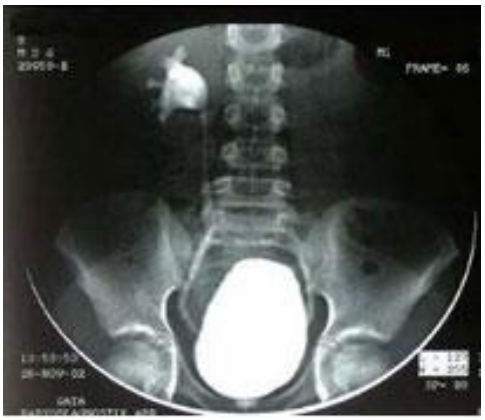

Figure (2): VCUG in a 3 month-old showing R>L vesicoureteral reflux of contrast into the upper urinary tract (ureter and renal pelvis).

Finding hydronephrosis on renal sonography can be variable and not diagnostic of the presence or absence of VUR.

DMSA scans are used to assess renal cortical function and monitor for renal scarring. Children with VUR may be managed either medically or surgically, and controversy exists regarding the optimal treatment. Medical management encompasses daily antibiotic prophylaxis and periodic radiologic reassessment of the urinary tract, since many children spontaneously resolve VUR. Surgical treatment of primary VUR includes open or laparoscopic ureteral reimplantation and subureteric endoscopic injection of various substances, including dextranomer-hyaluronic acid copolymer. Because secondary VUR has other causes than simple anatomical ones, it is imperative that these causes are ruled out in order to allow effective treatment ***(Martin and Peters, 2013).***

Ureteropelvic Junction Obstruction

Ureteropelvic junction (UPJ) obstruction is present in a minority of children born with hydronephrosis, but is the most common surgically correctible reason. This condition results from poor peristalsis of the UPJ or an anatomic abnormality consisting of either an "intrinsic," narrow segment with muscular discontinuity, or an “extrinsic” anatomic cause from aberrant vessels or a high insertion of the ureter into the renal pelvis **Fig 3**. Presenting symptoms include hematuria, UTI, abdominal mass or pain, nausea, or flank pain which worsens with diuresis because of urine production that overwhelms the ability of the UPJ to accommodate an equal volume of drainage and therefore leads to

distension of the renal collecting system and ultimately the relatively unyielding renal capsule ***(Elder, 2011)***.

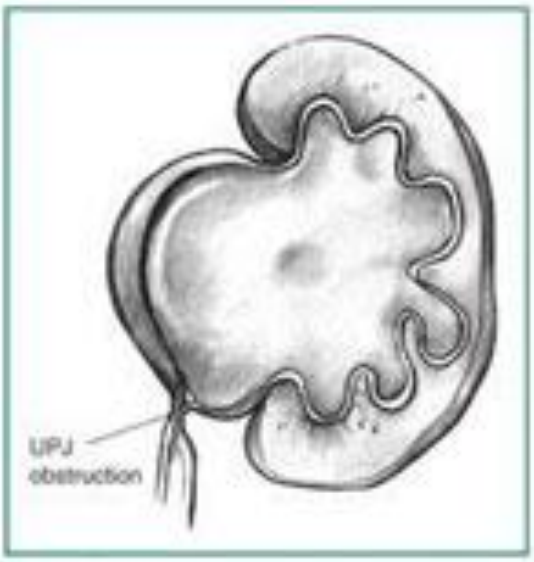

Figure (3): Example of ureteropelvic junction obstruction. (From: kidney.niddk.nih.gov)

Evaluation of UPJ obstruction includes renal ultrasonography, a VCUG to rule out VUR (33% of cases), and a MAG-3 diuretic renogram to look for delayed drainage on the affected side ***(Frokiaer and zeidel, 2012)***.

Management of UPJ obstruction is dictated by age at diagnosis, severity and stability of hydronephrosis, severity of delayed drainage, and degree of associated symptoms. In some asymptomatic children, UPJ obstruction will resolve spontaneously with expectant management. For many children, however, surgical repair is needed through either open or

laparoscopic pyeloplasty, robot-assisted laparoscopic pyeloplasty, and (rarely) percutaneous or retrograde endopyelotomy.

Ureteroceles

A ureterocele is a cystic dilatation of the terminal, intravesical portion of the ureter **Figure 4.** Eighty percent of ureteroceles drain the upper pole of a duplex kidney (two collecting systems). Sixty percent of ureteroceles have an ectopic orifice in the urethra. A UTI in the first few months of life is a common presentation for a child with a ureterocele. Sometimes the obstructed upper pole drained by a ureterocele is so hydronephrotic that it is palpable as an abdominal mass ***(Guay-Woodford, 2011)***.

Ureteroceles are diagnosed by ultrasonography, which typically shows a cystic intravesical mass in the posterior bladder, a dilated proximal ureter, and a hydronephrotic or dysplastic upper pole of a duplex kidney. Other imaging may demonstrate the "drooping lily" sign, which is a lower pole collecting system displaced downward by a dilated upper pole. This sign can be observed on VCUG, since up to 50% of ipsilateral lower pole moieties will reflux because of local distortion of the lower pole ureteral tunnel/passive flap mechanism ***(Becker, 2009)***.

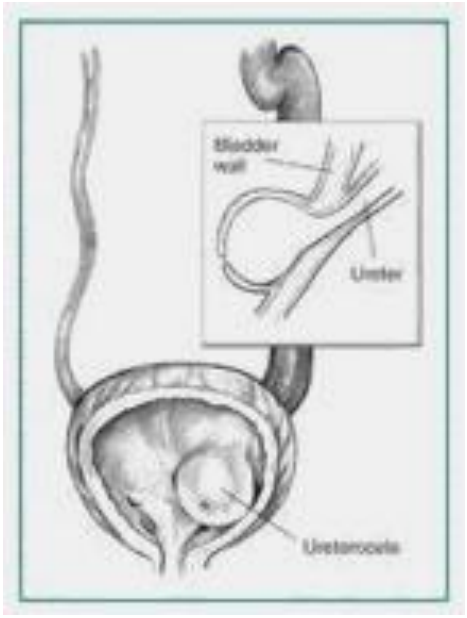

Figure (4): Example of a left sided ureterocele.

Treatment of ureteroceles is guided by clinical presentation and kidney function. Infants and children presenting with urosepsis are initially treated with endoscopic incision of the ureterocele to drain it and relieve obstruction. Ureteroceles draining nonfunctioning upper pole moieties can be treated by removal (heminephrectomy and ureterectomy) and the ureterocele itself can be removed through open reconstruction. Functioning units can have their drainage systems reconstructed to promote good drainage as needed ***(Peters et al., 2011)***.

Ectopic Ureters

A ureteral orifice is classified as ectopic when it lies caudal to the normal insertion of the ureter on the trigone of the