Review Article

Congenital Anomalies of Kidney and Urinary Tract (CAKUT)-Literature Review

Abstract:

Kidneys as well as urinary tracts are the major excretory organs of the human body and removes waste products of protein metabolism.They also remove surplus water and salts from the blood.Kidneys as well as urinary tracts also important for survival as they are crucial for preserving the fluid-electrolyte balance of the body tissue fluids.The inaccuracies in the embryogenesis of the outflow tractsalong with thekidneys are vulnerable to the environmental endargements and disturb the development throughout gestation.Mutations in the patient with CAKUT are responsible for the chronic renal diseases in the 1st three decades of life.Fetus dose not survive in severe cases of CAKUT as a result of non formation of kidneys and outflow tract, but in less severe cases there are more chances to survive and may identified in adulthood.Though the critical cases of CAKUT are infrequent, marginal nephron number is considerablyfrequent disorder exerting its effect on renal functions with increasing age.

Congenital anomalies of kidney and urinary tract have a wide range ofabnormalities inclusive offatalagenesis of both the kidneys andasymptomatic ectopic kidneys.Hence patient with the solitary kidney should follow-up regularly for better and close monitoring.

The clinical presentation of CAKUT along with its long term outcomes and epidemiology is covered in this review.With a comphrehensive knowledge of the roots of CAKUT and marginal nephron numbers, identification of preventive treatment and establishment of clinical guidelines for the patients can be begun.Comphrehension of relevant endangerments and changes in the epidemiological trends especially modified maternal factors and delivery services is vital for prompt detection and prediction of prognosis in the course of pregnancy due to subsequent morbidity and mortality as a result of the presence of CAKUT.

KEY WORDS:neuroblastoma, horse shoe kidneys; Pelviureteric junction obstruction; renal hypodysplasia, antibiotic prophylaxis

Introduction-Congenital anomalies of the kidneys and urinary tracts (CAKUT), which constitute two in ten of the congenital deformities observed in 0.2% of all live births, are disorders attributable to the flaws in renal embryogenesis along with their efflux tracts.

[1,2]Week 3 of the gestation period marks the beginning of the formation of the kidneys and nephrogenesis doesn't stop until 36th week, hence, the kidneys and efflux tracts are vulnerable to environmental endargementsthat disrupt embryogenesis during the course of pregnancy. [1] Several units of heredity incriminate renal embryogenesis as well as mutations are recognized CAKUT patients, the typical cause in the first three decades of life of chronic kidney disease. [1,3] The fetus does not survive in severe cases of CAKUT as a result of non-formation of kidneys whereas there is a chance of survival ,in cases of less severity, with efflux tract plus kidney defects or may be noted in adulthood.[1] It is noted that morbidity from CAKUTs may not be observed up until adulthood hence patients with a solitary kidney should follow up regularly for better and close monitoring, ideally for the entire duration of their life. [4]

Objectives-

1. To find out incidence of CAKUT.
2. To review the available literature on CAKUT

   The study is likely to conclude a hypothesis that CAKUT are common and certain CAKUT may predispose patient's urine to get stagnated which may then lead to infection and renal stone formation.

Epidemiology-Congenital anomalies of kidney and urinary tract (CAKUT)have broad spectrum abnormalities inclusive of bilateral renal agenesis as well as asymptomatic ectopic kidneys [5]. Majority of CAKUT are revealed in the antepartum or immediate postpartum period with a notable part, with severity of variable magnitude, ascertained in the adult population. [5] The sonographic detection reported the prevalence of CAKUT to be between 0.1 to 0.7 %.[6] In cases of live and still born infants, CAKUT incidence rate is 0.03 to 0.16 % and the incidence of non-renal anomalies in infants with CAKUT was noted in 30 % of such cases. By coalescence of CAKUT and non renal anomalies, over 200 syndromes are described.[7] The principal root of end-stage renal disease (ESRD) in pediatric age group is CAKUT which furthermore ensues difficulties of the excretory system as adults like nephrolithiasis,inflammation, high blood pressure, and renal failure.[5]It was concluded, after a thorough investigation of chronic renal disease cases worldwide, that roughly 30-50% of all the cases are due to CAKUT and that hardly any of these anomalies can predispose to adult-onset diseases.[8]

Chevalier RL[4] (2009) elaborated the various parameters that need to be closely monitored in CAKUT patients of paediatric age group. These parameters include diet and nutrition, growth, blood pressure, serum creatinine and proteinuria(microalbuminuria). This may include renal imaging as per the need [4].

Caiulo VA et al[1](2012) observed CAKUT frequency as 0.96% in 171 cases. The prevailing renal abnormality found were vesicoureteralrflux (39), ureteropelvic junction obstruction (33), ectopic kidney (26), renal dysplasia (19) etc[1].

Mnari W et al[9] (2013) stated that CAKUT are a frequent finding in paediatric age group and are a noteworthy root of morbidity in early childhood. Consequently for an accurate diagnosis and appropriate management a better strategy and knowledge of urologic anomalies are crucial.[11]

Santos Junior AC[8] (2014) et alput in a nutshell the plausible tools by which genes in charge of renal embryogenesisare probably responsible fordevelopment of CAKUT.[8]

Simoes AC et al[10](2015) summarized that cases of UTIs were observed more in males (3.7%) in comparison to females (2%). Signs and symptoms of UTI are indifferent, particularly in young children, fever being the solitary symptom.[10]
Vivante A et al[3] (2015) human CAKUT are a result of the mediating of TBX18 transcriptional repression with dominant-negative *TBX18* mutations, thus compromising with the development of unstriated muscle cell in the ureter leading to development of human CAKUT.[3]

Ramanathan S et al[5] (2016) highlighted in their study that congenital anomalies of kidney and urinary tract have several types ofabnormalitiesincludingfatal agenesis of both the kidneys as well as asymptomatic ectopic kidneys

Tain et al[11](2016) stated that CAKUT are linked with many maternal health endangerments.

Vieira M et al[12](2018) ponder that the primary source of chronic renal disease in paediatric population is CAKUT.

Perlman S[13] (2018) deliberated on their findings based on a study group of 83 fetuses: 35 fetuses presented with isolated severe hydronephrosis and 48 with associated CAKUT. The CAKUT group was found linked with an appreciably increased incidence of postnatal need

for surgery (17.6% vs 44.2%, *P* = .014), dysplastic kidney (0% vs 14%, *P* = .023), and total abnormal outcome (52.9% vs 86%, *P* = .001).[13]

Talati AN et al[2] addressed the monogenic origins of CAKUT, affiliated ultrasound features, and reflections for hereditary diagnosis and management,both at antenatal and postnatal levels.[2]

Okoronkwo et al[14](2020) stressed that the incidence of CAKUT is notable. The chief CAKUT were anomalies of the urethra while bladder anomalieswere noted minimally. The paediatricprevelanceofVUR in South African origin is marginalcompared to that offirst world nations. Regular medical follow-up of children with CAKUT should be done to avoid early and late complications.[14]

Wu CH et al[5](2020) stated that extension of *FOXC1* phenotype of pathogenic variants may be employed to explain allelism toward involvement of CAKUT.[15]

Manoharan et al[16] (**2020)** involved screening for anomalies of kidney and urinary tract of asymptomatic first degree relatives of children with CAKUT,familial clustering was pinpointed in 7.9% out of the 138 families (of the index cases) screened.[16]

Murugapoopathy V[21] (2020) discussed clinical presentation, genetic and environmental risk factors for CAKUT.

Embryology-

The excretory system-The development of the excretory system preceeds that of the genital system and includes the kidneys, a pair of ureters, a urinary bladder and a urethra [17].

Kidneys and ureters-The pronephros, mesonephrosandmetanephros are the three structures that come into view. Out of these three,the metanephros is incharge of the development of the permanent human kidney.Theureteric bud via the mesonephric duct and the metanephrogenic cap via the intermediate cell mass of mesenchyme of the lower lumbar and sacral regions are responsible for the development of the metanephros

Ureteric Bud-The protuberance of the mesonephric duct is the ureteric bud.The ureter develops from the ureteric bud and then goes on to expand at its apex thus leading to the formation of the renal pelvis.The major calyces are the branches given off by the renal pelvis and the minor calyces,as well as the collecting tubules,are the branches of the major.

Metanephrogenic Cap- The capsule of the glomerulus, the convolutedtubules(both the distal and proximal) as well as the loops of Henleis a result of the condensation of the metanephrogenic cap about the ureteric bud. The invagination,by a network of capillaries,of the capsule of the glomerulus occurs leading to glomerulusformation.Thecollectingtubule,derivative of the ureteric bud,is joined by both the distal convoluted tubules,derivative of the metanephrogeniccap.The lobulation of the renal surface which is present at the time of birth starts disappearing shortly after.The middle sacral artery,the perpetuation of the aorta in the pelvic region,provides the arterial supply to the developing kidney which is a pelvic organ at first and later makes its way up the posterior abdominal wall. The maturation of the body in the lumbosacral regions and the upright alignment of the curvature are responsible for the 'ascent of the kidneys'.Side-by-side elongation of the ureters takes place.

Progressively superior lateral splanchnic arteries, branches of the aorta, vascularize the kidneys. Level of 2nd lumbar vertebra is the ultimate situation of the kidney. The right side presence of the liver is the reason behind the slight beneath placement of the right kidney in comparison to the left.[25]

With the ascent of the kidney, now only the aorta provides the arterial supply. The most crucial events in the urinary tract embroyological timeline are-

1. End of 5th week-ureteric bud development from the mesonephric duct
2. 6th week-Union of the mesonephros and ureteric bud
3. 6th-7th week-Ascent of the kidneys

Duplication,agenesis or hypoplasiaare a result of any abnormality occurring in the first two stages.Additionally ectopic situation of the kidney or fusion abnormalities are due to any aberrance from the usual order in the third stage.[24]

Congenital anomalies of kidney and urinary tract(CAKUT)- Congenital anomalies of kidneys and urinary tract are classified as seen in the mindmap.

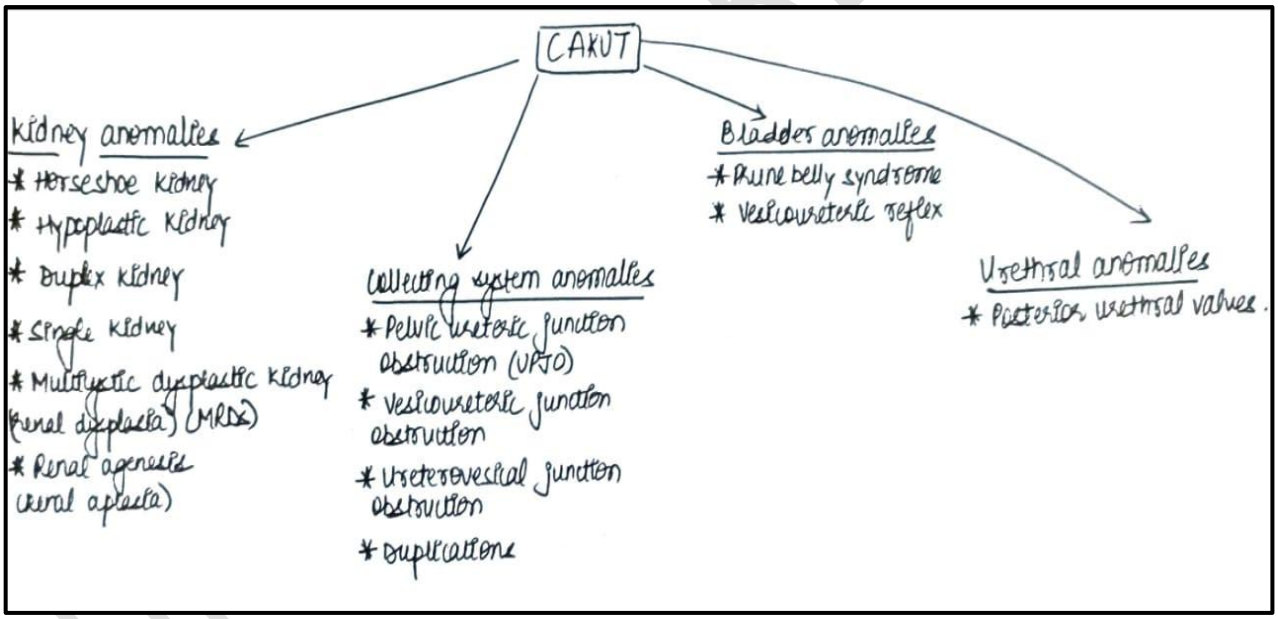
Categorization on the basis of embryology can be made into three broad categories:

- flaw in the development ofthe parenchyma of the kidney;
- deviation from the usual sequence of migration; and

- flaw in collecting system development.[5]

The disturbance in the embryologically expected migration of the kidneys leads to frequent congenital anomalies of the kidney and urinary tract (CAKUT),renal fusion and ectopy. The usual trend observed in paediatric population with these abnormalities is asymptomatic presentation yet some present with symptomsas a result of complications,for example infection, kidney stones, and obstruction of the urinary tract.[18]

Fig1:congenital anomalies of the kidney and urinary tract



Hand drawn mind map [18, 13]

Polycystic Kidney- It can be inherited from by either parent.Itpresents as cysts of congenital origin in the hepatic, pancreatic and pulmonary tissues.There is boundless growth of both the kidneys which are also perforated with numerous cysts.Flawinjoiningofcollecting and immature convoluted tubules lead to this condition.Retention cysts are formed due to urine accumulation in the proximal tubules.

Pelvic Kidney-The arrest in the usual ascent, commonly at the pelvic brim results in pelvic kidney. It may have an asymptomatic presentation with normal functionality. Cases of inflamed presentation -due to its abnormal situation- of an ectopic kidney, are normally a mistaken diagnosis.

Horseshoe Kidney-Horseshoe kidney comes into existence due to the fusion of the caudal ends of the two kidneys during development. The ultimate situation of the kidneys in the lower part of the lumbar region is due to the entrapment of the interconnecting bridge at the back of the inferior mesenteric artery during their ascent from the pelvic region.Infection and calculi formation may be a manifestation of the urinary stasis due to kinking of the pair of ureters in the course of their passage inferiorly over the bridge of tissue of the kidney.This condition may be corrected surgically by dividing the bridge.

Unilateral Double Kidney-Presence of two kidneys on one side with separate blood vessels and ureters is what is popularly known as ‘unilateral double kidney’.The top extremity unites with the bottom extremity and ureteric bud on one peripherytraverses the centerlineat the time of itsascend,of a kidney of normal situation. Kinking of the ureter results in urinary stasis and thus the need for surgical intervention.

Rosette Kidney- Union of the twokidneys takes place at their hilum and are found situated in the pelvis. They jointly form a rosette which is a result of the perfusion of the pair of ureteric buds.

Supernumerary Renal Arteries-They are comparatively frequent, noted as resolutefetal renal arteries originating in an orderfrom the aorta for the vascularization of the kidney during its ascent from its pelvic situation.They may ultimately result in a condition known as hydronephrosis which is a dilatation of the pelvis as well as the calyces due to urinary stasis as a manifestation of the crossing of the pelvi-ureteral junction by a supernumerary artery.Hence this anomaly draws clinical attention.

Double Pelvis-Generally unilateral,this anomaly is due to partition of the ureteric bud before time close to its termination.The drainage of the upper cluster of calyces is taken up by the upper pelvis and that of the middle and lower clusters by the lower pelvis,lower being larger in comparison to the upper pelvis.

Bifid Ureter-The pair may unite in the lower one-third of their route or may openvia a common opening into the bladderor may open as individual entities into the bladder (Figure 1).In the last-mentioned scenario,one passes over the other paving the way to urinary obstruction. The division of the ureteric bud before time is the reason behind the existence of bifid ureter.On radiological investigations,there exists a mere chance of spotting dual number of ureters and ureters.The likelihood of a bifid ureter becoming infected orbe the site of stone formation is more than that of a normal ureter.

Megaloureter-It may present with laterality, uni or bi, and with total absence of motility with an idiopathic cause. The ureter becomes prone to infection due to accumulation of urine. Surgical intervention of the speciality of plastic surgery, is crucial to revamp drainage rate

Postcaval Ureter-Obstruction of the right ureter by the inferior vena cava in case of the former's ascent posterior to the latter. The preferred treatment is surgical intervention by rerouting of the ureter along with re-implantation of the distal end into the bladder. The impact of environmental as well as epigenetic variables on natural history of CAKUT together with renal development is held up by several studies,thus drawing the conclusion of multifactorial pathogenesis of this syndrome.[13]

Detection of CAKUT-CAKUT are variable thus may show their effects on the kidney(s) alone and/or the lower urinary tract making radiological intervention indispensable.The assessment of children with a urinary tract abnormality query is clarified by the employmentUltrasonography (US),best suited modality for this purpose.The evaluation of the anatomy and abnormalities of the bladder and urethra is done using Voiding cystourethrography (VCUG) which in turn also determines which additional examinations are needed: intravenous urography (IVU), CT scan or MR imaging. One of the most crucial diagnostic tools in the assessment of neonates with hydroureteronephrosis is 99mTc-DTPA dynamic renal scintigraphy.[13]The principalradiological modalities employed in the detection of various CAKUT are ultrasonography,magnetic resonance imaging and computed tomography.[5]The majority of CAKUT are spotted by routine antenatal ultrasonography in gestational period.[6]An outstanding predictor of abnormal fetal renal function and CAKUT is

oligohydramnios at or after the 20th week of the duration of pregnancy.[6]Illustration of fetalurinary system from early second trimester is permitted by antenatal screening ultrasonography (US) which also ascertains numerousprincipal congenital anomalies of the urinary system.[5] Evaluation of the size, existence and situation of both kidneys and the assessment of their form and echogenicity, scrutiny of fetal bladder, external genitalia and the amount of amniotic fluid is reported in the ultrasound examination of the normal urinary tract. Thickened bladder, hydronephrosis,hydroureter, renal agenesis,small or dysplastic kidney and cystic kidney are some of the abnormalities detected in antenatal US. Antepartum identification of renal abnormalities calls for postpartum renal ultrasound shortly after birth which is to repeated at 4-6 wk of age as well as a physical examination.[5]To keep track of compensatory renal growth of unaffected kidneys in cases of unilateral CAKUT, progressive hydronephrosiswith mild/moderate obstructive uropathy, or changes in the affected kidneys serial ultrasounds are employed.[6]Therefore, it is essential to have prompt diagnosis and management, whether medical or surgical, to reduce renal damage and to avert or delay end-stage renal damage. Prompt diagnosis, follow-up,detection of complications ,surgical planning, and associated renal and extra renal malformations is made via radiological imaging.[5]

Implication-The review of literature will help in determining if some patients with certain CAKUT are predisposed in future for renal stone formation. This will ensure appropriate measures to be taken before any pathology develops. This may assist in better management of such cases at an earlier stage with proper medical intervention and consequently may help in prevention of complications like pyelonephritis, hydronephrosis, CRF etc.

Firstly,theepidemiology,its clinical presentation of CAKUT,andthe outcomes that follow in the long run are talked about followed by the endargerments for CAKUT, including participation of hereditary and environmental factors.Marginalnephron number is a by far morefrequentdisorder,despite severe CAKUT being rare,with its ramifications on renal function more and more apparent as a person ages. With the thorough knowledge of the roots of CAKUT and marginal nephron number, identification ofprophylaxis and establishment of clinical guidelines for follow up of these patients can be begun.Understanding of changes in epidemiological trends and relevant endangerments,specifically mutable maternal factors, is emphasized upon for prompt detection and prophecy of prognosis in pregnancy because the presence of CAKUT brings with it implications for ensuing morbidity and mortality. Maria

M Rodriguez[19] (2014) reviewed majority of CAKUT and described congenital renal anomalies and analyzed therapeutic interventions. Ishiwa Sho et al[20] (2019) observed HNF1β gene mutation in most of the patients with hypodysplastic kidney with multicystic dysplastic kidney.

Conclusion-Prompt diagnosis is the need of the hour in hand-picked anomalies to reduce renal damage, avert or slow down the inception of end stage renal disease (ESRD), and delivernurturing care to keep complex ramifications of ESRD at arm's length.However, literature lacks in knowledge about the contribution of congenital urinary tract malformations to chronic kidney disease and consequent renal failure in CAKUT patients as there are gaps in the comprehension of the genomics of the lower urinary tract development.As the inaccuracies in the embryogenesis of the outflow tracts and kidneys are vulnerable to the environmental factors that disturb the development throughout the gestation and mutation with the CAKUT are responsible for chronic,end stage renal diseases and stone formation;the need for better comprehension more environmental parameters should be studied in large number of cases.

References-

1. Caiulo VA, Caiulo S, Gargasole C, Chiriacò G, Latini G, Cataldi L, Mele G. Ultrasound mass screening for congenital anomalies of the kidney and urinary tract. Pediatric nephrology. 2012 Jun 1;27(6):949-53.
2. Talati AN, Webster CM, Vora NL. Prenatal genetic considerations of congenital anomalies of the kidney and urinary tract (CAKUT). Prenatal diagnosis. 2019 Aug;39(9):679-92.
3. Vivante A, Kleppa MJ, Schulz J, Kohl S, Sharma A, Chen J, Shril S, Hwang DY, Weiss AC, Kaminski MM, Shukrun R. Mutations in TBX18 cause dominant urinary tract malformations via transcriptional dysregulation of ureter development. The American Journal of Human Genetics. 2015 Aug 6;97(2):291-301.
4. Chevalier RL. When is one kidney not enough?. Kidney international. 2009 Sep 1;76(5):475-7..
5. Ramanathan S, Kumar D, Khanna M, Al Heidous M, Sheikh A, Virmani V, Palaniappan Y. Multi-modality imaging review of congenital abnormalities of kidney and upper urinary tract. World journal of radiology. 2016 Feb 28;8(2):132.

6. Waters AM, Rosenblum ND, Mattoo TK, Baskin LS, Kim MS. Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT).
7. Rosenblum ND, Baskin LS. Overview of congenital anomalies of the kidney and urinary tract (CAKUT). Waltham (MA): UpToDate. Available at: http://www.uptodate.com/contents/overview-of-congenital-anomalies-of-the-kidney-and-urinary-tract-cakut. July 2015; 17.
8. Santos Junior AC, de Miranda DM, Simões e Silva AC. Congenital anomalies of the kidney and urinary tract: an embryogenetic review. Birth Defects Research Part C: Embryo Today: Reviews. 2014 Dec;102(4):374-81.
9. Mnari W, Bouabidi S, Zrig A, Mezri M, Badii H, Salem R, Golli M. Congenital anomalies of the kidney and urinary tract (CAKUT). How to proceed for diagnosis?. European Congress of Radiology-ECR 2013.
10. Simoes AC, Oliveira EA. Update on the approach of urinary tract infection in childhood. Jornal de Pediatria (Versaoemportuguês). 2015 Nov 1;91(6):S2-10.
11. Tain YL, Luh H, Lin CY, Hsu CN. Incidence and risks of congenital anomalies of kidney and urinary tract in newborns: A population-based case–control study in Taiwan. Medicine. 2016 Feb;95(5).
12. Vieira M, Ferreira A, Nolasco F. Congenital kidney and urinary tract anomalies: a review for nephrologists. Portuguese Journal of Nephrology & Hypertension. 2018 Dec;32(4):362-8.
13. Perlman S, RoitmanL, Lotan D, Kivilevitch Z, Pode-Shakked N, Pode-Shakked B, Achiron R, Dekel B, Gilboa Y. Severe fetal hydronephrosis: the added value of associated congenital anomalies of the kidneys and urinary tract (CAKUT) in the prediction of postnatal outcome. Prenatal diagnosis. 2018 Feb;38(3):179-83
14. Okoronkwo, Nneka&Mudi, Abdullahi& Levy, Cecil &Khumalo, Tholang&Moonsamy, Glenda. (2020). Congenital anomalies of the kidney and the urinary tract in a South African paediatric nephrology setting. South African journal of child health. 4. 34-39. 10.7196/SAJCH.2020.v14.i1.01666.
15. Wu CH, Mann N, Nakayama M, Connaughton DM, Dai R, Kolvenbach CM, Kause F, Ottlewski I, Wang C, Klämbt V, Seltzsam S. Phenotype expansion of heterozygous FOXC1 pathogenic variants toward involvement of congenital anomalies of the kidneys and urinary tract (CAKUT). Genetics in Medicine. 2020 Oct;22(10):1673-81.

16. Manoharan A, Krishnamurthy S, Sivamurukan P, Ananthakrishnan R, Jindal B. Screening for renal and urinary tract anomalies in asymptomatic first degree relatives of children with congenital anomalies of the kidney and urinary tract (CAKUT). The Indian Journal of Pediatrics. 2020 Mar 20:1-6.

17. Moore, K. L., Persaud, T. V. N., &Torchia, M. G. (2016). *The developing human: Clinically oriented embryology* (10th edition.). Philadelphia, PA: Elsevier.
18. Carachi, Robert & Doss, Sameh. Clinical Embryology An Atlas of Congenital Malformations: An Atlas of Congenital Malformations. 2019; 10.1007/978-3-319-26158-4.
19. Rodriguez MM. Congenital Anomalies of the Kidney and the Urinary Tract (CAKUT). Fetal Pediatr Pathol. 2014 Oct-Dec;33(5-6):293-320. doi: 10.3109/15513815.2014.959678. Epub 2014 Oct 14. PMID: 25313840; PMCID: PMC4266037.
20. Ishiwa S, Sato M, Morisada N, Nishi K, Kanamori T, Okutsu M, Ogura M, Sako M, Kosuga M, Kamei K, Ito S, Nozu K, Iijima K, Ishikura K. Association between the clinical presentation of congenital anomalies of the kidney and urinary tract (CAKUT) and gene mutations: an analysis of 66 patients at a single institution. Pediatr Nephrol. 2019 Aug;34(8):1457-1464. doi: 10.1007/s00467-019-04230-w. Epub 2019 Apr 1. PMID: 30937553.
21. Murugapoopathy V, Gupta IR. A Primer on Congenital Anomalies of the Kidneys and Urinary Tracts (CAKUT). Clin J Am Soc Nephrol. 2020 May 7;15(5):723-731. doi: 10.2215/CJN.12581019. Epub 2020 Mar 18. PMID: 32188635; PMCID: PMC7269211.