THE VALUE OF PERINATAL AUTOPSY IN THE EVALUATION OF GENITOURINARY AND ANORECTAL MALFORMATIONS

DISSERTATION

SUBMITTED FOR

M.D. in PATHOLOGY

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY, CHENNAI

DEPARTMENT OF PATHOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES& RESEARCH

PEELAMEDU, COIMBATORE- 641 004

TAMILNADU, INDIA

Certificates

CERTIFICATE

This is to certify that the dissertation work entitled **"THE VALUE OF PERINATAL AUTOPSY IN THE EVALUATION OF GENITOURINARY AND ANORECTAL MALFORMATIONS"** submitted by **Dr. D. Pavithra,** is a bonafide work done by her, during the post-graduation study period in the department of Pathology of PSGIMS & R, from June 2017 to April 2020. This work was done under the guidance of **Dr. G. Umamaheshwari,** Associate Professor, Department of Pathology, PSGIMS & R.

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CERTIFICATE

This is to certify that this dissertation work entitled **"THE VALUE OF PERINATAL AUTOPSY IN THE EVALUATION OF GENITOURINARY AND ANORECTAL MALFORMATIONS"** submitted by **Dr. D. Pavithra,** with registration Number **201713401** to The Tamilnadu Dr MGR Medical University, Chennai, for the award of **Doctor of Medicine in Pathology,** is a bonafide record of research work carried out by her under my guidance. The contents of this dissertation, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma.

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DECLARATION

I, **Dr. D. Pavithra,** do hereby declare that the thesis entitled **"THE VALUE OF PERINATAL AUTOPSY IN THE EVALUATION OF GENITOURINARY AND ANORECTAL MALFORMATIONS"** is a bonafide work done by me under the guidance of Dr G. Umamaheswari, Associate Professor, in the Department of Pathology, PSG Institute of Medical Sciences &Research. This study was performed at the PSG Institute of Medical Sciences & Research, Coimbatore, under the aegis of the The Tamilnadu Dr MGR Medical University, Chennai, as part of the requirement for the award of the MD degree in Pathology.

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Ref: Project No. **17/3**26

Date: October 14, 2017

Dear Dr Pavithra,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 12.10.2017 for approval of case report entitled "*Uncommon cause of paediatric alopecia*" in the IHEC meeting held on 13.10.2017.

The following documents were reviewed and approved:

1. IHEC Submission form
2. Case description
3. Confidentiality statement
4. Informed consent
5. Current CVs of Principal investigator, Co-investigators

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 13.10.2017 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr D Vijaya (Member – Secretary, IHEC)	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes
3	Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr Sudha Ramalingam	MD	Epidemiologist, Ethicist Alt. member-Secretary	Female	Yes	Yes
5	Dr G Subhashini	MD	Epidemiologist	Female	Yes	Yes

The case report is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of the study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

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Dear Dr Pavithra,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 29.11.2017 to conduct the research study entitled *"The value of perinatal autopsy in the evaluation of genitourinary and anorectal malformations"* during the IHEC meeting held on 22.12.2017.

.The following documents were reviewed and approved:

1. Project submission form
2. Study protocol (Version 1 dated 29.11.2017)
3. Application for waiver of consent
4. Confidentiality statement
5. Data collection tool (Version 1 dated 29.11.2017)
6. Permission letter from concerned Heads of Department
7. Current CVs of Principal investigator, Co-investigator
8. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 22.12.2017 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

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https://www.researchgate.net/publication/43130498_Spinal_dysraphism_with_anorectal_malformation_lumbosacral_magnetic_resonance_imaging_evaluation_of_120_patients
https://www.researchgate.net/publication/11046308_Urorectal_septum_malformation_sequence_Insights_into_pathogenesis

Instances where selected sources appear:

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Introduction

INTRODUCTION

The word autopsy means “a seeing with one’s own eyes” which is derived from Greek word[1]. The more familiar term is “post mortem examination” which includes the inspection and dissection of body after death to determine the cause of death[1]. Human embryo after eighth week of gestation is called as foetus. When the autopsy is being done on foetus or a neonate its termed as perinatal autopsy. The most common indications for perinatal autopsy includes termination of pregnancies for anomalies, intrauterine foetal demise and inevitable abortion[1].

Intrauterine death or still birth is the major indicator of perinatal mortality, pregnancy wastage and there by tells about the quality of health care in the community[2].

Urogenital and anorectal malformations is one of the commonest congenital anomaly and are seen only next to the anomalies of central nervous system and cardiovascular system. It is extremely heterogenous with diverse etiology and often present with other associated congenital anomalies or as a part of a genetic syndrome. Although imaging studies has an important role in diagnosing these disorders prenatally, foetal autopsy has a major contribution. It has a vital role in identifying the exact defect, its etiopathogenesis with cause analysis and its associated other congenital

anomalies. Susceptibility of genetic syndrome or chromosomal aberrations can also be identified by foetal autopsy.

Foetal autopsy has a crucial role in confirming the congenital anomalies documented by the antenatal sonographic reports. It aids in giving additional information regarding the anomalies which could have been missed by antenatal ultrasound, thereby leads to assignment of syndromes and sequences. It also guides for further genetic testing and counseling[3].

The clinician can be benefited by knowing the cause of death and to take further actions for safe confinement of future pregnancies. By giving proper explanation to the parents, we can facilitate the progress of grieving and planning for future pregnancies.

The perinatal autopsy gains more importance nowadays because autopsy can provide a new diagnosis or can change the clinical diagnosis[1]. Some of the soft tissue abnormalities can be missed by sonography which could have been picked up by foetal autopsy, thus providing additional secondary diagnosis which was unexpected clinically that would lead to a change in management or counseling[3].

Our ultimate aim is to detect the cause of death which includes investigations comprising of foetal autopsy, placental examination and genetic studies including karyotyping[1]. Thus in spite of modern antenatal

diagnostic modalities, foetal autopsy plays an important role in confirming the diagnosis, delineating a spectrum of anomalies and helps in embryological understanding.

Aims and Objectives

AIMS AND OBJECTIVES

1) To emphasize the role of foetal autopsy in urogenital and anorectal malformations
2) To analyse the gross and microscopic examination of these foetuses with its placental findings.
3) To categorize the structural abnormalities and to explore the associated multi system manifestations of urogenital and anorectal anomalies.
4) To correlate the final autopsy findings with prenatal ultrasound features of these foetuses.

Review of Literature

REVIEW OF LITERATURE

Among all the congenital malformations, one third anomalies are seen in urogenital system. They are a part of complex multisystem anomalies both chromosomal and non chromosomal, either syndromic or in casual combination[4].

Urorectal septum malformation sequence (URSM) is a rare congenital anomaly that occurs due to abnormal urorectal septum during embryogenesis. It includes a spectrum of malformations involving urogenital system and gastrointestinal tract[5]. The caudal end of mesoderm gives rise to many structures of lower gastrointestinal and urogenital system. When there is a defect in the caudal end of mesoderm the urorectal septum fails to fuse with cloacal membrane there by an abnormal urorectal septum is formed and leading to variety of malformations[3].

The most severe type in this spectrum is complete URSMS, intermediate type is partial URSMS including urogenital sinus and the mild type is anterior anal canal due to urorectal hypoplasia[3]. Cloacal dysgenesis syndrome, female pseudohermophroditism with caudal dysgenesis are some of the alternative names used for urorectal septum malformation sequence[3].

EPIDEMIOLOGY :

In world wideurorectal septum malformation sequence has an incidence of 1 in 50000 to 250000 neonates[5]. In south west india the incidence of urorectal septum malformation sequence is 1 in 60000 live births[6]. The prevalence of partial urorectal septum malformation sequence was estimated to be 2.8 per 100000 total births (1 in 35000 live births)[7]. Anorectal anomalies has a prevalence of 1.9 per 100000 total births[7].

The prevalence of anorectal malformation is 1 in 5000 live births with male preponderance, one third being isolated and remainder associated with other congenital abnormalities[8,9]. Cloacal anomalies are seen in 1 in 35000 to 250000 live births[10]. Renal anomalies constitute approximately 17% of all anomalies diagnosed prenatally[11]. VACTERL ASSOCIATION had an incidence of 1 in 10000 to 1 in 40000 live born infants[12].

HISTORY:

The term urorectal septum malformation sequence was first described by Rocheus in 1542[13,14]. The synonyms of urorectal septum malformation sequence are caudal dysgenesis, caudal dysplasia, sacral agenesis, sacral dysplasia, caudal spinal aplasia or agenesis and lumbosacral agenesis.

Complete urorectal septum malformation sequence was first described by Escobar in 1987[3].

The term partial urorectal septum malformation sequence was first defined by Wheeler and Weaver to describe a distinct phenotype between complete urorectal septum malformation sequence which has no opening, persistent urogenital sinus that has two openings and anterior anus having three openings[7]. Partial urorectal septum malformation sequence is also called as persistent cloaca in females[7].

Cloacal abnormalities are described in humans 300 years ago[15]. The word cloaca is derived from latin word for sewer or drain[35].

EMBRYOLOGY:

UROGENITAL SYSTEM:

The urogenital system is divided functionally into urinary system and genital system. But anatomically and embryologically the two systems are intimately interwoven[4]. Because they develop from common mesodermal ridge (intermediate mesoderm) along the posterior part of abdominal cavity. The excretory ducts of both urinary and genital system enter a common cavity called cloaca[4]. Severe bilateral abnormalities are seen in second trimester by the time of routine fetal anomaly scan done at 20 weeks[11].

URINARY SYSTEM[16]:

Three kidney systems are formed in a cranial to caudal sequence in the intrauterine life. They are

1) Pronephros

2) Mesonephros

3) Metanephros

PRONEPHROS :

At the beginning of fourth week of intrauterine life 7 to 10 solid cell groups in cervical region forms pronephros. They form nephrotomes which are vestigeal excretory units. By the end of fourth week all pronephric systems disappear.

MESONEPHROS :

The mesonephros and mesonephric ducts are formed from intermediate mesoderm derived from upper lumbar (L3) segments. By the time the regression of pronephros is occurring, the first excretory tubules ofmesonephros starts appearing. They increase in their length and form a s shaped loop, acquire tuft of capillaries which forms the glomerulus at medial extremity. Around the glomerulus the bowmans capsule is formed by tubules which together forms renal corpuscle. Laterally tubule enter the collecting duct is called as mesonephric duct or wolffian duct.

In the middle of second month an ovoid organ is formed by mesonephros on either side of midline. The ridge formed by both organs is called as urogenital ridge. The cranial tubules and glomeruli show degenerative changes and many have disappeared whereas the caudal tubules are still differentiating.

By the end of second month the caudal tubules and mesonephric duct persist in males and participate in formation of genital system. But in females it completely disappears.

METANEPHROS (THE DEFINITIVE KIDNEY):

During the fifth week metanephros develops from metanephric mesoderm. By eighth week the kidneys ascend to the lumbar region.

COLLECTING SYSTEM:

Collecting ducts develop from ureteric bud, which is outgrowth of mesonephric duct near its entrance into the cloaca. The bud penetrates metanephric tissue, dilates and forms primitive renal pelvis[16]. This divides into cranial and caudal portions, the major calyces.

Each calyx forms two buds during the penetration of metanephric tissue. The bud divide subsequently until 12 or more generations of tubule have formed. Till the end of fifth month more tubules are formed at the

periphery. The second generation tubules enlarge and absorb the third and fourth generation and forms minor calyces of renal pelvis. Subsequently during further development collecting tubules of the fifth and successive generations elongate and converge on minor calyces forming the renal pyramid.

Thus ureter, renal pelvis, major and minor calyces and 1 to 3 million collecting tubules develop from ureteric bud.

EXCRETORY SYSTEM:

The newly formed collecting tubules are covered by metanephric tissue cap at its distal end. The cells of tissue cap forms small vescicles called renal vescicles which give rise to small s shaped tubules[4]. At one end of s capillaries grow into pocket and differentiate into glomeruli. The tubules along with glomeruli constitute nephrons or excretory units.

The proximal end of nephrons forms bowmans capsule, indented by glomerulus. The distal end is connected to one of collecting tubules. The lengthening of collecting tubules results in the formation of loop of Henle and tubules including both proximal and distal convoluted tubules.

Thus kidney develops from

1) Metanephric mesoderm which give rise to excretory units
2) The ureteric bud which forms collecting system

Urine production starts soon after differentiation of the glomerular capillaries by tenth week. There are approximately 1 million nephrons in each kidney at birth. Corticomedullary differentiation takes place with increasing gestation and renal pelvis and calyceal pattern can be identified[18].

DEVELOPMENT OF URETER:

Ureter develops from the ureteric bud situated between the pelvis of kidney and the vesicourethral canal.

DEVELOPMENT OF BLADDER AND URETHRA[17]:

During fourth to sixth week the cloaca divides into urogenital sinus anteriorly and anal canal posteriorly. Between them is a layer of mesoderm forming the urorectal septum. The tip of septum forms perineal body.

Three portions of urogenital sinus are identified

1) The upper and largest part – urinary bladder
2) The narrow canal – pelvic part of urogenital sinus
3) The last part – phallic part of urogenital sinus

Initially bladder is continuous with allantois, later lumen of allantois is obliterated, then a thick fibrous cord called urachus connects apex of bladder to umbilicus. In adult this forms median umbilical ligament. The pelvic part of urogenital sinus gives rise to prostatic and membranous part of urethra in males. The phallic part of urogenital sinus is flattened from side to side and it is pushed ventrally as the genital tubercle grows.

During the differentiation of cloaca the caudal part of mesonephric ducts are absorbed into the wall of urinary bladder. The ureters which outgrowths from mesonephric ducts enter the bladder separately. When the ascend of kidney occurs, the ureteric orifice is pushed cranially and mesonephric ducts become close to each other to enter prostatic urethra. It forms ejaculatory ducts in males. Both ureters and mesonephric ducts originate from mesoderm, the mucosa of bladder formed by invagination of ducts (the trigone of bladder) is also mesodermal. With further growth the trigone is replaced by endodermal epithelium.

The urethral epithelium in both sexes are endodermal in origin. But surrounding connective tissue and smooth muscle are mesodermal in origin. By the end of third month prostatic urethral epithelium begins to proliferate and forms many outgrowths which penetrates the surrounding mesenchyme. These buds form prostate gland in males. Urethral and paraurethral glands are formed in females.

GENITAL SYSTEM:

Sex differentiation is mainly based on sex determining region on Y chromosome. The testis determining gene called SRY (sex determining region on Y) is located on short arm (yp11). The protein product of this gene initiates a cascade of genes and determines the fate of rudimentary sexual organs. When SRY protein is present the sex is male, in its absence the sex is female.

GONADS :

Initially a pair of longitudinal ridge called genital ridge or gonadal ridge is formed by proliferation of epithelium and condensation of mesenchyme. By sixth week the germ cells appear in the genital ridge.

In third week the primordial germ cells originated from epiblast which reside among endodermal cells in yolk sac.

During fourth week they move to dorsal mesentry of hindgut. By fifth week they reach the primitive gonads and invades the genital ridge by sixth week. If there is failure to reach the ridges gonads does not develop. Just before the arrival of primordial germ cells the genital ridge epithelium proliferates and penetrate the underlying mesenchyme and form primitive sex cords.

EMBRYOLOGY OF URORECTAL SEPTUM:

Two theories are considered to explain the differentiation of the hindgut in to urogenital (ventral) and anorectal (dorsal) parts[19]. They are

1) The theory of the septation of the cloaca
2) The theory of the migration of the rectum

Development of hindgut:

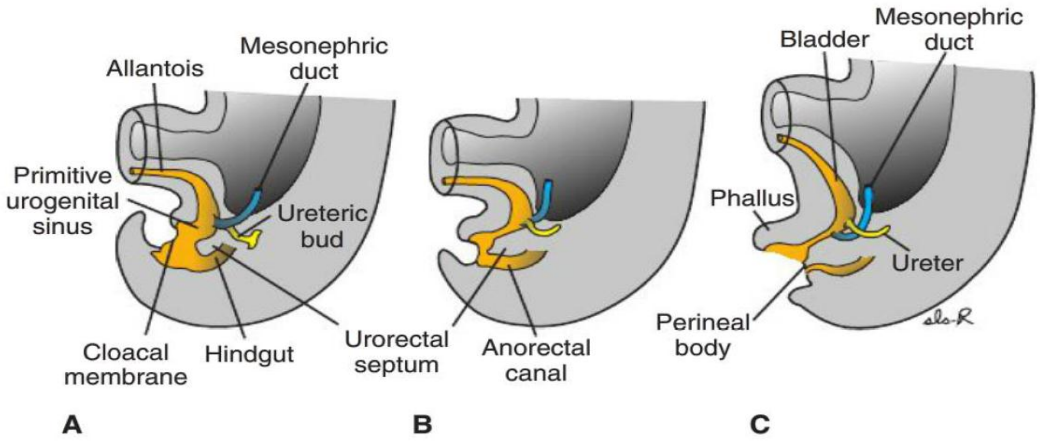
Hindgut is the structure which is the continuity of the midgut cranially. Caudally it forms cloacal membrane and is in contact with ectoderm. Between fourth and sixth week of gestation the primitive hindgut and the allantois enter in to the cloaca[19]. The urorectal septum is formed by a coronal sheet of mesenchyme which divides the primitive cloaca in to dorsal and ventral parts. The urorectal septum is separated from the amniotic cavity by the cloacal membrane.

By the end of seventh week the cloaca is divided in to ventral part (the urogenital sinus) and dorsal part (the rectum and proximal anal canal) as shown in Figure 1. The tip of the urorectal septum becomes the perineal area. The urogenital sinus divides in to vesicourethral canal and definitive urogenital sinus[20]. The vesicourethral canal forms the bladder and definitive urogenital sinus forms the prostate urethra and phallus. The mesonephric

duct is gradually absorbed into the wall of the urogenital sinus and the ureters enter separately.

Figure 1[16]: Division of cloaca into the urogenital sinus and anorectal canal.

A - 5 weeks; B - 7weeks; C - 8weeks;



The cloacal membrane ruptures by apoptosis producing two orifices in perineum. One is urogenital on ventral side and other is anus on dorsal side. Also by the end of seventh week a secondary occlusion of anorectal canal occurs by the formation of epithelial plug and by the adhesion of the walls[20].

By the end of eighth week thin secondary closed anal orifice ruptures and recanalises by apoptosis[20].The migration of the rectum takes place during normal development from high position to the normal area of anal opening[19].

In 1986 Vander putte modified the theory of rectal migration. He speculated that there is shift of dorsal cloaca. This shift brings cloaca to the area of tail groove and forms the future anal opening[19].

To summarise, by the end of fourth week cloaca develops. By sixth week embryonic cloaca is divided in to ventral urogenital sinus and dorsal hindgut. By the end of sixth week urorectal septum is formed completely. By twelveth week anal canal, vaginal and urethral openings are formed.

The cloacal mesenchymal cells are playing important role in expressing intrinsic regulators to balance the epithelial cell death (apoptosis), cell growth and maturation which are essential in the process of cloacal separation[21].

Defects are seen when there is anomalies of cloacal development. When there is extroversion of cloaca (ectopia cloaca) no urorectal septum is formed. Feature of mesenchymal migration around ventral body to support umbilicus. Thus large abdominal defect with central colonic component and bilateral bladder components are formed.

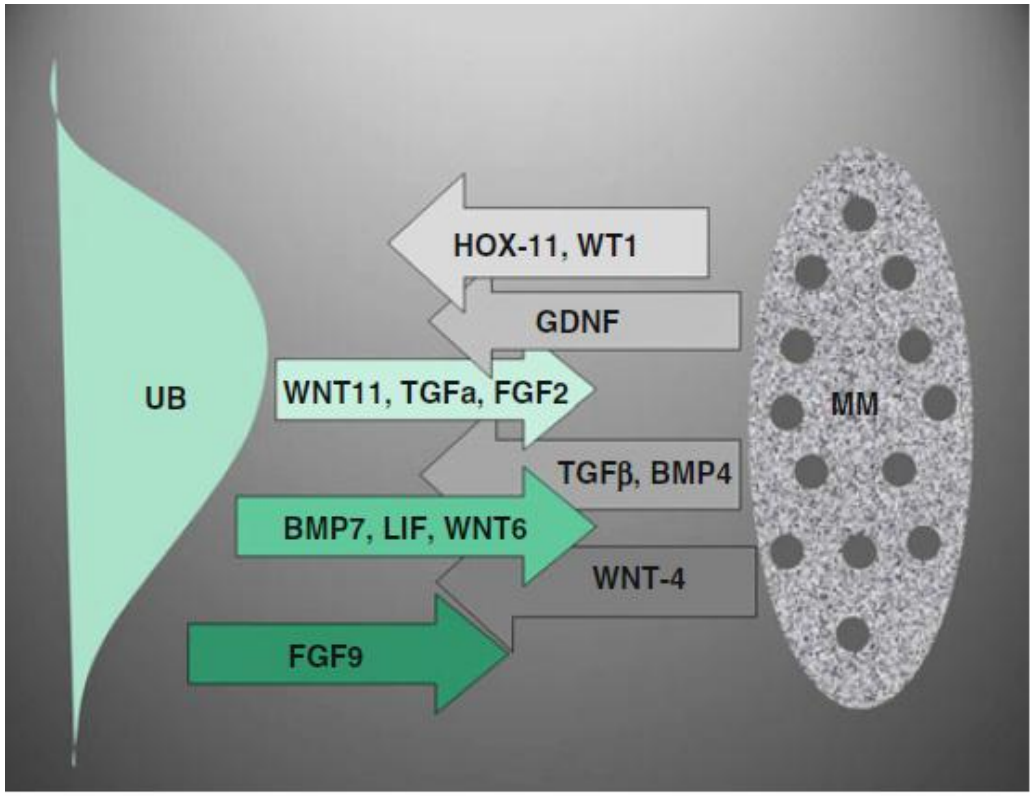
When partial development of urorectal septum occurs urogenital sinus remains high confluence of bladder, vagina and rectum. The cloacal membrane would have been abnormally elongated or prematurely ruptured before the formation of urorectal septum.

The cloacal mesenchymal cells are playing important role in expressing intrinsic regulators to balance the epithelial cell death (apoptosis), cell growth and maturation which are essential in the process of cloaca separation[22].

PATHOGENESIS[23] :

The understanding of signaling pathways between the metanephric mesenchyme and ureteric bud is necessary to know about the fetal renal diseases (Figure 2)[23].

Figure 2: Signaling pathways between UB &MM



UB - ureteric bud; MM - metanephric mesenchyme

The formation of metanephric kidney is initiated by the expression of two sets of transcription factors HOX11 and WT1 in metanephric mesenchyme to respond to the ureteric bud. Another signal GDNF (glial cell line derived neurotrophic factor) is also expressed from metanephric mesenchyme. Those lacking GDNF dies of renal agenesis.

The ureteric bud responds by expressing WNT 11 there by ureteric bud enters the metanephric mesenchyme and grows as well as secretes FGF2 and BMP7 (bone morphogenic protein 7) for preventing apoptosis of metanephric mesenchyme. Leukemic inhibitory factor (LIP) and WNT6 from ureteric bud induces mesenchymal cell aggregation and convert it in to epithelium. Leukemic inhibitory factor acts in the presence of FGF2 only where as WNT6 is FGF2 independent. After the metanephric mesenchyme induction the cells start condensing and secretes WNT4 which is essential for transcription of mesenchyme into epithelium. Two other proteins polycystin 1 and 2 are also essential in converting the aggregated cells in to nephrons.

Ureteric bud branching is regulated by four molecules from metanephric mesenchyme. They either act as agonist or antagonist for adequate progression of branching.

1. GDNF (glial cell line derived neurotrophic factor) regulates initial and secondary buds

2. TGF B1 acts as antagonist and stabilizes the branch by promoting the synthesis of extracellular matrix proteins and inhibiting metallo proteinases which digest the matrices.
3. BMP4 acts as antagonist by restricting the branching
4. Collagen xviii is needed for specificity of branching pattern and is found on branches of kidney not on tips.

ANOMALIES INVOLVING THE KIDNEY AND URINARY TRACT:

Congenital anomalies of kidney occurs at frequency of 3-6/1000 live births[24]. CAKUT is a wide spectrum including renal agenesis, renal hypo/dysplasia, multicystic kidney dysplasia, duplex renal collecting system, ureteropelvic junction obstruction, megaureter, posterior urethral valve and vesicoureteral reflux[24].

HORSE SHOE KIDNEY[25]:

This is the commonest fusion abnormality. When the ureteric buds are more medially located or if inducible metanephric mesenchyme is continuous at lower pole then a fused horse shoe kidney is developed. It is placed at a lower level than normal kidneys.

CROSSED FUSED RENAL ECTOPIA[25]:

Crossed fused renal ectopia is a positional anomaly which occurs when the kidney crosses the midline and gets fused with the opposite kidney.

ECTOPIC KIDNEY:

When the location of kidney is in pelvis and not in usual position it is ectopic kidney. This is seen in chromosomal aneuploidies.

RENAL AGENESIS:

Unilateral renal agenesis is more common in males. It occurs at an incidence of 1/1000 live births[26]. In bilateral renal agenesis both kidneys and ureters are absent. The incidence is 1/3000 to 1/4000 live births[26]. The reason for agenesis is either failure of ureteric bud development or metanephric mesenchyme unable to respond to ureteric bud stimulation.

RENAL APLASIA:

It is extreme renal hypoplasia where only tiny remnants of renal tissue is seen.

RENAL CYSTIC MALFORMATIONS:

CLASSIFICATION OF CYSTIC RENAL DISEASES[26]

1. Polycystic disease
    A) Autosomal recessive polycystic kidney disease(ARPCKD)
        I) Classic infantile polycystic disease
        II) ARPCKD and congenital hepatic fibrosis in older individuals
    B) Autosomal dominent polycystic kidney disease (ADPCKD)
        I) Classic adult polycystic disease
        II) ADPKD in infants (glomerulocystic disease)
2. Glomerular cystic disease
3. Localized cystic disease
4. Renal cysts associated with syndromes of multiple manifestations
5. Medullary cystic disease
    A) Medullary sponge kidney
    B) Familial nephronophthisis- medullary cystic disease(FNMCD)
6. Multilocular renal cysts
7. Renal dysplasia with cysts
8. Simple renal cysts
9. Acquired renal cystic disease
10. Miscellaneous extrarenal cysts

INFANTILE POLYCYSTIC KIDNEY:

Its an autosomal recessive disease. There are bilaterally enlarged, diffusely spongy cystic kidneys. Associated with congenital hepatic fibrosis.

ADULT POLYCYSTIC KIDNEY DISEASE:

Kidneys are bilaterally enlarged. May be present in newborn but remains asymptomatic. Symptoms arise by fourth decade. Cysts of varying sizes are seen anywhere in nephrons. Cysts are also seen in other organs like liver, lung or pancreas.

RENAL DYSPLASIA:

The nephrons and collecting ducts are reduced in number and are immature. The differentiation of renal mesenchyme and ureter is arrested in early development. Cystic dilatation develops in glomeruli and collecting tubules. It is associated with many syndromes for example Meckel gruber syndrome[26].

Bilateral dysplasia is seen in oligohydrmnios sequence. Unilateral dysplasia is associated with meningomyelocele, coarctation of aorta, intestinal atresia and isolated ventricular septal defect.

HYDRONEPHROSIS[26] :

Dilatation of renal pelvis and atrophy of some of the renal parenchyma occurs due to obstruction of ureter or urethra. The causes of obstruction are

1.Pressure by aberrant blood vessels on ureter

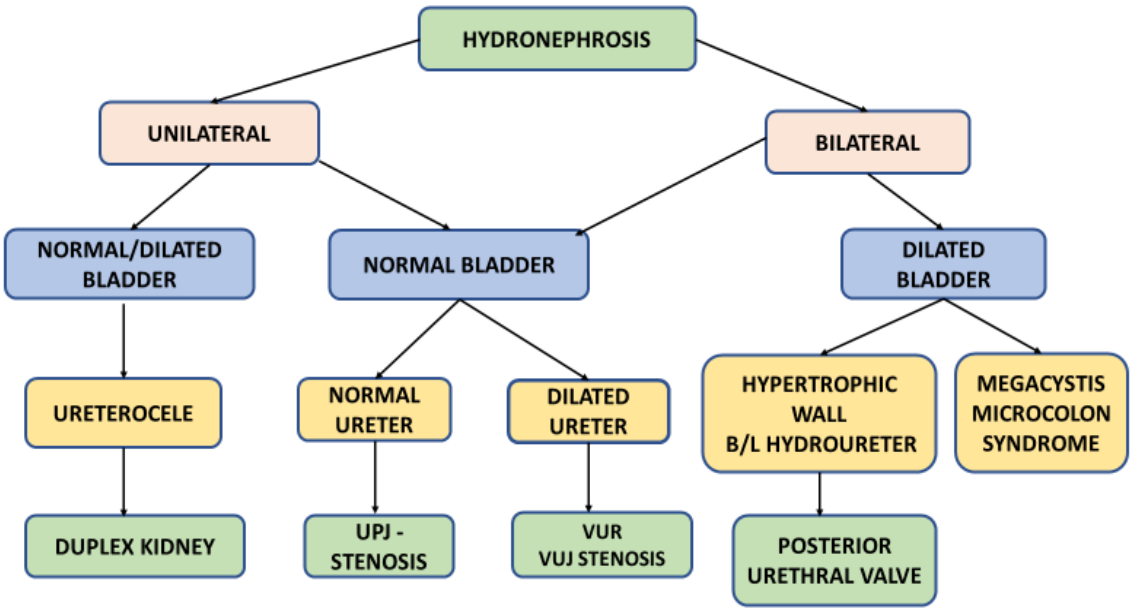
2.Ureteropelvic junction (upj) obstruction

3.Bladder diverticuli near the ureteric orifice

4.Posterior urethral valve (puv)

5.Ureter muscle abnormality

Clinical algorithm for the differential diagnosis of fetal hydronephrosis is illustrated in the flowchart[28].



UPJ- Uretero pelvic junction; VUR- Vesicoureteral reflux;

MEDULLARY CYSTIC KIDNEYS[26]:

Intrapapillary ducts ectasia affecting pyramids results in medullary cysts with calcific concretions. Renal cysts associated with multiple syndromes like autosomal trisomy, short rib polydactyly syndrome, jeune asphyxiating thoracic dystrophy, Zellweger syndrome, vonhippellindau syndrome, tuberous sclerosis and Meckel gruber syndrome.

CONGENITAL ABNORMALITIES OF URETER AND PELVIS[27]:

This includes duplication, vesicoureteric reflux, ureteric ectopia, ureterocele, retrocaval ureter, congenital hydrocalycasis and ureteric dilatation

CONGENITAL ABNORMALITIES OF BLADDER:

This includes congenital absence of bladder, bladder duplication and bladder exstrophy. Megacystis occurs associated with other anomalies[46].

CONGENITAL ABNORMALITIES OF URETHRA:

This includes posterior urethral valve, anterior urethral valve, megacystis/megaureter syndrome, urethral atresia, urethral duplication, prostastic utricle(Mullerian duct cysts), verumontanum polyp, megalourethra, urethral diverticula and hypospadias[28].

POSTERIOR URETHRAL VALVE[26]:

Urethral mucous membranes form valvular folds which is seen only in males. Three types of valvular folds are there of which type 1 and 3 causes obstruction.

Type 1: Two folds are present and it extends from verumontanum to lateral wall of urethra and block urine outflow

Type 2: The folds extend posteriorly from verumontanum without causing obstruction

Type 3: Distal to the verumontanum the transverse diaphragm blocks the urethra

PRUNE BELLY SEQUENCE:

It occurs at a rate of 1/3500 to 1/5000 live births. Seen in males only. Prune belly sequence consists of urinary tract abnormalities, cryptorchidism and abdominal muscle deficiency. Dilated bladder and ureter, hydronephrotic or dysplastic kidneys, posterior urethral valves, atresia, stenosis or urethral absence are also found[26].

SPECTRUM OF URORECTAL SEPTUM MALFORMATIONS[29]:

The Spectrum of malformations from most severe to least severe are

1. Complete urorectal septum malformation sequence (no opening)

2. Partial urorectal septum malformation sequence (one opening)
3. Urogenital sinus (two opening)
4. Anterior anus (three opening)

COMPLETE URORECTAL SEPTUM MALFORMATION SEQUENCE:

The criteria for Complete urorectal septum malformation sequence is the absence of perineal opening, ambiguous genitalia and associated with internal cloaca. This was first described by Escobar et al in 1987[5].

Complete urorectal septum malformation sequence is associated with poor prognosis and survival rate is reported only in 4 cases out of 73[5,30]. The other associated anomalies include cystic dysplasia or agenesis of kidneys, anorectal or colon atresia, lung hypoplasia, sacral agenesis or hypoplasia, vertebral anomalies, cardiac anomalies and tracheoesophageal atresia.

PATHOGENESIS :

Fusion of urorectal septum with cloacal membrane results in development of urogenital sinus and anal canal. If the urorectal septum does not fuse with cloacal membrane, cloaca or fistulous tract will form. For the formation of anus, urethra and vaginal outlets urogenital and anal membrane

should break down appropriately in seventh week of gestation[30]. If this does not happen then external genital anomalies are noted.

Thus lack of proper formation of external genitalia is due to improper induction of tissue which forms the genitalia. This improper induction of tissue would have been resulted from failure of fusion or incomplete fusion of urorectal septum with cloacal membrane[6]. Also contributing to this is deficiency of mesoderm migration into the caudal region of the embryo which remains the basic cause of urorectal septum malformation sequence.

The mesodermal activity during blastogenesis is implicated with various genes like sonic hedgehog (SHH), HOX, PAX, Ephrin B2[6]. Spontaneous or teratogenic mutation of these genes leads to gli protein amplification abnormality. Thus altered gene expression results in caudal mesodermal deficiency. This SHH activity via gli 3 was first reported by Ruiz Altaba in 1999[6].

Pallister Hall syndrome associated with gli 3 mutation charecterised by imperforate anus was first reported by Mc Kusick in 2002[14].

The spectrum of disorders due to caudal endodermal and mesodermal deficiencies abnormal development and or lack of cloacal membrane breakdown are grouped under urorectal septum malformation sequence[38]. The most severe form is complete urorectal septum malformation sequence where there is lack of perineal and anal openings. These individuals have

ambiguous external genitalia and renal agenesis or dysplasia. The cause of death in these cases in neonatal period is due to pulmonary hypoplasia.

PARTIAL URORECTAL SEPTUM MALFORMATION SEQUENCE:

Partial urorectal septum malformation sequence have single perineal or anal opening that serves as a common outlet for urine and feces to outside. It is less severe form of urorectal septum malformation sequence and Wheeler and Weaver was the first to name this as partial urorectal septum malformation sequence[7]. It has a persistent cloaca[29]. This sequence is more common in females with male to female ratio of 0.87[5].

The most common finding in females are apparent virilization with enlarged clitoris and or fused labia[29]. Males have hypospadias, bifid scrotum, penoscrotal transposition and absent penis.

In partial urorectal septum malformation sequence there is partial breakdown of cloacal membrane. The reason is lack of mesodermal cellsin the caudal region, incomplete descent of urorectal septum and deficient development of hindgut[29]. As a result a single common perineal or anal opening is formed.

The underlying cause of urorectal septum malformation sequence is unknown. Sulik and his associates found that several different teratogens, ochratoxin A (fungal toxin) in chick embryos and etretinate (retinoic acid

derivative) in mouse embryos damage the mesoderm and leads to complete or partial urorectal septum malformation sequence[29].

In complete urorectal septum malformation sequence there is severe renal and internal genital anomalies and long term survival of these cases is very less.

In partial urorectal septum malformation sequence there is less severe renal and internal genital anomalies.These cases have good prognosis for long term survival with appropriate surgical management[29].

Both complete and partial urorectal septum malformation sequence are associated with other anomalies[29]. The renal anomalies include dysplastic kidney, hydronephrosis of one or both collecting systems which is secondary to vesicourethral reflux. The central nervous system anomalies include meningomyelocele of the lower thoracic and lumbar spine, hydrocephalus status post stunt, Arnold chiari malformation and moderate developmental delay. The other associated anomalies include sacral hypoplasia and cardiac anomalies. The cardiac anomalies include ASD,VSD,TAPVC and TOF.

ANORECTAL MALFORMATIONS:

Anorectal malformations are complex group of congenital anomalies involving rectum and anus. There is slight male preponderance. Anus does not get perforated and may end blindly resulting in atresia or fistula in to urinary or genital tract or perineum[20].

Anorectal malformations results from abnormal development of urorectal septum . By seventh week urorectal septum and cloacal membrane are formed. Cloaca is divided in to ventral (urogenital sinus) and dorsal (anus and rectum). The cloaca membrane ruptures by apoptosis and produces two openings namely anus and urogenital openings[20].

By the end of seventh week secondary occlusion of anorectal canal by adhesion of walls and formation of epithelial plug. This will rupture and recanalise by the end of eighth week[31]. So embryologically Anorectal malformations can be grouped into two according to when the disturbances occur[20].

1.If there is early abnormal development of the dorsal part of cloaca and cloacal membrane (4 to 7 weeks), manifestation will be ectopic anal orifice or fistula.

2.If there is defective recanalisation of the occluded orifice (7 to 8 weeks), manifestation will be as abnormal anus in normal position.

CLASSIFICATION OF ANORECTAL MALFORMATIONS[20]:

Wingspread classification (1984) divides Anorectal malformations into three types depending on the location of rectal pouch with the puborectal sling.

1. Low Anorectal malformations- when the rectal pouch is located below puborectal sling

2. Intermediate Anorectal malformations- when the rectal pouch is located at the level of puborectal sling

3. High Anorectal malformations- when the rectal pouch is located above the puborectal sling

Krickenbeck classification differentiates five types of fistulas[20].

1. Rectoperineal

2.Rectovestibular

3.Recto-urethral bulbar

4.Recto-urethral prostatic

5.Recto-vesical

Wingspread classification tells about the location of blind rectal pouch, whereas Krickenbeck classification tells about the anatomical evaluation of rectal pouch and location of fistulas.

CLOACAL DYSGENESIS[32]:

The primary malformation in cloacal dysgenesis is phallus like structure, smooth perineum and absence of urethral, vaginal and anal openings. It is always associated with other anomalies in other organ systems including vertebral, pulmonary and genitourinary tract. This anomaly occurs when there is a defect in cloaca formation during first 50 days of gestation.

The intraembryonic mesoderm and ectoderm (cloacal membrane) forms the genitourinary system. By third to fourth week intraembryonic mesoderm divides into paraxial, intermediate and lateral plate. Adjacent to the cloacal membrane lies the primitive hindgut (endoderm) which forms the expanded structure called cloaca.

The cloaca divides into anterior urogenital sinus and posterior urorectal septum (mesoderm) by 4 to 6 weeks. The cloacal membrane (ectoderm) and urorectal septum (mesoderm) fuses and forms anterior urogenital membrane and posterior anal membrane. In 7^{th} week these two membranes rupture to form external urogenital sinus and anus. Perineum is the point of fusion of two membranes.

The primitive urogenital sinus develops into bladder. Pelvic urethra and penile urethra in males. In females it forms membranous urethra, bladder and vestibule of vagina[35]. So any insult to the embryo during during

7th week results in cloacal dysgenesis sequence with a single common channel[33]. So the drainage of urine, stool and vaginal secretions in to a common channel called “cloaca” is formed[34]. The most common cause of death in cloacal dysgenesis sequence is pulmonary hypoplasia and renal failure.

Some of the syndromes have been associated with cloacal exstrophy. One such is OEIS complex. It has an incidence of 1 in 200000 to 400000 live births[36]. It has male preponderance. The components are omphalocele, exstrophy of bladder, imperforate anus and skeletal defects. The basic embryological defect is failure of mesodermal ingrowth into cloacal membrane resulting in premature rupture. If rupture occurs prior to fusion with urorectal septum cloacal exstrophy occurs. If late rupture occurs after fusion of cloacal membrane with urorectal membrane then less severe form bladder exstrophy occurs[37].

Materials & Methods

MATERIALS AND METHODS

All foetal and perinatal autopsies performed at the department of pathology, between January 2014 to December 2018 were analysed. Of the received 225 autopsies, 40 cases of foetal anorectal and urogenital malformations / abnormalities were identified and included in the study. Indications for sending the foetuses for autopsy study include spontaneous abortion, termination of pregnancy for foetal anomalies, early neonatal deaths and still births.

The ethical committee approval of the instituition was obtained for the study. The foetuses of above 12 weeks of intrauterine life and within 7 days of postnatal life were taken into consideration. Foetuses with intrauterine death and other system abnormalities were excluded from the study.

After receiving the foetus for examination, an informed consent was obtained from either of the parents. Maternal data collection was done including age of the mother,obstetric history, gestational age, consanguinity status and history of any medications. Pregnancy outcome (termination of pregnancy/still born/live born/neonatal death) and mode of delivery were documented. The autopsied foetuses had been examined prenatally with the ultrasound examination and the results were taken. The sonograms were

carried out by both radiologists and also by obstetricians with ultrasound examination skills.

X ray examination (foetogram) was performed for all the foetuses including anteroposterior and lateral views of the entire body.Photographs of the foetuses were taken before evisceration. Supine, prone with right and left lateral positions were taken. Closer pictures and insitu photographs were taken to document the abnormal features if any. Anthropometric measurements including body weight, head circumference, chest circumference, crown rump length, crown heel length and foot length were recorded.

The external examination was performed systematically from head to toe including the general appearance and the skin. The internal examination was done using a linear incision starting from the chin to the neck, extending in the midline through thorax and abdomen[39]. The incision is then curved around the left side of the umbilicus up to the symphysis pubis. In cases suspicious of urethral stenosis/ cloacal malformations or hydrops of unknown etiology, the incision was also extended on each sides of the external genitalia to include the anal opening.

After the initial incision, the skin and the subcutis were dissected away till the exposure of the ribs. Then the chest plate was incised and the thoracic organs were exposed. Insitu examination of the thoracic and

abdominal structures were done and documented. A curvilinear incision was made above the level of uvula and all organs of the neck, chest, abdomen including tongue was removed as one unit. Internal dissection of the organ block was done. After reflecting the aorta with the thoracic organs (above) and esophagus into abdominal organs (below), the thorax is separated from the abdomen at the level of diaphragm. Each organ systems were examined meticulously and organs were separated, weighed and the bits were given for microscopic examination.

Removal of the brain was done by making an incision in the scalp starting from behind one ear through the cranium and extend down behind the other ear. After reflecting the scalp anteriorly and posteriorly, two nicks were made in the lateral corner of the anterior fontanelle. After reflecting the falx cerebri, insitu examination of the brain was done and it is removed intact, weighed and fixed by hanging in formalin using gauze. After fixation,brain was sliced and relevant bits were given.

The placenta and cord were also examined, photographed and relevant sections were given. It includes two bits from the cord and membrane roll. The parenchyma is cut at 1 cm interval and a few full thickness parenchymal bits were given, including any macroscopic lesions. The sections were stained with hematoxylin and eosin and examined under

microscope. After microscopic analysis, the results were correlated with clinical, prenatal ultrasound findings and final results were drawn.

Results

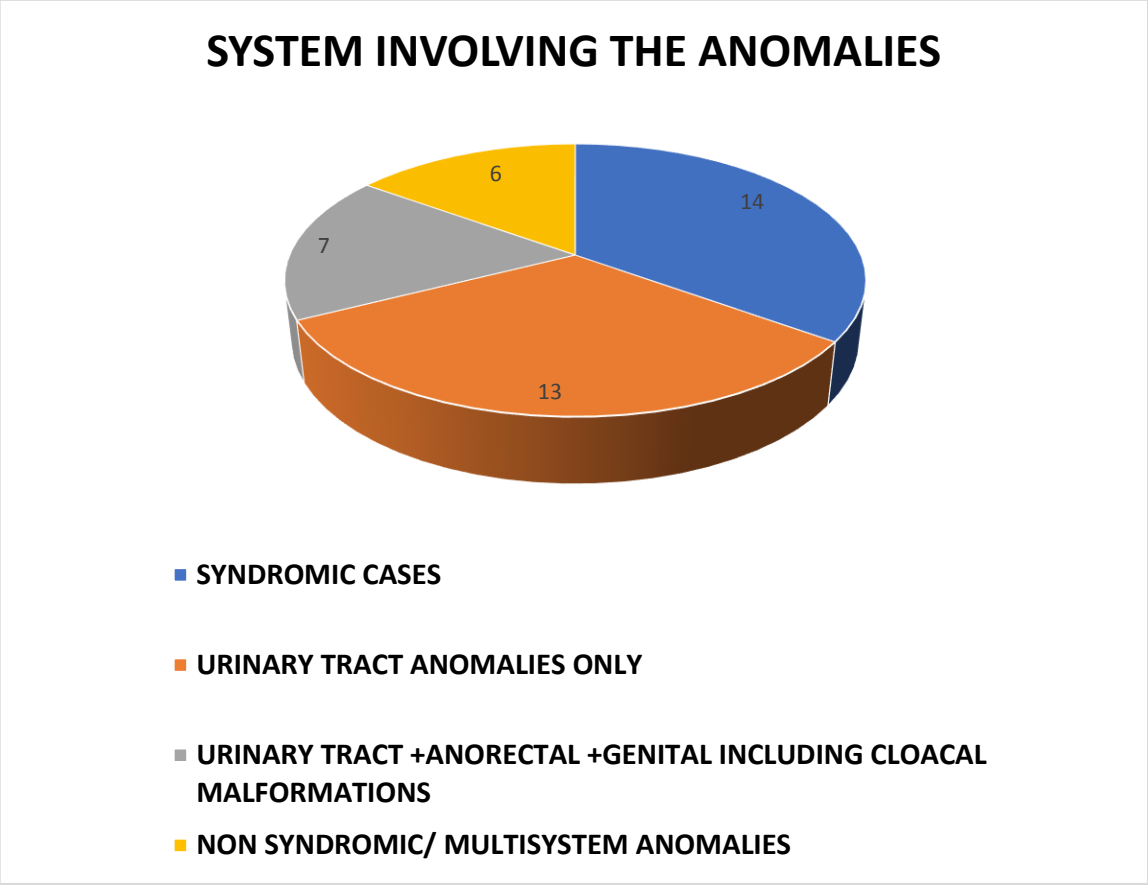
RESULTS

Among the 225 foetuses received during the study period , 40 foetuses with urogenital and anorectal anomalies were identified. Maternal age was between 19 to 35 years. The comorbid conditions associated with the mother includes maternal hypothyroidism, (3 cases) diabetes mellitus, (3 cases) and a case of preeclampsia. In 6 cases, there was a history of consanguinity. Past history of spontaneous abortion was present in one case (6 timemiscarriage).The mothers were of primi to gravida 7.

Oligohydramnios was noted in most of the cases. The other prominent prenatal ultrasound findings include ectopic presacral kidneys, bilateral hydronephrosis, single umbilical artery, bladder outlet obstruction, unvisualised anus, renal agenesis and dysplastic kidneys. Single umbilical artery was observed in 16 cases. Gestational age of foetuses varied from 13w1d to 26w2d. There were 28 males and 12 females. Ambiguous genitalia with phallus like structure was noted in few cases.

The most common associated malformations in foetuses with urogenital and anorectal anomalies were classified broadly as follows. (Table:1)

SL. NO.	SYSTEM INVOLVING THE ANOMALIES	NUMBER OF CASES (N=40)
1.	Urinary tract anomalies only	13
2.	Urinary tract+anorectal+genital anomalies including cloacal malformations	7
3.	Syndromic cases	14
4.	Multisystem anomalies/ non syndromic cases	6



Of the studied 40 cases, 13 cases of congenital anomalies involving only the urinary tract (and including kidneys/ureter/bladder/urethra) were identified. Urinary tract anomalies with associated malformations in genital, anorectal tracts including cloacal dysgenesis/ urorectal septum malformation sequence were noted in 7 cases.

14 cases of syndromic causes were encountered, among which VACTERL ASSOCIATION was the commonest syndrome and seen in 6 cases.

Non syndromic causes /multisystem anomalies occurred in 6 cases and involving CVS,RS,GIT,CNS and skeletal systems.

A) URINARY TRACT ABNORMALITIES:

1) Congenital anomalies of the kidney:(Table: 2)

PRIMARY RENAL ANOMALIES	No of cases
Renal agenesis -Unilateral -Bilateral	4 4
Renal ectopia	2
Crossed fused ectopia	2
Horse shoe kidney	1
Cystic renal diseases - ARPCKD - ADPCKD - Multicystic renal dysplasia	2 2 10
Hydronephrosis secondary to Bladder outlet obstruction	12

Renal anomalies were present in almost all cases either alone or in combination with other system anomalies. Renal agenesis was observed in 8 cases, of which one of the foetus with bilateral renal agenesis also had single median lower limb with common 5 toes and a pseudotail. (Fig: 14)

Abnormal renal shape and position including 2 cases each of Renal ectopia and Crossed fused ectopia and one case of Horse shoe kidney were observed.

Renal cystic diseases identified in our study group were of heterogeneous type. The common abnormality encountered were multicystic renal dysplasia (10 cases) and hydronephrosis (12 cases) secondary to urinary obstruction predominantly at bladder outlet level. Parenchymal atrophy and cystically dilated tubules were observed microscopically. The other cystic kidney diseases noted were ARPCKD, ADPCKD, Cortical and medullary cysts.

Associated potters sequence (Fig: 8) in the form of pulmonary hypoplasia and club foot were noted in few cases.

2) Congenital anomalies of the urinary system, including bladder, ureters and urethra (Table 3):

BLADDER OUTLET OBSTRUCTION	Number of cases
Megacystis - PUV -DUS -Megalourethra -Renal obstructive dysplasia	3 7 1 1
Absent bladder	2
Hypoplastic bladder	4
Extrophy of bladder	1
URETER	
Ureteric stenosis	2
URETHRA	
Megalourethra	1
Urethral duplication	1
Urethral atresia	5

Bladder outlet obstruction causing megacystis was noted in 12 cases. The causes of bladder outlet obstruction were posterior urethral valve (Fig: 7) (3 cases), distal urethral stenosis(7 cases), megalourethra(1case) and renal obstructive dysplasia(1case). The detailed autopsy findings of cases with megacystis with other associated findings of few cases were summarized in Table 4.

Table 4: Summarizes the autopsy findings of foetuses with megacystis :

CASE	GESTATIONAL AGE	CAUSE OF MEGACYSTIS	BLADDER	AMNIOTIC FLUID VOLUME	KIDNEY	OTHER ASSOCIATED FINDINGS	DIAGNOSIS
1	14 weeks 4 days	Megalourethra	Distended	Reduced	Absent right kidney and ureter.	Vesico urachal diverticulum. Micro colon. SUA.	Congenital megalourethra
2	24 weeks	Mid urethral stenosis	Distended	Oligohydramnios	Bilateral dilatation of pelvicalyceal system	Female pseudohermaphroditism, Hydrops, Persistent cloaca, Mild stenosis of ductus ateriosus.	Complete urorectal septum malformation sequence (cloacal dysgenesis)
3	20 weeks 2 days	Urethral atresia	Distended	Anhydramnios	Multicystic renal dysplasia	Hydrops. Cleft palate. Bilobed right lung. Urethral atresia.	Cleft palate with bladder outlet obstruction
4	18 weeks	Distal urethral stenosis	Mildly dilated	-	Normal	Distal urethral stenosis with dilatation and hypertrophy of the urinary bladder.	Bladder outlet obstruction (distal urethral stenosis)
5	18 weeks	Urethral stenosis	Enormously distended	-	Bilateral hydronephrosis	Hydrops foetalis BOO due to urethral stenosis causing dilated posterior urethra, bladder and ureters. Hypoplasia of ductus, right and left pulmonary arteries, distal aortic arch and left subclavian artery. Ventriculomegaly, absent corpus callosum	Non immune hydrops foetalis bladder outlet ostruction

Non immune Hydrops foetalis was observed in one case of bladder outlet obstruction secondary to posterior urethral valve and was not diagnosed antenatally.

Bladder was absent in 2 cases and one of the case had an associated complete urorectal septum malformation sequence.

Ureteric stenosis was noted in 2 cases. We did not encounter any case of ureteral duplication.

The commonest urethral malformations noted was urethral atresia/stenosis.The other anomalies included were megalourethra and urethral duplication.

The bladder was either thin or thick in outlet obstruction. But, in most cases, the bladder was dilated with thin walled and shows less trabeculations. The bilateral ureters were also dilated, tortuous and thin walled. The kidneys also enlarged in most cases with marked dilatation of pelvicalyceal system and exhibit cystic renal dysplasia. (Fig: 13) In a few cases ,they were small, irregular shaped and showed multiple cysts. Cortico medullary differentiation was not made out.

Microscopically, there were thin cortex with subcapsular cortical cysts, dilated tubules and calyces and interstitial fibrosis. We did not come across islands of cartilage in dysplastic kidneys. Instead, we encountered

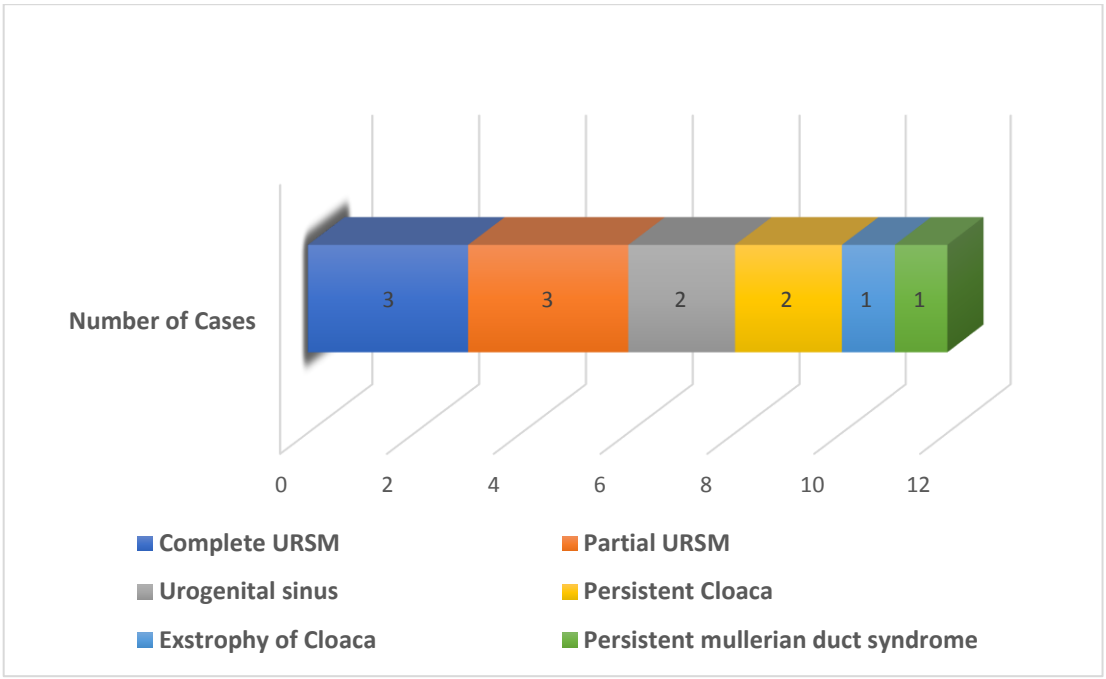
cystically dilated primitive/undifferentiated ducts surrounded by undifferentiated mesenchyme forming fibromuscular collars in some cases.

Most of the cases with megacystis had an associated pulmonary hypoplasia due to oligo/anhydramnios.

B) SPECTRUM OF URORECTAL SEPTAL (CLOACAL) MALFORMATIONS : (TABLE:5)

Cloacal malformations	Number of cases
Complete URSM	3
Partial URSM	3
Urogenital sinus	2
Persistent cloaca	2
Exstrophy of cloaca	1
Persistent Mullerian duct syndrome	1

SPECTRUM OF URORECTAL SEPTUM (CLOACAL) MALRORMATIONS:



We identified 12 cases of urorectal septum malformation sequence. Of which 3 cases each of complete (Fig: 5) and partial urorectal septum malformation sequence were observed. The diagrammatic representation of our cases of complete urorectal septum malformation sequence was depicted in figure 1 and partial urorectal septum malformation sequence was shown in figure 2. The detailed summary of the complete and partial URSM is tabulated in table 6.

TABLE: 6 COMPARISION OF COMPLETE URSM (3 CASES) AND PARTIAL URSM (3 CASES)

PARAMETERS	COMPLETE URSM			PARTIAL URSM		
	CASE 1	**CASE 2**	**CASE 3**	**CASE 1**	**CASE 2**	**CASE 3**
Gestational age	16 weeks	13 weeks 3 days	24 weeks	13 weeks	22weeks	18 weeks
Sex of baby	External genitalia-ambiguous Internally- male	External genitalia-ambiguous Internally-female	External genitalia-ambiguous Internally- female	Male	Female foetus	Female foetus
USG findings	Oligohydramnios. Moderate HUN of right kidney with echogenic parenchyma and a cyst in the upper pole and nonvisualised left kidney and urinary bladder	Foetus shows omphalocele with exstrophy of distended urinary bladder. The foetal anus is not seen. The nasal bone is seen. Features suggestive of OEIS complex with SUA	Oligohydramnios. Fetus shows urinary bladder obstruction with bilateral gross HUN with dysplastic parenchyma and patent urachus most probably urethral atresia.	Fetus shows cystic hygroma and cardiac anomaly	Marked oligohydramnios, fetus shows multiple anomalies.	Fetus shows multiple anomalies with SUA -VACTERL anomaly-
Autopsy findings (URSM)	Cloacal malformation – male foetus with ambiguous genitalia, smooth / intact	Female foetus with ambiguous genitalia, intact/smooth perineum(no	Female pseudohermaphroditism Megacystis with HUS. Urethral duplication	Male foetus with intact / smooth perineum (no anal opening). Anal agenesis	Imperforate anus with anal atresia DUS with HUN.	Urogenital sinus. Distal urethral stenosis and anteriorly placed anus.

	perineum (without urethral or anal orifices) and rectal pouch with posteriorly directed anal canal.	urethral, vaginal and anal openings)	with mid ureteric stenosis of ventral urethra.Persistent cloaca.	with recto-vesical fistula.		
Additional autopsy findings	Renal dysplasia Absent bladder, ureters draining into anal canal	Omphalocele Pelvic pouch ?connecting to ureters and fallopian tubes Colonic atresia	Hydrops foetalis. Mild stenosis of ductus ateriosus	Hydrops foetalis Cystically dilated bladder with distal urethral stenosis. Bilateral dysplastic kidneys. TGA with VSD Brain : Mild ventriculomegaly.	Hypoplastic aortic arch Absent ductus venosus CVC liver. Bicornuate uterus	Hydrops foetalis SUA.Left renal agenesis. Pre axialpolydactyly of right upper limb and lower limb scoliosis with shortened and deformed left upper limb and right lower limb.
Final diagnosis	Consistent with cloacal dysgenesis sequence with absent bladder.	Complete URSM with omphalocele and pseudocyst of the umbilical cord.	Complete URSM sequence	Partial URSM (cloacal dysgenesis sequence)	Partial URSM with absent ductus venosus	Partial URSM with VACTERL ASSOCIATION

URSM- Urorectal septum malformation sequence; HUN- Hydroureteronephrosis; SUA-Single umbilical artery; DUS- Distal urethral stenosis;

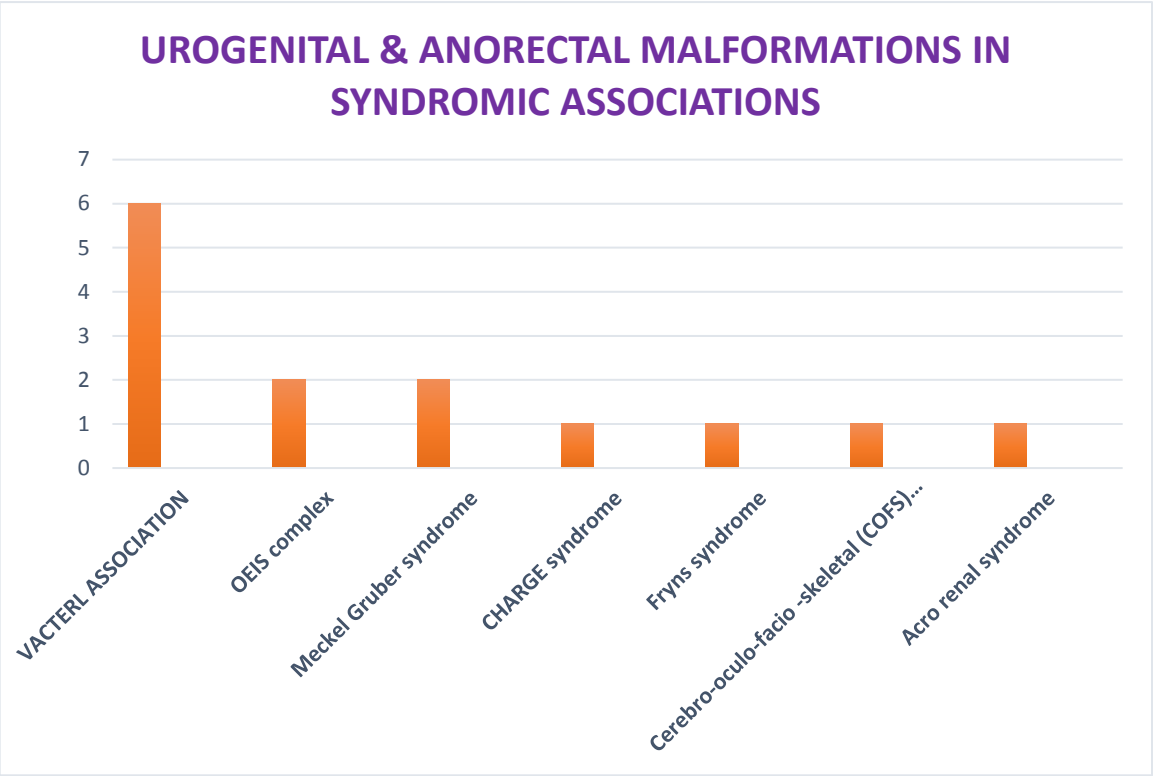
In a case of Persistent Mullerian duct syndrome, (Fig: 6) the external genitalia showed labia majora, stretched over a mound of darker skin that had a spot/punctum at its summit . This could not be probed. A raphe extended from this, posteriorly, towards a dimple situated at the lower end of the spine. The anus was imperforate. The ureters were mildly dilated and the bladder was slightly enlarged, thin walled and empty. There was marked narrowing of the urethral orifice. The rest of the urethra was markedly dilated ,somewhat globular and occupied the area seen as a mound between the fused labio-scrotal folds (buried penis).The glans penis was seen at the tip of the distal urethra and this too was buried under the skin. The gonads(testes) were pelvic in position. Each was connected to the inguinal region by a short cord of white translucent tissue-gubernaculum. They were also related , medially to a tortuous ,fine, thread like structure(oviduct) to paired tubes(Mullerian ducts). It was reported as Persistent Mullerian duct syndrome with anorectal atresia and bladder outlet obstruction.

In one of the 2 cases of persistent urogenital sinus, the karyotyping revealed 22q micro deletions and ultrasound showed single umbilical artery with features suggestive of cloacal malformation. During foetal autopsy, we observed a midline large pelvic pouch (? urinary bladder), 2.2x2.4x1.5 cms, in which both the dilated ureters and lower part of vagina open. The dome of the pouch is attached with the umbilical cord through

urachus. The pouch contains grey white friable material (? keratin) and ends blindly. There was no direct connection between the pelvic pouch and the external opening (external os). The rectum joins with patulous, anteriorly placed anus. There was vesico vaginal fistula with a pelvic pouch connecting to the external opening through an atretic passage, compatible with partial urorectal septum malformation. The diagnosis given was spectrum of urorectal septum abnormalities suggestive of persistent urogenital sinus.

C) UROGENITAL & ANORECTAL MALFORMATIONS IN SYNDROMIC ASSOCIATIONS: (TABLE: 7)

SYNDROMES	NUMBER OF CASES
VACTERL ASSOCIATION	6
OEIS complex	2
Meckel Gruber syndrome	2
CHARGE syndrome	1
Fryns syndrome	1
Cerebro-oculo-facio -skeletal (COFS) syndrome	1
Acro renal syndrome	1



The foetuses with associated malformations were classified into groups with syndromic (recognized syndromes, associations, sequences) and non syndromic multiple congenital anomalies;

The most common syndromes related to Urogenital & anorectal malformations identified in our study were VACTERL Associations (6 cases), OEIS complex(2 cases) and Meckel-Gruber syndrome(2 cases). The other syndromic associations identified were one case each of CHARGE syndrome, Fryns syndrome, Cerebro-oculo-facio -skeletal (COFS) syndrome and Acro renal syndrome.

RECOGNIZED SYNDROMES:

VACTERL ASSOCIATION (N=6)

VACTERL ASSOCIATION was observed in 6 cases. The presence of any three anomalies among the vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities were included in this syndrome. (Fig: 10 & 11) Apart from the core components of VACTERL, additional findings were also noted in our present study and are summarized in Table 8.

Some studies suggest that the first letter "V" in VACTERL was meant for vascular anomalies, because single umbilical artery was observed in many cases. We also had an associated single umbilical artery in 5 out of 6 cases.

TABLE 6: VACTERL/VATER ASSOCIATION

PARAMETERS	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6
Gestational age	23 weeks	22weeks 5 days	18weeks 5days	13weeks 1 day	23 weeks	23 weeks 6 days
Sex	Male	Male	Female	Male	Male	Male
USG findings	SUA, TOF, ectopic hydronephrotic Left kidney, Left club foot with absent 2nd to 5th digits	Anhydramnios. SUA, partial sacralagenesis,segmentationanomaly of lumbar spine, bilateral short bowed femur & tibia, absent fibula & feet.Foetal urosonogram report – Unilateral renalagenesis and ectopic presacral one kidney with gross hydronephrosis.	Multiple anomalies with SUA-VACTERL anomaly.	Shows radial ray aplasia with SUA	USG findings Intestinal malrotation with multiple anomalies could be VACTERL association.	Oligohydramnios, persistent left SVC with interrupted IVC left renal agenesis. Right ectopickidney, ? sacral agenesis / ? closed spinal dysraphism
AUTOPSYFINDINGS: **V**ertebral	Foetogram-hemivertebra in upper dorsal spine and sacrum, fusion of ribs on the left side	Foetogram- sacral agenesis, fusion of the pelvic bones, bilateral short bowed femur, bilateral short tibia, absent fibula and feet	Foetogram-scoliosis with hemi vertebra at L2 spine, left radial hypoplasia with deformity of right leg with single bone	normal	normal	normal
Anal	Atresia of distal sigmoid, rectum and anus.	Imperforate anus	Anteriorly placed anus	-	Imperforate anus	anal atresia
Cardiac	TOF with right aortic arch and left sided PDA	-	-	Perimembranous VSD	Perimembranous VSD with overriding of aorta	-
Trachea and **E**sophagus	-	Esophageal atresia withTEF type-A	-	Esophageal atresia with TEF	-	-

Renal	Fused crossed renal ectopia with hydronephrosis	Absent right kidney, ureters and urinary bladder. Left renal ectopia with hydronephrosis and dysplasia	Left renal agenesis Distal urethral stenosis	-	Right renal agenesis Mid urethral stenosis.	Single, midline, hypoplastic dysplastic kidney. Absent ureters and urethra.
Limbs	Left club foot with a single digit	Bilateral short thigh, short blind ended legs with no feet	Pre axial polydactyly of right upper limb and lower limb Scoliosis with shortened and deformed left upper limb and right lower limb	Radial aplasia	Left congenital talipes equinovarus	Absent right forearm, right thumb and bilateral talipes.
Other associated findings	SUA	Lung hypoplasia Cloacal malformation with smooth perineum and absent external genitalia. SUA	Hydrops foetalis SUA	Hypoplastic right lung.Enlarged trilobbed left lung. SUA	Micrognathia Pulmonary stenosis Large penis with epispadias.IntestinaL malrotation.Bilateral unilobedlungs.Absent gallbladder and appendix	Pulmonary hypoplasia. Intestinalmalrotation, Pyloric atresia Cloacal malformation with no perineal opening. SUA
Final diagnosis	VACTERL ASSOCIATION	VACTERL ASSOCIATION	VACTERL ASSOCIATION	VACTERL ASSOCIATIO N	VACTERL ASSOCIATION.	VACTERL ASSOCIATION.

SUA- single umbilical artery; TOF- Tetralogy of fallot; TEF- Tracheo esophageal fistula; VSD- Ventricular septal defect; PDA- Persistent ductus arteriosus

OEIS SEQUENCE (N=2):

Among the foetuses with Urogenital & anorectal malformations, OEIS complex was identified in 2 cases. One of the foetuses showed a midline anterior abdominal wall sac measuring 2.0x1.5x1.0cm, covered by thin transparent membrane (omphalocele) and contains liver and intestines. Umbilical cord was attached to the centre of the sac and had only two vessels (single umbilical artery). The sac was connected to the abdominal cavity through a defect measuring 1.0cm in greatest dimension. External genitalia was not made out. There was imperforate anus. Limbs were normal. (Fig: 9)

During internal examination, we found a defect in the anterior wall of the urinary bladder .The penis was also embedded in the omphalocele sac. The small and large intestines were normal with anal atresia.

Hydrocephalous, bilateral renal agenesis and scoliosis were noted in addition. Both prenatal ultrasonogram findings and autopsy findings favour the diagnosis of OEIS complex.

MECKEL GRUBER SYNDROME (N=2) :

There were 2 cases of Meckel Gruber syndrome, of which one was a small female foetus, exhibiting microcephaly, depressed nasal bridge, micrognathia and elevated upper lips. There were occipital meningocele

with hydrocephalus and shallow posterior fossa. The cerebellum was small with hypoplastic cerebellar vermis connecting the posterior portion of the cerebellar hemispheres. The trans cerebellar diameter is 2.0cms. (Fig: 3)

The kidneys were enlarged and showed persistent foetal lobulation with diffuse multiple tiny cysts ranging in size from <0.1 to 0.2 cm. These cysts were seen throughout the cortex and medulla and appears spongy. Microscopic examination of the kidneys revealed sub-capsular nephrogenic zone with normal glomeruli and numerous cysts of varying sizes lined by flat to cuboidal epithelium. There was no evidence of dysplasia.

Bilateral hypertrophied limb muscles with hypoplasia of lungs, heart, liver and brain, left talipes, postaxial polydactyly - Type B defect (skin tag) were also observed in the foetus.

CHARGE SYNDROME (N=1):

A case of CHARGE syndrome comprising of bilateral posterior choanal atresia, lop ears, micrognathia, microphthalmia, persistent cloaca and lefthydronephrosis was identified in syndromic associations. This case had ultrasound evidence of Pierre syndrome, but autopsy findings favoured CHARGE syndrome.

FRYNS SYNDROME (N=1):

A foetus showed cleft lip and palate, congenital diaphragmatic hernia, pulmonary hypoplasia, membranous VSD with coarctation of aorta, renal cortical cysts with hydroureteronephrosis and remnant of vitello intestinal duct. Apart from the thoraco-abdominal findings, the foetus also had olfactory bulb agenesis, agenesis of corpus callosum and hydrocephalus. With the above features the diagnosis of FRYN syndrome was made in autopsy. Cardiovascular and central nervous system anomalies were not identified in antenatal ultrasonogram.

CEREBRO-OCULO-FACIO -SKELETAL (COFS) SYNDROME (N=1):

In a case of COFS syndrome ,the external examination of the foetus showed microcephaly, slopping forehead, opaque lens, low set ears, depressed nasal bridge with small nose, small mouth, deviated tongue, micrognathia with very short neck and hirsutism. Fixed flexion of upper limbs and fixed extension of lower limbs with crossing of left leg over the right leg was also identified externally.

Internal examination revealed, hydrops, hydraencephaly, hypoplastic pituitary, rudimentary posterior fossa and diffuse villous hyperplasia of choroid plexus. Pulmonary hypoplasia, small and flat adrenals, enlarged

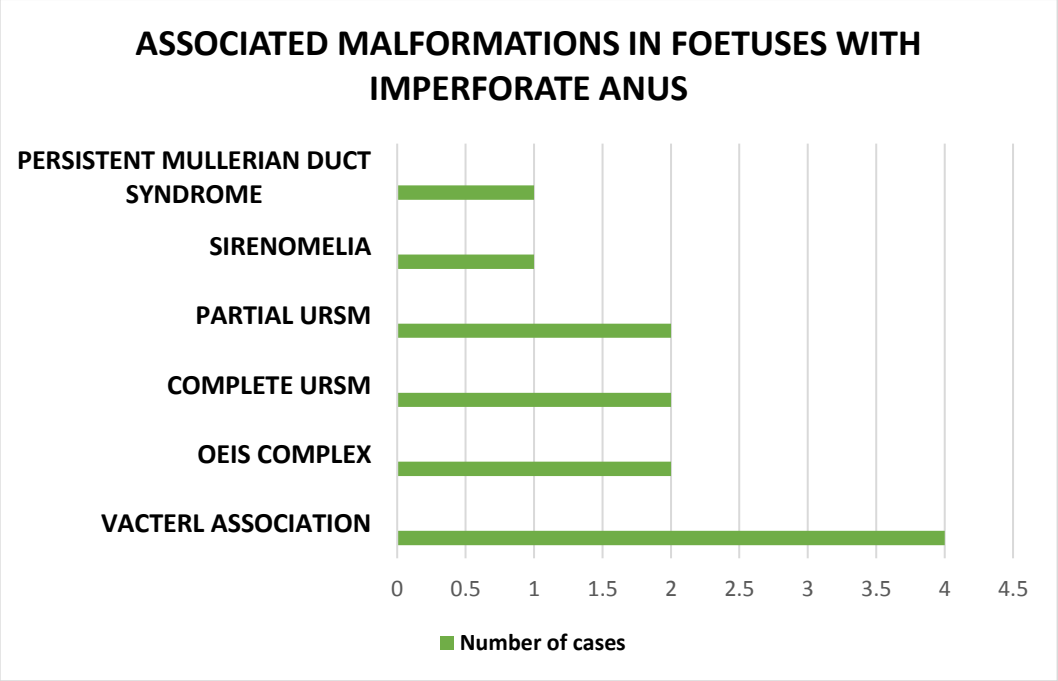
spleen and distended bladder with dilated pelvicalyceal system with features of persistent urogenital sinus were also found.

ACRO RENAL SYNDROME(N=1):

The diagnosis of acro-renal syndrome was made in a foetus with distal urethral stenosis, hypoplastic elongated bladder, bilateral renal and urethral agenesis with associated pulmonary hypoplasia and hand abnormalities.

TABLE:9 Associated malformations in foetuses with imperforate anus

S. No	Imperforate anus with associated malformations	Number of cases (n=12)
1	VACTERL ASSOCIATION	4
2	OEIS COMPLEX	2
3	COMPLETE URSM	2
4	PARTIAL URSM	2
5	SIRENOMELIA	1
6	PERSISTENT MULLERIAN DUCT SYNDROME	1



D) NON SYNDROMIC MULTISYSTEMIC CONGENITAL ANOMALIES ASSOCIATED WITH UROGENITAL & ANORECTAL MALFORMATIONS: (TABLE: 10)

System	Associated malformations	Number of cases
GIT	Microcolon	1
	Colon malrotation	3
	Duplication cyst	1
	Esophageal atresia with TEF	2
	Rectovesical fistula	1
	Rectourethral fistula	1
	Omphalocele	3
	Colonic atresia	1
	Pyloric atresia	1
	Hepatic fibrosis	1
	Absent gall bladder & appendix	1
	Imperforate anus	9
	Anorectal atresia	3
	Anal atresia	2

RS	Pulmonary hypoplasia	10
	Congenital diaphragmatic hernia	1
	B/L Unilobed / bilobed lungs	2
CVS	TOF	1
	R Aortic arch with L ductus	2
	VSD	6
	TGA with VSD	1
	Hypoplastic left heart with AS&MS	2
	Tricuspid atresia	1
	Hypoplastic right ventricle	1
CNS	Cerebellar hypoplasia	1
	Absent corpus callosum	2
	Hydrocephalus	8
	Hypoplastic pituitary	1
	Microcephaly	2
	Occipital encephalocele	1
GENITAL SYSTEM	Ambiguous genitalia	3
	Male pseudohermaphroditism	1
	Female pseudohermaphroditism	1
	Vesicovaginal fistula	1
	Large penis with epispadias	1
	Absent external genitalia	2
SKELETAL SYSTEM	Left club foot with single digit	1
	B/L Short thigh, short legs with no feet	1
	Pre and Post axial polydactyly	2
	Scoliosis with shortened and deformed limbs	1
	Radial aplasia	1
	Talipes equinovarus	4
	Abnormal short fingers	1
	Feet with syndactyly and nail dysplasia	1

Among the non syndromic multisystemic congenital anomalies associated with Urogenital & anorectal malformations, gastrointestinal abnormalities were the most frequently observed, with imperforate anus with anorectal atresia, colonic malrotation and Omphalocele as the most common findings.

Pulmonary hypoplasia secondary to oligohydramnios was noted in 10 cases and was the common cause of death in most of the cases with urogenital and anorectal anomalies.

Ventricular septal defect was the most frequent anomaly seen in the Cardiovascular system in our study.

Among the central nervous system anomalies, hydrocephalus was the commonest one, and two of them were associated with aqueductal stenosis. Complete agenesis of corpus callosum was noted in 2 cases.

3 cases of ambiguous genitalia were noted in the present study, of which one case showed large penis with epispadias and it was associated with many other anomalies and diagnosed as VACTERL association.

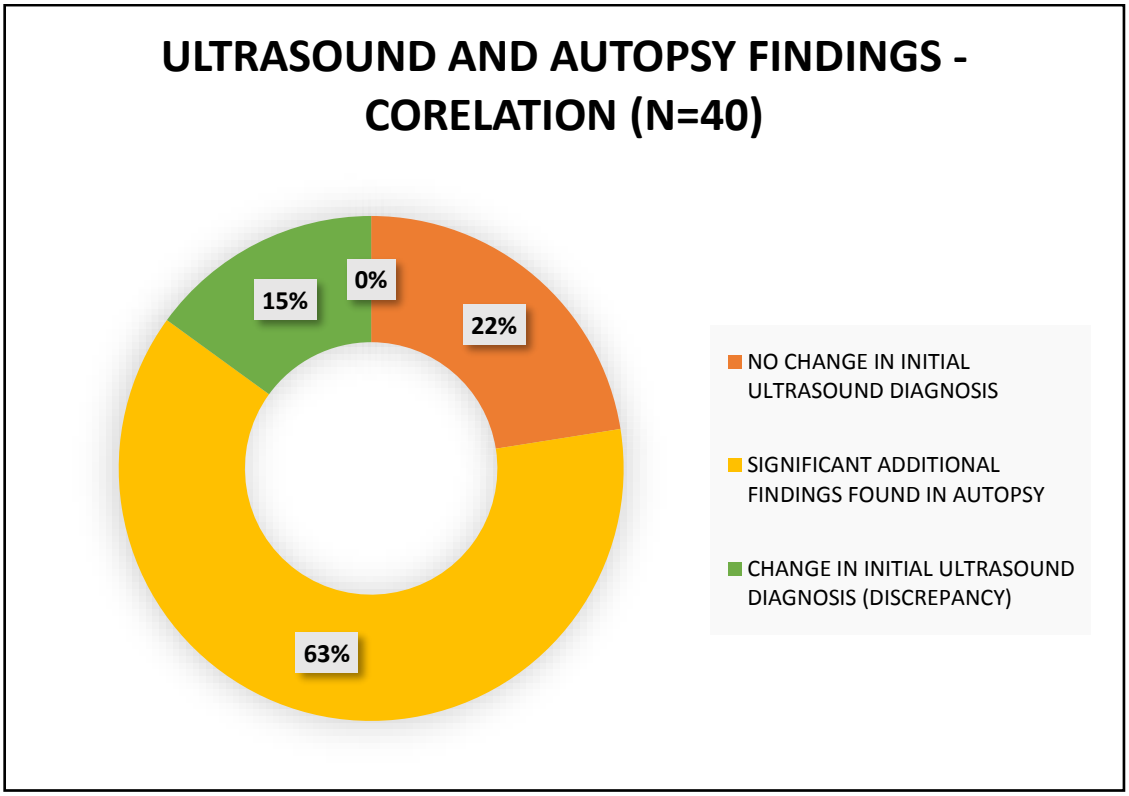
Chromosomal analysis was done in only one of the 40 cases which showed 22q deletion. None of the foetuses had both ovarian and testicular tissue hence there was no case of true hermaphroditism in our study.

An associated skeletal system malformations was identified in 12 cases and the commonest one was talipes equinovarus. The other skeletal abnormalities included were congenital hand, foot and digits abnormalities.

TABLE:11 ULTRASOUND AND AUTOPSY FINDINGS

CORRELATION:

TOTAL CASES	NO CHANGE IN INITIAL ULTRASOUND DIAGNOSIS	SIGNIFICANT ADDITIONAL FINDINGS FOUND IN AUTOPSY	NEW DIAGNOSIS AFTER AUTOPSY EXAMINATION
40	9	25	6



In 9/40 cases, the antenatal ultrasound findings were correlated with final autopsy diagnosis. Significant additional findings were frequently observed after final autopsy diagnosis (23/40 cases).

Discrepancies between ultrasound and autopsy findings were seen in 6/40 cases which is detailed in table12. Some of the syndromic causes were diagnosed only after autopsy examination, which was missed in antenatal ultrasound. USG showed evidence of Joubert's syndrome in one of the foetus, but autopsy findings favoured Meckel gruber syndrome. Oligohydramnios secondary to bladder outlet obstruction was noted in many of the cases. Similarly, single umbilical artery was also seen in 16/40 cases.

TABLE:12 DISCREPANCY BETWEEN ULTRASOUND AND AUTOPSY FINDINGS

S. No	Gestational age	USG findings	Summary of autopsy findings	Final diagnosis in autopsy
1	18 weeks	Normal study	DUS with dilatation and hypertrophy of the urinary bladder.Pulmonary hypoplasia	Bladder outlet obstruction (DUS)
2	18 weeks 1day	Moderate ascites and bilateral pleural effusion-hydrops fetalis	Hydrops foetalis. Bladder outlet obstruction due to urethral stenosis/?posterior urethral valves causing dilated posterior urethra, bladder, ureters and bilateralHUN Hypoplasia ductus, right and left pulmonary arteries, distal aortic arch and left subclavian artery. Ventriculomegaly, absent corpus callosum, deep posterior fossa.	Non immune hydrops foetalis, bladder outlet obstruction
3	23weeks 4 days	Pierre Syndrome, left hydronephrosis due to pelviureteric obstruction	Bilateral posterior choanal atresia,lop ears, micrognathia and ?microphthalmia. Persistent cloaca. Left hydronephrosis	Suggestive of CHARGE syndrome.
4	23 weeks 3 days	Foetus shows fetal akinesia deformation sequence with multiple anomalies. (Subcutaneous edema, non-visualized stomach,fixed flexion of	Microcephaly, slopping forehead, opaque lens, low set ears, depressed nasal bridge with small nose,small mouth, deviated tongue, micrognathia with very short neck and hirsutism. Hydrops foetalis.Hydraencephaly, hypoplastic pituitary, rudimentary posterior fossa and diffuse villous	suggestive of cerebro-oculo-facio-skeletal (COFS) syndrome

		upper limbs and fixed extension and crossing of lower limbs with plantar flexion of feet, sloppy forehead and micrognathia.)	hyperplasia of choroid plexus.Fixed flexion deformityofall limbs and fixed extension of lower limbs. Pulmonary hypoplasia. Distended bladder, dilated pelvicalyceal system with features suggestive of persistent urogenital sinus	
5	23 weeks	SIUG of 18 weeks + 1 D, liquor reduced, AFI - 4 cms. Foetal activity reduced.	DUS with hypertrophy of the urinary bladder. Pulmonary hypoplasia.	Bladder outlet obstruction (distal urethral stenosis).
6	19 weeks	SLIU 18 weeks. Foetus with increased NT, anhydramnios, bilateral renal agenesis with lying down adrenal sign, absent urinary bladder with cord around the neck.	Hydrops fetalis with depressed nasal bridge and low set ears. Abnormal hand with abnormal short fingers, syndactyly and right post axial skin tag. Feet with syndactyly and nail dysplasia. Bilateral renal agenesis with associated bilateral ureteral agenesis and flat, oval adrenals. Elongated, hypoplastic bladder with DUS. Pulmonary hypoplasia.	Bilateral renalagenesis, pulmonary hypoplasia and hand abnormalities. the possibility of 'acro-renal syndrome' needs to be considered

DUS- Distal urethral stenosis; NT – Nuchal Thickness

PLACENTA :

The placenta was included for examination along with foetal autopsy in 37 cases(37/40). The notable gross abnormalities found were single umbilical artery (16 cases), hypercoiled cord (Fig: 12a) (9 cases) and hypocoiled cord (1 case). Velamentous cord insertion was observed in a placenta of foetus diagnosed as CHARGE syndrome. The histological features of placenta included were amnion nodosum, (Fig: 12c & 12d) maternal vascular malperfusion, foetal vascular malperfusion, villous edema, intervillous thrombus and acute chorioamnionitis.

In a case of VACTERL association we had marked villous edema with placental hydrops. We received a still born male foetus at 24 weeks of gestation for examination. The cause of death was secondary to hypercoiled cord with stricture and foetal vascular malperfusion. Pelviectasia was found as an incidental finding in this case.

Discussion

DISCUSSION

The spectrum of Urogenital and anorectal malformations is extremely vast, but occur in significant frequency and varies from mild to syndromic to severe anomalies, which are incompatible with life. The urogenital and anorectal malformations arise from a defective development of the cloaca which leads to incomplete division or fusion of the cloacal membrane with urorectal septum. A gamut of anomalies may develop depending upon the severity level of the defects.

In this study, we have analysed 40 foetuses with urogenital and anorectal malformations and could provide an overview of the aetiopathogenesis of the underlying causes with associated malformations.

In 50% (20/40) of the cases, urogenital and anorectal malformations was part of the syndromic and non syndromic multisystem anomalies. Out of the remaining 50% of the cases , 32.5%(13/40) accounted purely of urinary tract (kidney+ ureters+ bladder+ urethra) malformations and rest of the 17.5%(7/40) of the cases constituted by the anomalies of the urinary tract combined with anorectal, genital and cloacal malformations.

RENAL ANOMALIES:

Renal abnormalities were observed in almost all foetuses. Malformations of the kidney can be classified into anomalies of number, size and position.

Anomalies of number:

This includes both unilateral and bilateral renal agenesis. Eventhough bilateral agenesis is rare compared to unilateral we encountered 4 cases each of unilateral and bilateral agenesis in which males were predominant(M:F =3:1). It was speculated that failure of the development of the ureteric bud leads to deficiency/degeneration in metanephric blastema, resulting in renal agenesis.

Three of the four unilateral agenesis cases were seen as part of 'VACTERL association'. The other kidney showed features of cystic renal dysplasia, dilated pelvis and ectopia.

The associated abnormalities found in bilateral renal agenesis (n=4) were OEIS complex(1), acrorenal syndrome(1), sirenomelia (1) and potter sequence(1). Apart from bilateral renal agenesis, the foetus of sirenomelia found to have single midline lower extremity, anal atresia with imperforate anus, colonic malrotation, single umbilical artery and hypoplasia with failure of fusion of mullerian ducts. There is considerable similarity between

sirenomelia and caudal dysgenesis since both the conditions were associated with defective early mesodermal development[27]. Surprisingly, there was no history of maternal diabetes in this case.

Anomalies of position :

Failure of ascent of the kidney is called ectopia and usually seen in pelvis. One of the infrequent congenital renal malformation is crossed fused renal ectopia[52].

In one of the crossed fused renal ectopia cases (n=2) the kidneys were present unilaterally fused in vertical plane. The right sided enlarged and distorted kidney had two hila with both ureters facing medially. The upper ureter coursed straight down to open on the right side of bladder. The lower ureter crosses the midline in the lower aspect at the level of aortic bifurcation to open on the left side of bladder. The left renal fossa showed flat adrenal and absence of left kidney. This case also had VACTERL association and orofacial clefts.

The commonest renal fusion anomaly in literature is horse shoe kidney[53,54]. In contrary, we encountered crossed fused renal ectopia (n=4) more commonly than horse shoe kidney (n=1). It was found incidentally in 21 week male foetus and had associated major anomalies such as aqueductal stenosis, hydrocephalus, VSD, hypoplasia of bladder, thumb and lungs.

Anomalies of form: (Cystic renal diseases):

Among the primary ciliopathies kidneys are the most commonly affected organs. A varied group of parenchymal disease causing renal cysts were identified and included in our study. They were ARPCKD (N=2), ADPCKD (N=2) and multicystic dysplastic kidney (N=10).These cystic renal diseases can be seen as a developmental, hereditary or acquired disorder. It can also occur in a background of obstructive uropathy.

ARPCKD is the most frequently encountered ciliopathy seen in utero and in infants due to an abnormality in the development of renal collecting ducts. Grossly, the kidneys were symmetrically enlarged retain its reniform shape and shows persistence of foetal lobulations. Cut surface of the kidneys show diffuse, multiple tiny cysts seen through out the cortex and medulla giving spongy appearance with no cortico medullary differentiation. Histologically, there were radially oriented elongated medullary cysts with dilated collecting ducts, tubules and interspersed normal glomeruli. The foetus also had bile ductular proliferation and periportal fibrosis. Since the polycystic kidney hepatic disease 1 ($PKHD_1$) gene encodes a protein which is situated in primary cilia of kidneys and biliarytract, renal cystic disease and intrahepatic biliary disease were identified simultaneously[58]. Both the cases of ARPCKD also showed severe pulmonary hypoplasia and oligohydramnios.

Apart from ARPCKD we identified 2 cases of ADPCKD. It was difficult to differentiate these two entities due to overlapping features. ADPCKD is also considered as one of the ciliopathies. Histology revealed renal parenchymal disorganisation, cystically dilated tubules, interstitial fibrosis with interspersed few preserved glomeruli. We did not hit upon any extra renal manifestations of ADPCKD such as cysts in other organs, cardio vascular disease or intracranial aneurysm.

A considerable number of foetuses (25%) in our study showed bilateral multicystic renal dysplasia with an associated obstructive component. The malformed, irregularly cystic kidney showed disorganised renal parenchyma with immature tubules surrounded by collarette of condensed mesenchyme[45]. Cystically dilated tubules were also noted. We did not observe metaplastic cartilage. Among our foetuses with dysplastic kidneys, 2 each had VACTERL and Urorectal septum malformation sequence (with absent bladder), 1 each of FRYN syndrome, MECKEL GRUBER syndrome and persistent Mullerian duct syndrome. Hypoplastic urinary bladder and urethral atresia were also identified.

Abnormalities of urethra causing urogenital malformations were identified and included. They were distal urethral stenosis/atresia, posterior urethral valve and megalourethra.

Urethral stenosis:

A complete obstruction or narrowing of the urethra (urethral stenosis/atresis) was the underlying cause of bladder outlet obstruction in 6 male foetuses and 1 female foetus. In addition, the female foetus found to have associated complex abnormalities such as pseudohemaphroditism, hydrops, megacystis with bilateral hydroureteronephrosis, urethral duplication and persistent cloaca. The distal urethra could not be probed with absence of external urethral meatus. Microscopically, there were dilatation and hypertrophy of urinary bladder and ureters.

Posterior urethral valve:

Posterior urethral valve is one of the most common cause of lower urinary tract obstruction identified in our series. The cases of PUV had abdominal distention, megacystis, tortuous and dilated ureters. The kidneys often show subcapsular peripheral cysts with dilated pelvis and multicystic dysplasia.

Dewan and Goh were the first researchers proposed about congenital obstructive posterior urethral membrane and subsequently it was histologically confirmed by Baskin[40,41]. According to Young's classification in 1919 type 1 of PUV was the commonest which was found in our study too. It consists of prominent anterolateral mucosal folds which are nothing but plicae colliculi exaggeration. The other two types included were

extension of valves from verumontanum to bladder neck (type2) and mucosal diaphragm (type3). Histologically, we observed bladder wall thinning with fine mucosal trabeculations. The kidney show marked thinning of renal parenchyma with cystic dilatation of tubules, bowman's space and reduction in number of nephrons.

Congenital megalourethra[44]:

One of the uncommon cause of bladder outlet obstruction was congenital megalourethra. It was classified into scaphoid and fusiform variants by Dorairajan in 1962[43]. Deficiency of corpus spongiosum alone was noted in scaphoid type. In contrast, fusiform variant found to have both spongiosum and cavernosal deficiency. Here one of our foetuses had a greatly enlarged urethra covered by puboscrotal swelling and ended blindly. Histologically the sections from the penile urethra showed urethral walls with concentrically arranged spindle cells. The spongiosum and cavernosum were not identified (fusiform variant of congenital megalourethra).

One of the important component of amniotic fluid is foetal urine. When the foetal urine production is decreased due to bladder outlet obstruction of various causes, it leads to oligohydramnios and anhydramnios resulting in megacystis (bladder distension) with bilateral hydroureteronephrosis and subsequently leads to cystic renal dysplasia. Massively distended bladder and kidney compress the adjacent organs and

abdominal muscles, affects its growth and produces atrophy. Similarly, it will prevent normal intestinal positioning and testicular descent and resulting in intestinal malrotation and undescended testis. We also observed some of the cases with the above findings due to megacystis[27]

Chun.shunwu highlighted the mechanism by which oligohydramnios causes pulmonary hypoplasia. They observed that presence of oligohydramnios during pseudoglandular stage of lung development decreases the collagen and elastic tissue of the foetal lung. Structural alteration of the respiratory system with decreased intrathoracic cavity size disrupts lung growth and leads to pulmonary hypoplasia[42]

Potter syndrome was first coined by Dr.Edith Potter in 1946[27]. She described the typical physical appearance and lung hypoplasia secondary to oligohydramnios. Similarly most of our foetuses with oligohydramnios also had depressed nasal bridge, low set ears, micrognathia and limb abnormalities. Mechanical deformities due to oligohydramnios causing rocker-bottom feet is also identified.Surprisingly we did not come across cases with Prune belly syndrome (deficiency of abdominal muscle. Undescended testis and urinary tract malformations).

SPECTRUM OF UORECTAL SEPTUM MALFORMATIONS:

URSM Sequence(N=8):

The term 'URSM' sequence was coined by Escobar et al in 1987 and he reported 6 cases with URSM only in females[5]. In 1997, wheeler et al noted URSM cases in male foetuses also with the Male : female ratio of 7:6[5]. In 2006, Patil &Phadke reported ratio of males to female URSM cases as 0.87. In contrary, we encountered URSM in 4 female and 1 male foetuses. Apart from this, remaining 3 foetuses had phallus like nodular structure with fused labia, which made the sex determination more difficult . However, internal examination revealed testicular tissue in 2 foetuses and uterus with tubes and ovaries in one case. Hence the male: female ratio of 0.6 (3:5 cases) with female predominance was observed in our series (shown in table 1).

Table – 1 Sex Distribution of cases in URSM sequence

Genitals	**COMPLETE URSM**			**PARTIAL URSM**			**UROGENITAL SINUS**	
External	ambiguous	ambiguous	ambiguous	M	F	F	F	F
Internal	M	M	F	M	F	F	F	F

In 2001,Wheeler and Weaver reported a non lethal form of URSM and called it as partial URSM, which is characterized by single perineal/anal opening with an imperforate anus. Since partial URSM cases have a good

prognosis in contrast to Complete URSM, it is mandatory to differentiate these 2 entities. In our study, We found 3 cases each of complete and partial URSM. Cases with hypospadias and large penis with epispadias were noted in 2 male foetuses. Prominent clitoris was observed in female foetuses. In addition, Non immune Hydrops foetalis was present in three cases of URSM.

Many theories have been described in the pathogenesis of URSM and included were lateral compression theory, vascular steal phenomenon and teratogenic theory. Experimental evidence suggested that deficiency of Caudal mesoderm migration with or without irregularities of the notochord (especially during blastogenesis), may cause URSM sequence. Alterations in homeobox (Hox) and sonic hedgehog were also implicated in deficiency of Caudal mesoderm[48].

Karyotyping was done in one case of persistent urogenital sinus, which revealed 22q microdeletion.

SYNDROMIC CAUSES:

VACTERL Association was the commonest syndrome identified in our study. Uehling, Gilbert and Chesney described the urologic implications of VATER[12]. The closest differential diagnosis of VACTERL included was URSM, since both the conditions can have vertebral abnormalities with

limb defects, cardiac defects, imperforate anus, tracheo - esophageal fistula and renal anomalies.

According to Chien et al, anomalies of genitalia, urinary tract, anal atresia and sacral Hypoplasia were frequently found in URSM than VACTERL. Similarly, in our study we observed more chances of anomalies involving the genital (ambiguous),lower GI (colonic atresia) and urogenital tracts and sacral agenesis than VACTERL. The renal abnormalities were common in both the conditions.

High occurrence of vertebral (hemivertebrae), limb anomalies (talipes, radial aplasia, polydactyly, absent forearm and feet) cardiac defects (TOF, PDA, VSD, right aortic arch) and atresia /fistula of upper aerodigestive tracts (TEF, esophageal atresia, pyloric atresia, absent gallbladder & appendix) were encountered in cases with VACTERL. Interestingly, we found VACTERL Association with coexistent URSM in two of our cases (each with partial and complete URSM).

OEIS complex represents an extended phenotype for exstrophy of cloaca. In 1978, Carney et al coined the term ‘OEIS complex’ as an acronym and is characterised by abnormalities involving the lower region of the body. This includes omphalocele, exstrophy of bladder, imperforate anus and spinal defects.

Apart from the findings in acronym, we also found hydrocephalus, bilateral renal agenesis, absent external genitalia and persistent mullerian duct remnants (in a male foetus) in our OEIS foetuses.

The following possible hypothesis that explains the development of exstrophy are

1. The development of exstrophy may be due to an early or delayed timing of rupture of the cloacal membrane coupled with insufficient descent of urorectal septum.

2. Insufficient invasion of the cloacal membrane by mesoderm can lead to defective growth of anterior abdominal muscles and pubic bones[49]

MECKEL GRUBER SYNDROME is a lethal, autosomal recessive ciliopathic genetic disorder affecting many organ systems. Primary cilia generally exist in almost all the cells in the body and its mutations can affect multiple systems and are broadly termed as “ciliopathies”. In our case series ,we found two cases of Meckel Gruber syndrome, which is characterized by the presence of multicystic kidney dysplasia, CNS malformations, orofacial clefts, polydactyly and congenital hepatic fibrosis.

Apart from the occipital encephalocele, other CNS anomalies have been identified in our study were small cerebellum with partial agenesis of vermis, hydrocephalus, shallow posterior fossa, microcephaly and

ependymal cyst. The additional findings detected were hypoplastic left heart syndrome, right ventricular hypertrophy and lung hypoplasia. Orofacial clefts were not identified.

NON SYNDROMIC MULTI SYSTEMIC CONGENITAL ANOMALIES ASSOCIATED WITH UROGENITAL AND ANORECTAL MALFORMATIONS:

Urogenital and anorectal malformations were frequently associated with anomalies of other systems, among which Gastrointestinal (32.5%) and Skeletal system defects (30%) were most commonly seen, followed by Cardiovascular (22.5 %) and Central nervous system (15%). Most of the foetuses had pulmonary hypoplasia secondary to oligohydramnios.

The combination of urinary tract with anorectal and genital anomalies was generally acceptable, since lower GIT and urinary tract have a common origin(cloaca) during development.

We encountered Imperforate anus in nine cases, of which 6 were males and 3 were females. A detailed and anatomically specific classification was presented by Stephens and Smith[50]. They have classified anorectal malformations into high, intermediate and low types in both the males and females. In our study we have not divided the anorectal malformations depending upon the location of the defect. But we have documented anal/rectal/anorectal atresia in 4 cases and each case of

rectovesical /rectourethral fistula. Apart from that we also observed imperforate anus in complete URSM, Sirenomelia, VACTERL and OEIS complex.

PLACENTAL EXAMINATION:

Apart from causing severe oligohydramnios and fatal pulmonary hypoplasia foetuses of urogenital malformation also showed amnion nodosum, a placental sign of severe and prolonged oligohydramnios. Amnion nodosum has a gross appearance of multiple tiny yellow brown granular to nodular lesions, 0.1 to 0.3 cms on the foetal surface and also onto the membranes near umbilical cord insertion. Microscopically, the amniotic epithelium showed patchy nodules consisting of eosinophilic amorphous material interspersed with squames, hair and sebum.

Many speculated theories for amnion nodosum were formulated[51] and includes

1) In cases of antepartum bleeding hemorrhagic effusion produces layers of serum with contracted coagula over the amniotic epithelium.
2) Due to amniotic metaplasia or grafting of foetal epithelial cells.
3) Inflammation
4) Since the amniotic epithelium lacks vasculature it entirely depends on the amniotic fluid for its nourishment. Lack of amniotic fluid in cases of severe oligohydramnios leads to degeneration and defect over

which vernix is deposited as a nodular pattern – most accepted pathogenesis[51].

Eventhough it appears late in pregnancy both of our amnion nodosum cases were of second trimester. We also encountered placenta with maternal vascular malperfusion (in gestational diabetes cases), foetal vascular malperfusion, villous edema (in cases of hydrops) and acute chorioamnionitis.

ULTRASOUND AND AUTOPSY FINDINGS CORRELATION:

We correlated prenatal ultrasound findings and final autopsy results of our foetuses with urogenital and anorectal malformations. Complete agreement between prenatal ultrasound findings and autopsy findings was found in only 9 cases (22.5%). These cases were persistent urogenital sinus, bilateral multicystic dysplastic kidneys, VACTERL association, OEIS complex, bilateral renal agenesis and CAKUT.

This is in contrast to a study done by Antonella et al in 2012, where there was a 49% of complete agreement[55,56].

In 62.5% of cases autopsy added additional findings with revision of diagnosis and this caused significant change in recurrence risk.

COMPARISON OF AUTOPSY AND ULTRASOUND FINDINGS IN VARIOUS STUDIES[39]:

STUDIES	TOTAL NUMBER OF CASES	NO CHANGE IN INITIAL ULTRASOUND DIAGNOSIS	SIGNIFICANT ADDITIONAL FINDINGS FOUND IN AUTOPSY	CHANGE IN INITIAL ULTRASOUND DIAGNOSIS (DISCREPANCY)
Our study	40	22.5%	62.5%	15%
Sankar and Phadke	134	41%	58%	1.49%
Andola et al	39	50	29.54	9.09
Vimercati et al	144	71	35	17
Yeo et al	88	65	35	-
Grover et al	40	32.5	42.5	25
Venkatasamy C	45	37.7	22.2	33.3

When compared to the results of other study ours showed more of additional findings especially of urorectal septum malformation sequence. Anomalies of all systems were correlated in their study, in contrast we compared only of urogenital and anorectal malformations.

Complete discrepancy was noted in 15% of cases. Anomalies that were picked up by autopsy examination were distal urethral stenosis, choanal atresia, tracheo esophageal fistula, hand and facial abnormalities and urorectal septum malformation sequence.

Accurate diagnosis for the cause of non immune hydrops foetal is cases, especially secondary to bladder outlet obstruction was possible by thorough autopsy examination.

Reasons for discordance in ultrasound findings can be due to foetal position, operator experience, amniotic fluid volume and maternal obesity leading to poor visualization of foetal anatomy[57]. The highest rate of discordance was found in multiple anomalies.

LIMITATIONS :

1. Retrospective nature of our study
2. Most of our cases were not correlated with chromosomal test results, hence an associated chromosomal aberrations cannot be totally excluded.
3. We have not classified anorectal malformations in to high, intermediate and low types.
4. Still birth with superimposed autolytic changes cases distorted anatomy of few cases.

A large prospective study including chromosomal analysis in future will contribute in enhance our understanding of the disease process and also will help in parent counselling.

The clinical autopsy has long been an indispensable aspect of medical practice. Nevertheless over a past few decades, there is a dramatic reduction in the utilization rate of clinical and foetal autopsy, which causes a major concern. The foetal autopsy will contribute to establish the cause of death, to understand the disease process and to confirm the prenatal diagnosis. It will also help us to find out the effectiveness of treatment (artificial reproductive techniques) and to identify the new or re-emerging disease. Families can be made aware of the possible cause of death and its hereditary implications. Autopsy results can also contribute to medico legal aspects, research, audit and be helpful as quality check for prenatal ultrasound examination.

Modern imaging techniques, advancements in prenatal diagnosis, genetic analysis and in utero targeted therapeutic options are being considered to support, but not to replace the vital aspect of autopsy. It cannot be overemphasized that the effect of any form of therapy is primarily dependent on meticulous autopsy examination and its clinico pathological correlation.

Summary and Conclusions

SUMMARY AND CONCLUSIONS

Urogenital and anorectal malformations are a complex group of congenital abnormalities having a sporadic and rare hereditary occurrence. It is one of the commonest abnormalities seen in malformed foetuses and are usually preceded by Cardio vascular and Central nervous system abnormalities.

In this study, we have analysed 40 foetal autopsy cases with urogenital and anorectal malformations. Placental examination was also included in most of the cases.

A modification of the foetal autopsy evisceration technique is warranted in cases of suspected Urogenital and anorectal malformations. Entire Urogenital and anorectal organ system involving perineal anal opening should be included while doing the 'enbloc' organ removal.

The associated renal abnormalities was found in almost all the foetuses of our series, and include uni /bilateral renal agenesis, multicystic renal dysplasia and polycystic kidney disease.

Distal urethral stenosis was most commonly observed as a cause of megacystis in our study and was followed by posterior urethral valve.

Uro rectal septum malformations /cloacal dysgenesis sequence, a lethal form of urogenital and anorectal anomalies, represented frequently and accounted for 20% of our cases.

Syndromic associations constituted 35% of our Urogenital and anorectal foetuses. The most common syndrome identified was VACTERL association followed by OEIS complex and Meckel Gruber Syndrome.

The associated non syndromic other system abnormalities were also encountered in our study, comprised of gastrointestinal tract, central nervous system and cardiovascular systems in a descending order. Skeletal system malformations secondary to severe oligohydramnios were also identified.

The cause of urogenital and anorectal malformations appears to be heterogenous with diverse aetiology. The prognosis and survival of the foetus is usually determined by the underlying cause. The finding of oligo/ anhydramnios should trigger a thorough examination of urogenital and anorectal system. It should also direct us to look for an associated other systemic malformations for grouping them into syndromic/ non syndromic multisystem involvement/ chromosomal aberrations.

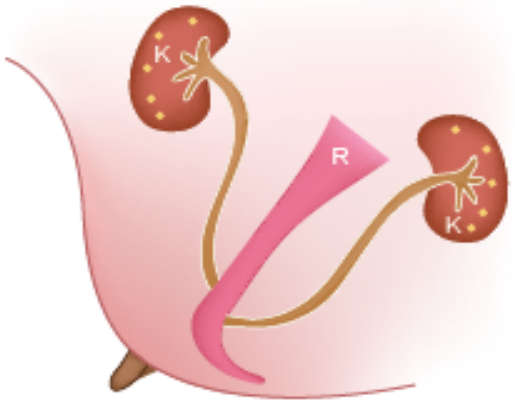
A meticulous post mortem examination of the foetus with cause analysis play a vital role to arrive at a final diagnosis and help us to understand the aetio pathogenesis. Foetal autopsy not only confirms the prenatal ultrasound findings, but also adds additional findings or changes the final diagnosis. Since some of the congenital anomalies have genetic preponderance, the establishment of correct diagnosis will help us to assess the recurrence risk and to counsel the parents regarding next pregnancy outcomes. It will also guide the clinicians and parents for early intervention or in utero targeted therapy.

Recent advancement in imaging studies, genetic and molecular techniques can complement but cannot replace a complete and thorough autopsy examination. Hence our present study emphasize the crucial role of foetal autopsy in all cases of suspected urogenital and anorectal malformations.

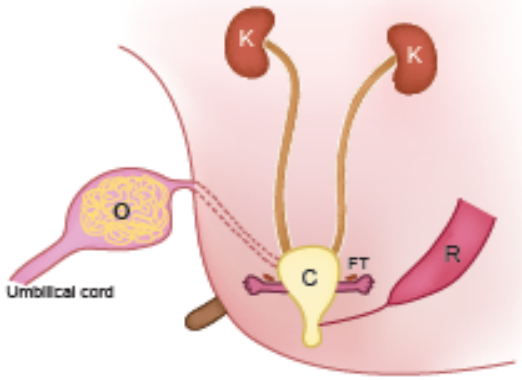
Images

COMPLETE URORECTAL SEPTUM MALFORMATION SEQUENCE (FIGURE 1)

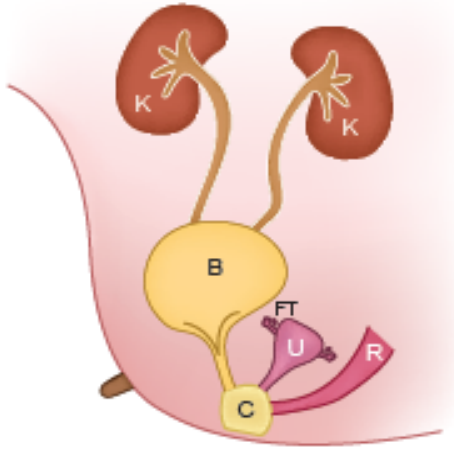
♂ ♀ ♀



- 16 weeks male foetus with ambiguous genitalia – Phallus like structure.
- Smooth perineum without urethral or anal orifice.
- Rectal pouch with posteriorly directed anal canal Anal atresia
- Absent bladder, ureters draining into atretic anal canal.
- Bilateral multicystic renal dysplasia.



- 13 weeks female foetus with ambiguous genitalia.
- Smooth perineum without urethral, vaginal and anal openings.
- Omphalocele.
- Ureters and fallopian tube draining into pelvic pouch.

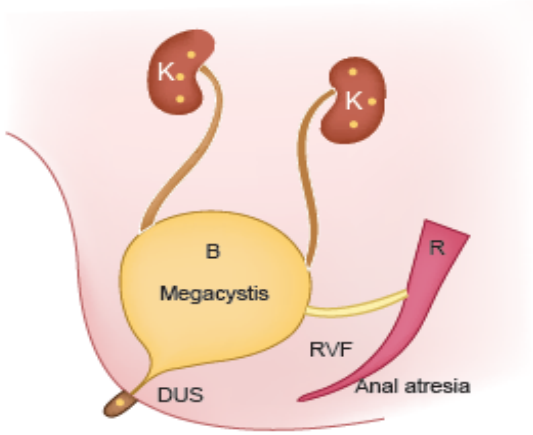


- 24 weeks female foetus
- External genitalia – phallus like structure
- Female pseudohermaphroditism
- Megacystis with bilateral hydroureteronephrosis, urethral duplication.
- Urethral, vaginal and anal openings are entering into the persistent cloaca.

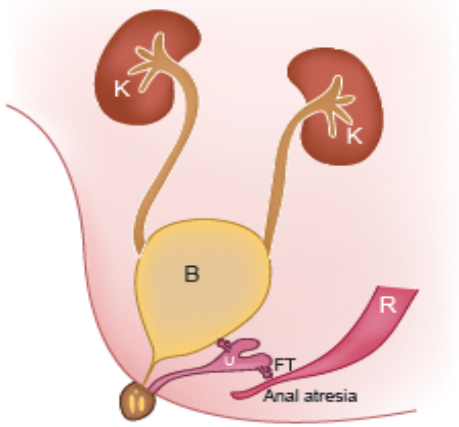
K - Kidney **U - Uterus** **R - Rectum** **C - Cloaca** **O - Omphalocele** **B- Bladder** **FT - Falloplan Tube**

PARTIAL URORECTAL SEPTUM MALFORMATION SEQUENCE (FIGURE 2)

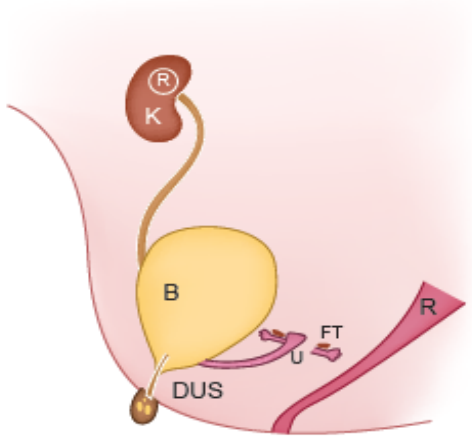
♂ ♀ ♀



- 13 weeks male foetus with phallus like external genitalia.
- No anal opening.
- Anal atresia with recto vesical fistula (RVF).
- Megacystis with distal urethral stenosis (DUS).
- Bilateral dysplastic kidneys.



- 22 weeks female foetus
- Anal atresia with imperforate anus
- Distal urethral obstruction with bilateral hydroureteronephrosis.
- Bicornuate uterus



- 18 weeks female foetus
- Left renal agenesis with ureteral agenesis.
- Distal urethral stenosis (DUS).
- Right fallopian tube attached to elongated uterus which is draining into bladder
- Left fallopian tube lies freely with no attachment.
- Anteriorly placed anus with normal opening

K - Kidney **U - Uterus** **R - Rectum** **B- Bladder** **FT - Fallopian Tube**

Figure – 3 - Autosomal Dominant Polycystic Kidney Disease (ADPCKD) :

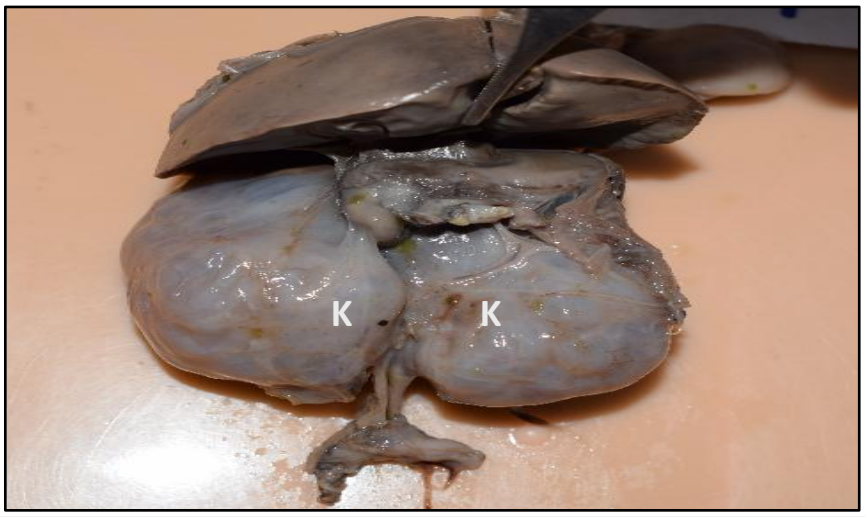


Figure 3a – Gross Appearance - Both kidneys are enlarged with hypoplastic bladder.

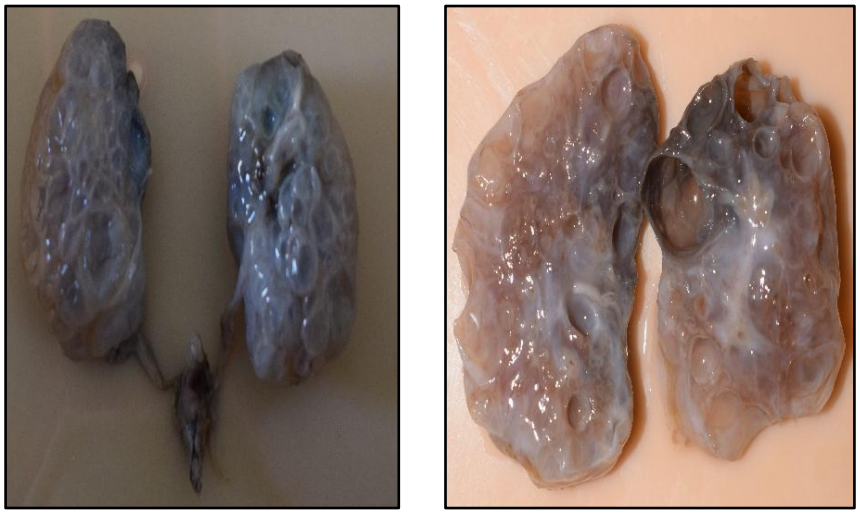


Figure 3b & 3c - External and cut surfaces shows multiple cysts replacing entire cortex and medulla, ranging in size from 0.2 to 1.0cm.

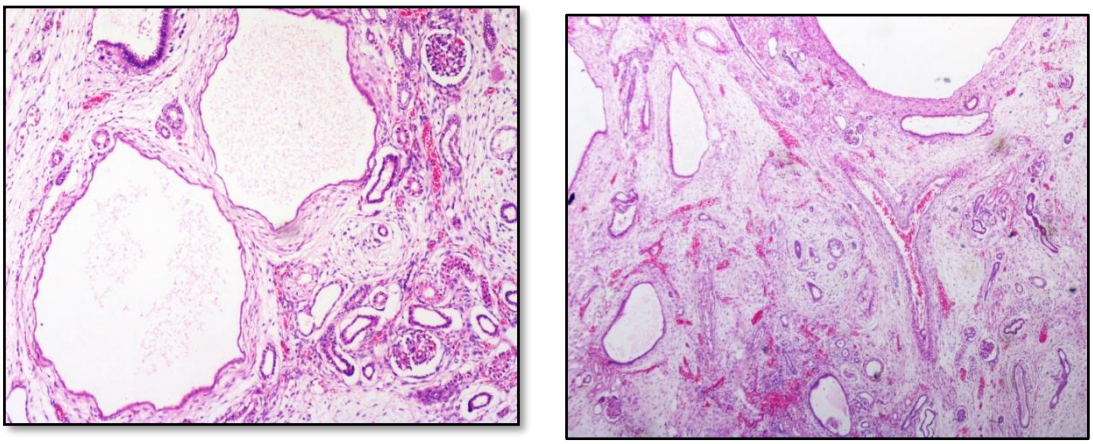


Figure 3d & 3e : HPE - Shows multiple cysts lined by cuboidal epithelium. Normal preserved glomeruli are seen between the cysts. Interstitium is loose, shows congested vessels.

Figure – 4 -MECKEL GRUBER SYNDROME WITH THE FOLLOWING FEATURES:

4a. to 4d - ARPCKD:

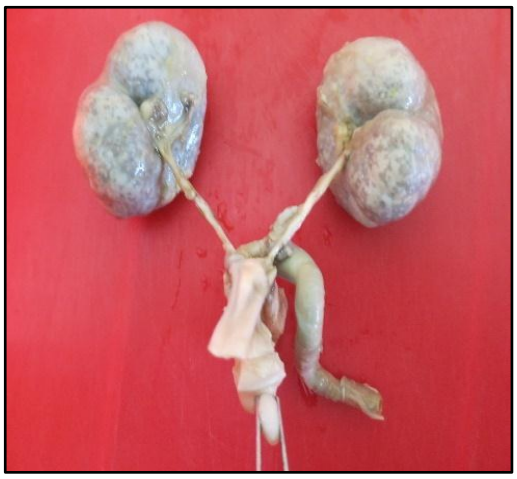
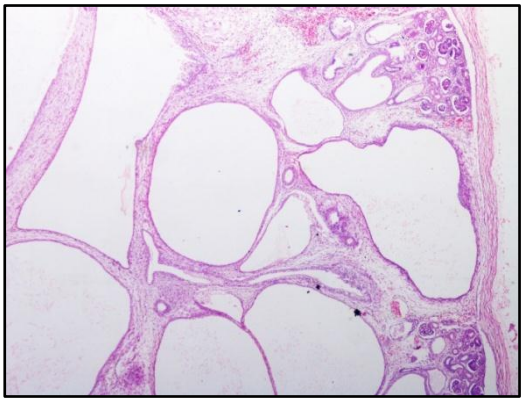


Fig 4a - B/L kidneys are enlarged and shows persistent foetal lobulation.

Fig 4b - The cut surface shows diffuse multiple tiny cysts seen throughout the cortex and medulla and gives spongy appearance.



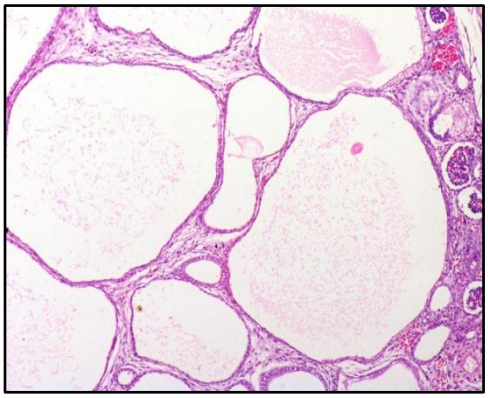


Fig. 4c & 4d – HPE - Shows patchy sub-capsular nephrogenic zone with normal glomeruli. The remaining cortex and medulla show numerous cysts of varying sizes lined by flat to cuboidal epithelium.

Fig. 4e. - OCCIPITAL ENCEPHALOCELE

Fig 4e - The occipital region shows a skin covered swelling, consists of soft reddish brown fibrous tissue. It overlies a defect in the occipital bone, through which meninges and brain substance herniate

Fig. 4f. - HYPOPLASTIC LEFT HEART SYNDROME

Fig 4f. Hypoplastic left atrium, ventricle, ascending aorta and arch, right ventricular hypertrophy

Figure – 5 - COMPLETE URSM:

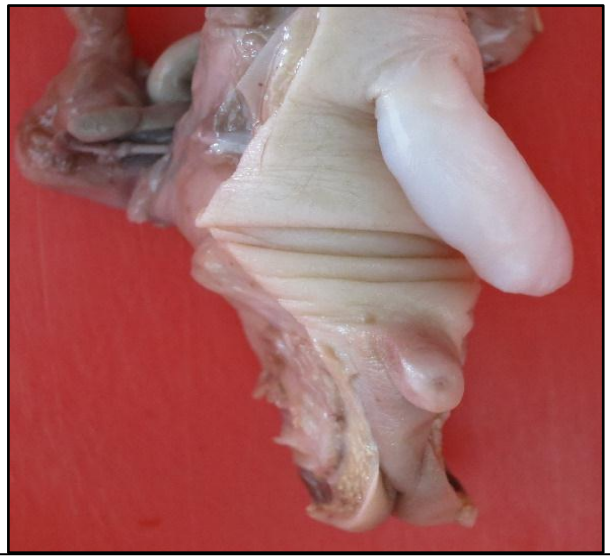
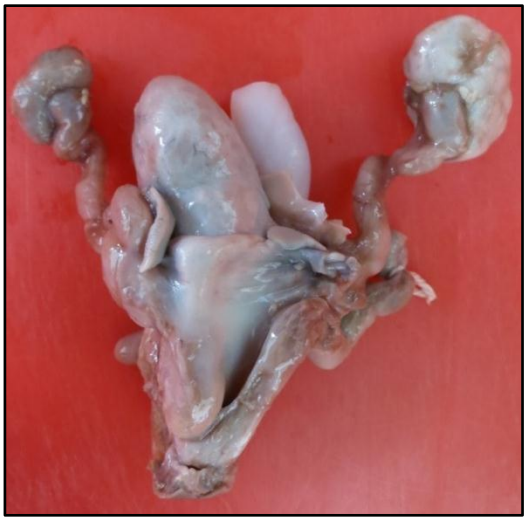


Fig 5a - Female pseudohermaphroditism - ambiguous genitalia with phallus like structure



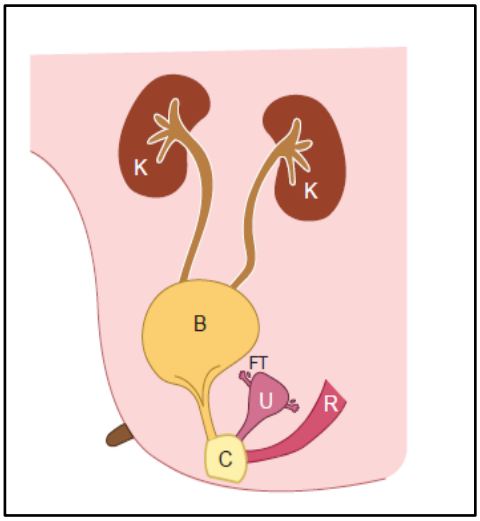


Fig 5b - Megacystis with hydroureteronephrosis, dilated and tortuous ureters and a cloacal pouch

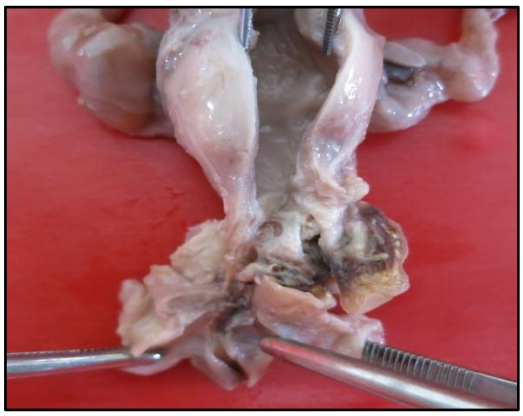


Fig 5c - Persistent cloaca; Urethral duplication with mid ureteric stenosis of ventral urethra.

Figure – 6 - PERSISTENT MULLERIAN DUCT SYNDROME:

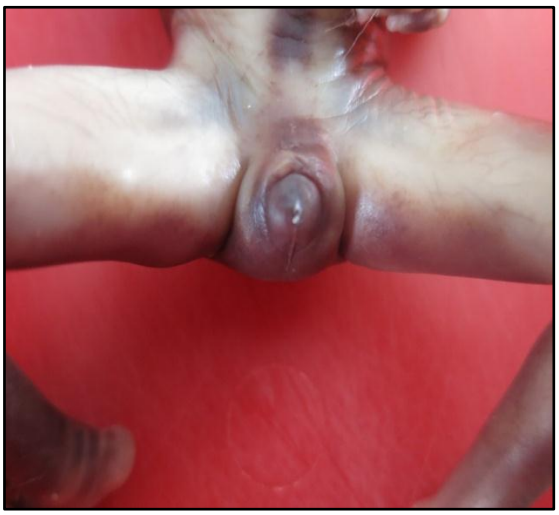


Fig. 6a - Ambiguous genitalia with Male pseudo hermaphroditism.
The external genitalia showed labia majora, stretched over a mound of darker skin that had a spot/punctum at its summit .

Fig 6b - Anorectal atresia. Bladder outlet obstruction with bilateral hydronephrosis and renal obstructive dysplasia.

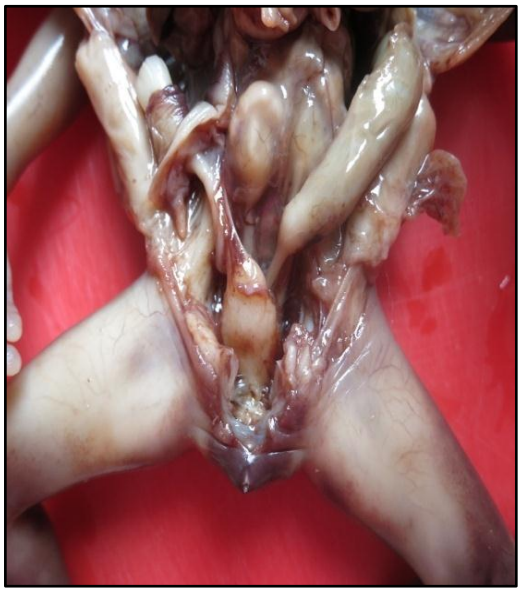


Fig.6c & 6d - The gonads(testes) were pelvic in position. Each was connected to the inguinal region by a short cord of white translucent tissue-gubernaculum. They were also related , medially to a tortuous ,fine, thread like structure(oviduct) to paired tubes(Mullerian ducts).

Figure 7 - POSTERIOR URETHRAL VALVE:

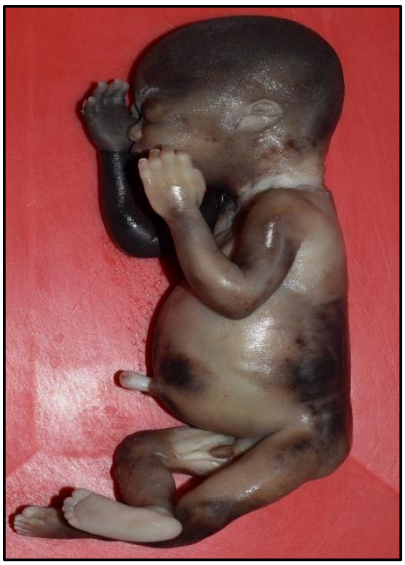


Fig 7a. Well developed male foetus shows congestion of skin over abdomen, right hand and lower left side of back. The ears are low set. Abdomen is distended.

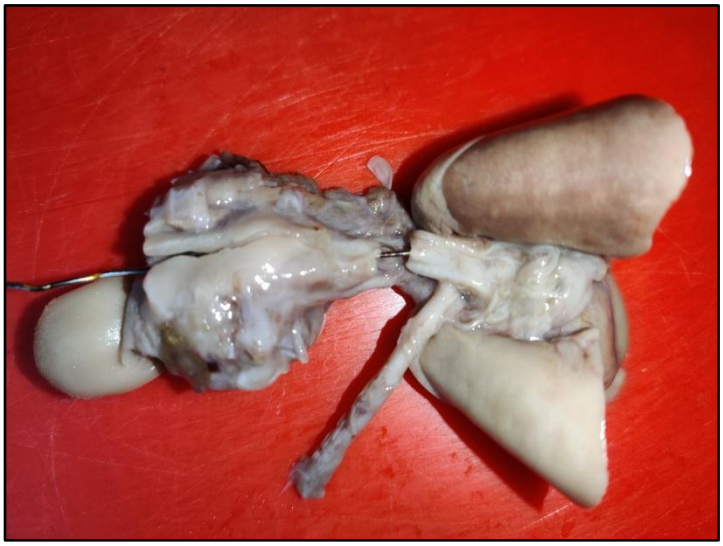
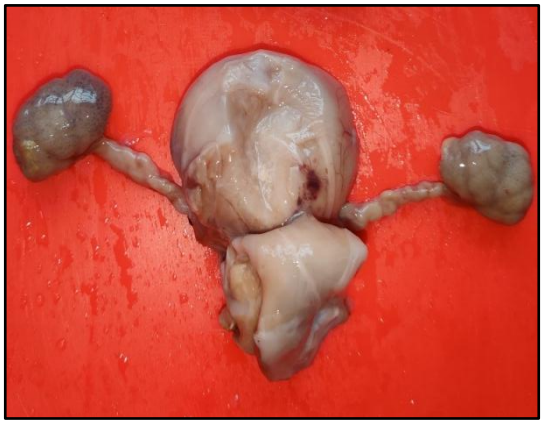


Fig 7b. Tracheal agenesis; bilobed right lung



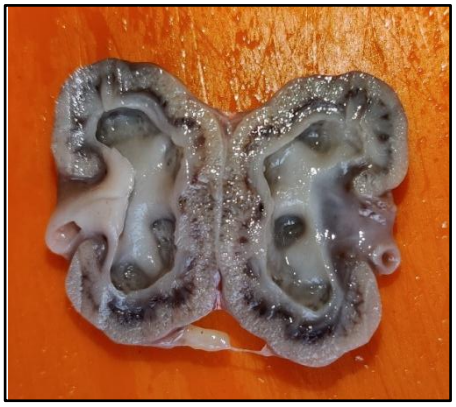


Fig 7c & 7d. Megacystis with hydroureteronephrosis. External surface of both the kidneys show tiny cysts. Bilateral ureters are dilated, tortuous with markedly dilated pelviureteric junction. The bladder is markedly distended, cyst like mea.5x4.5x2.8cm.

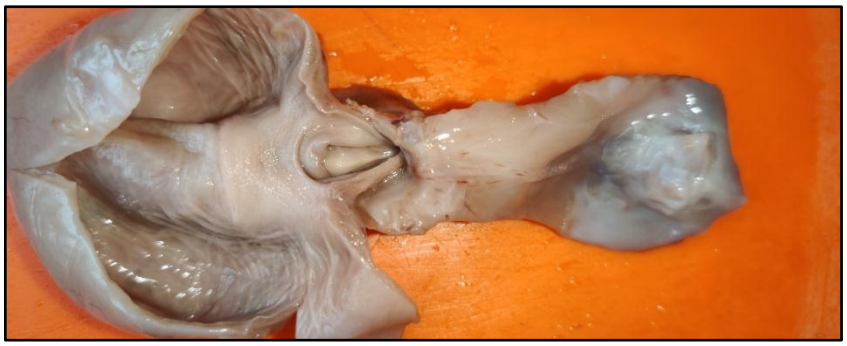


Fig 7e. Posterior urethral valve -The bladder wall is thinned out. Folds of mucosa forming a membrane like structures, which is extending from verumontanum to bladder neck causing obstruction and cystic dilatation

Figure 8 - POTTERS SEQUENCE

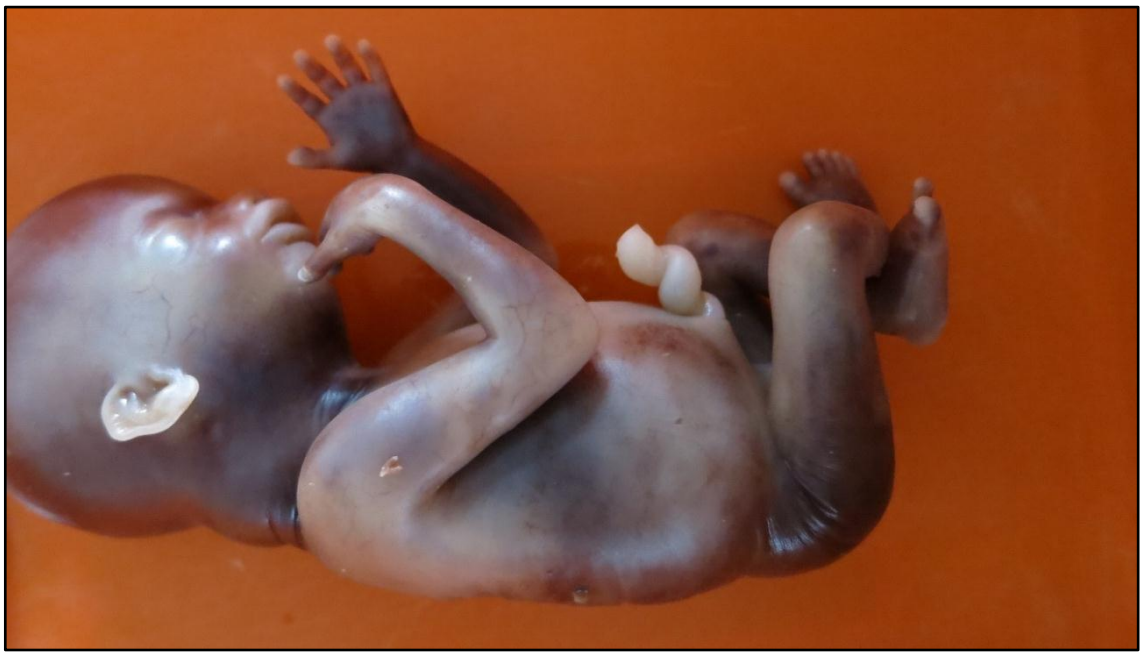


Fig 8a. The right ear is low set with depressed nasal bridge and retrognathia.

Fig 8b. Bilateral kidneys and ureters are absent. Bladder is hypoplastic thin and cord like mea. 0.5x0.3cm. Adrenals are enlarged.

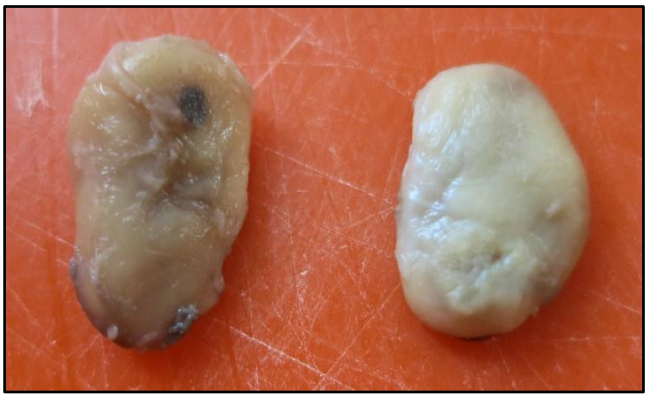


Fig 8c. Both the adrenal are oval and disc shaped.

Figure 9 - OEIS CCOMPLEX:

Fig 9a & 9b. Omphalocele containing portion of liver, gallbladder, small and large intestines including appendix and rectum.

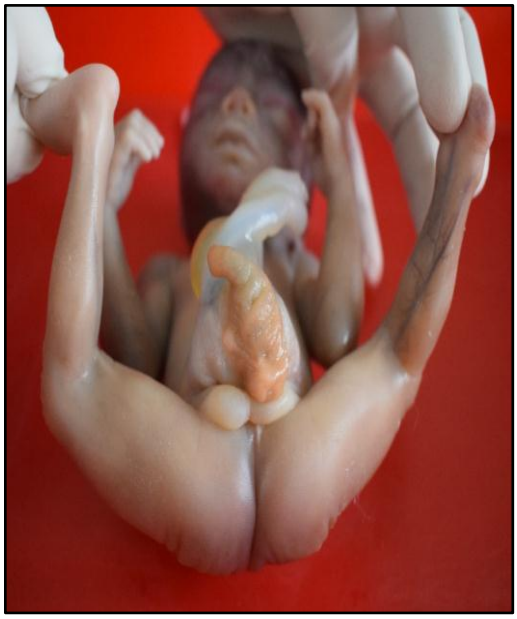
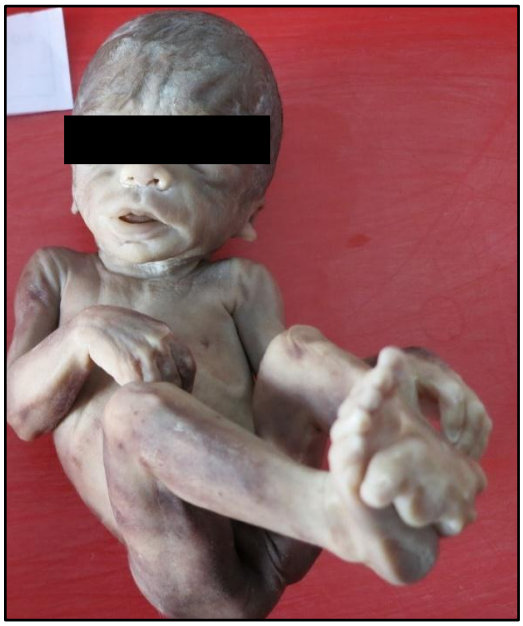


Fig 9c. Absent external genitalia. Imperforate anus with no urethral opening

Fig 9d. Exstrophy of cloaca with blind ending hindgut (anal atresia) terminating in the cloacal pouch.

Figure 10 - VACTERL ASSOCIATION:



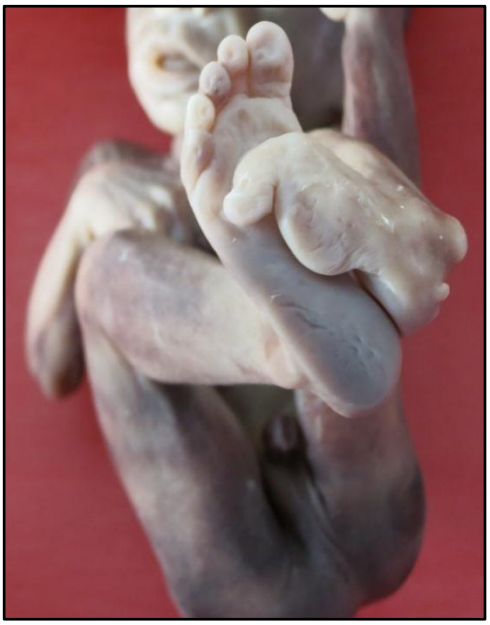
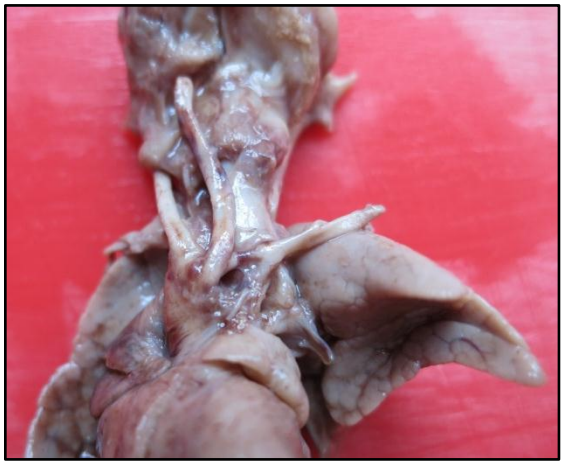


Fig 10a & 10d. The left clubfoot with a single digit. The right foot is 'rocker bottom' in type



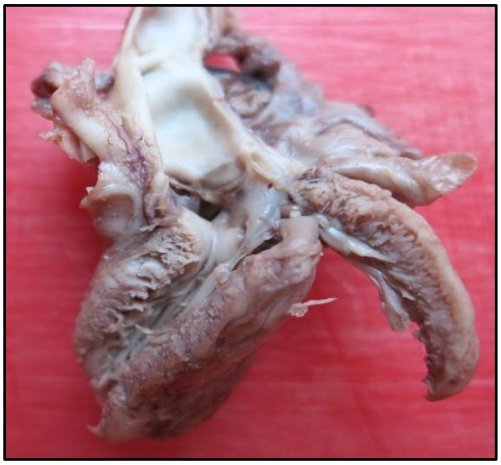


Fig 10c & 10d. Tetralogy of Fallot with ventricular septal defect, right aortic arch and left sided patent ductusarteriosus

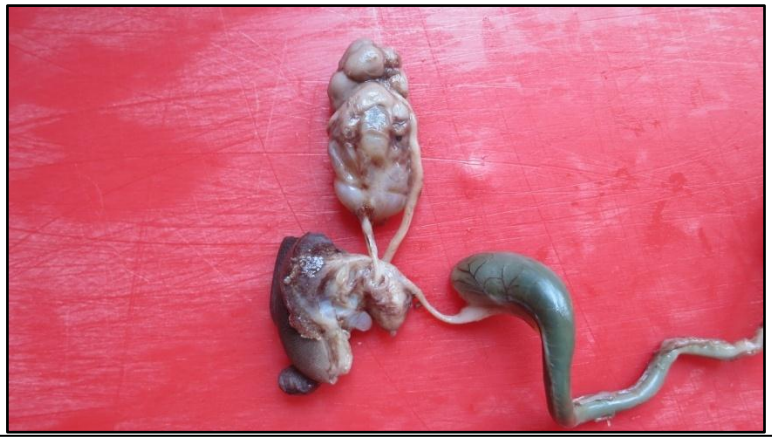


Fig 10e. The kidneys are fused in the vertical plane, together measure 5.0x1.8x2.0 cm.Fused crossed renal ectopia with hydronephrosis. Atresia of distal sigmoid, rectum and anus.

Figure 11 - VACTERL ASSOCIATION

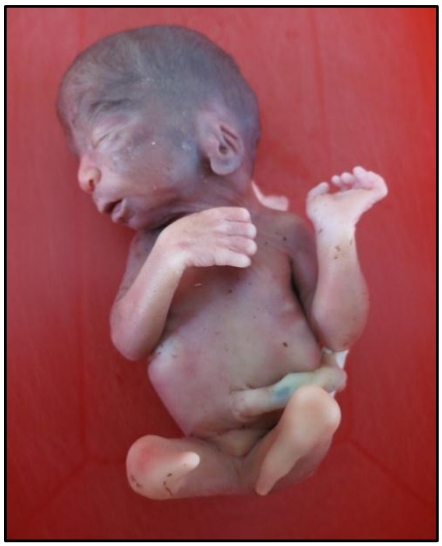


Fig 11a. Both lower limbs show short thigh with single blind ended, bony protruberance at the portion of the leg. There are no feet

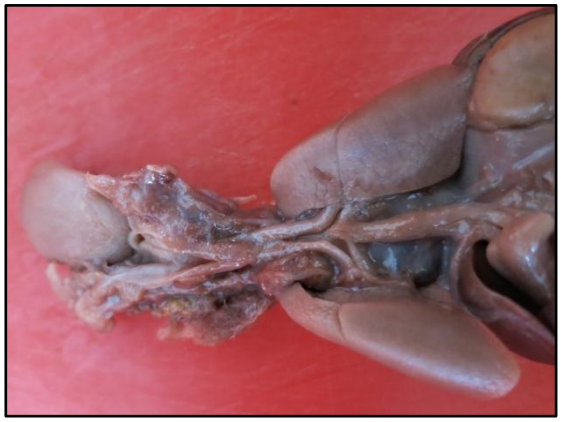


Fig 11b. The upper portion of the esophagus ends blindly. A fistula is connecting the carina of the trachea and proximal end of the lower esophageal segment (TEF type-A).

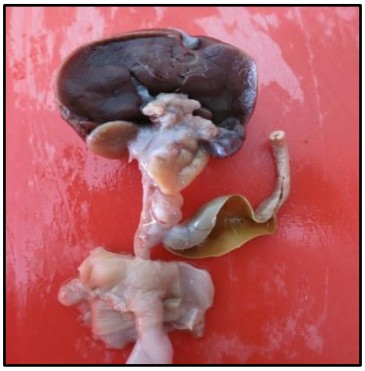


Fig 11c. The rectum is distended with meconium and enters into a pouch like midline structure, 1.0x1.5 cms. The pouch is thick walled with inner linear striations.

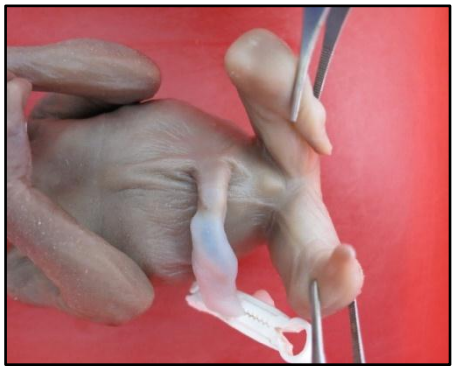


Fig 11d. Cloacal malformation –male foetus with smooth / intact perineum(without urethral or anal orifices) and absent external genitalia

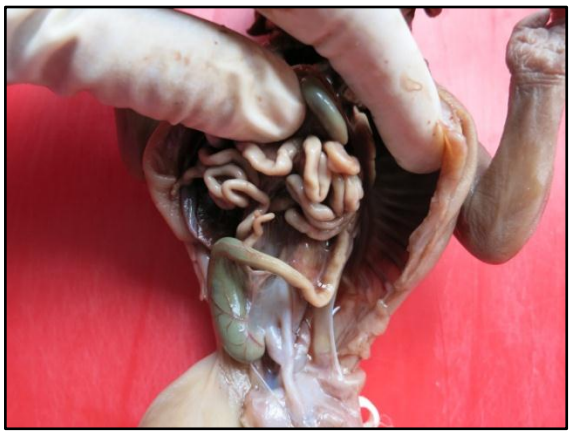


Fig 11e. Large intestinal malrotation, vitello intestinal duct remnant with atresia of rectum and anus.Absent right kidney, ureters and urinary bladder.

Figure 12 - PLACENTA ABNORMALITIES

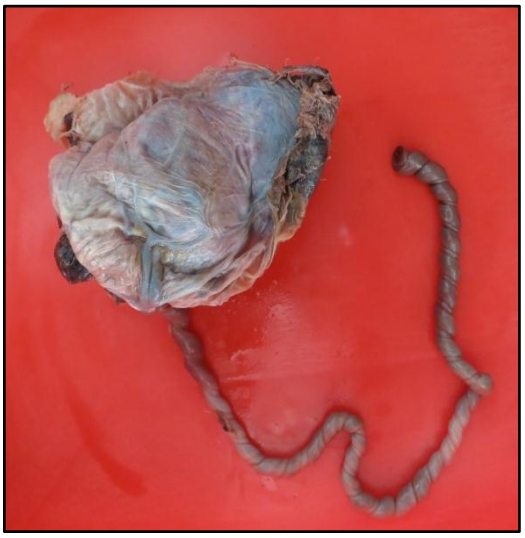


Fig 12a. Gross appearance of placenta showing hypercoiled cord

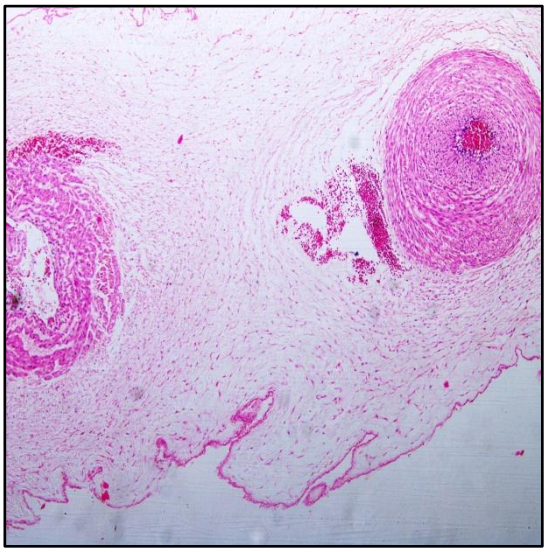
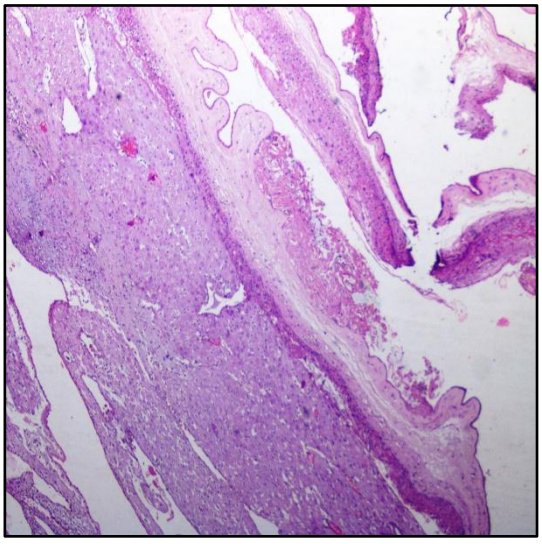


Fig 12b. SINGLE UMBILICAL ARTERY: HPE - Umbilical cord shows a single artery and a vein.



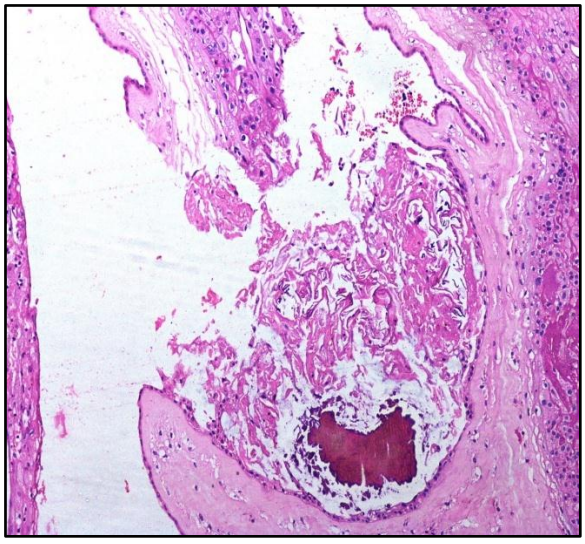


Fig 12c&12d. AMNION NODOSUM: HPE - Membrane roll shows eosinophilic fibrinous material with entrapped squamous cells.

Figure 13 - MULTICYSTIC KIDNEY DYSPLASIA

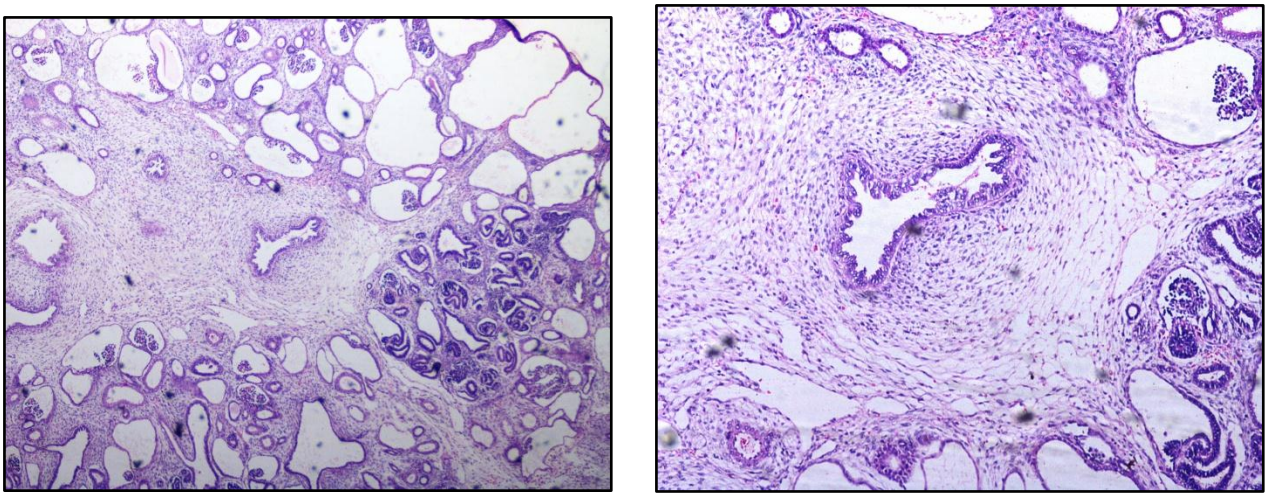


Fig 13a (10x) & 13b (40x). HPE: Shows disorganised renal parenchyma with immature tubules surrounded by collarette of condensed mesenchyme. The stroma is loose and shows fibroblastic proliferation.

Figure 14 – SIRENOMELIA

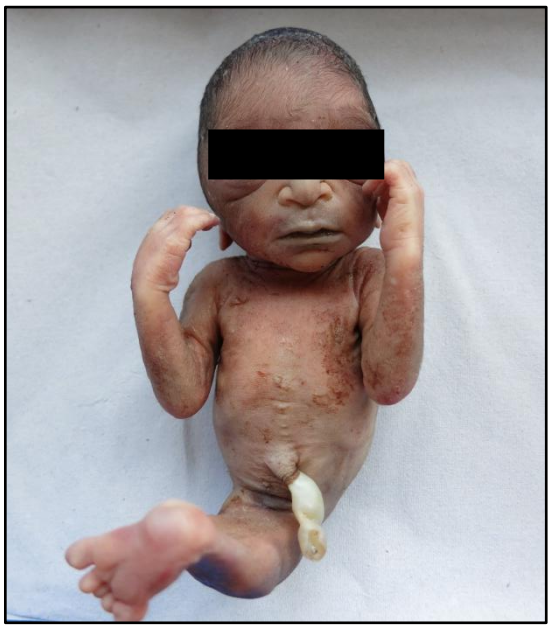


Fig 14. 'Mermaid foetus' with a single, median lower limb with the knee flexing posteriorly and the sole placed anteriorly.

Abbreviations

ABBREVIATIONS

SUA	-	Single umbilical artery
TOF	-	Tetralogy of Fallot
TEF	-	Tracheoesophageal fistula
URSM	-	Urorectal septum malformation
CURSM	-	Complete urorectal septum malformation
PURSM	-	Partial urorectal septum malformation
ARPCKD	-	Autosomal recessive polycystic kidney disease
ADPCKD	-	Autosomal dominant polycystic kidney disease
BOO	-	Bladder outlet obstruction
PUV	-	Posterior urethral valve
DUS	-	Distal urethral stenosis
AS	-	Aortic stenosis
MS	-	Mitral stenosis
GIT	-	Gastro intestinal system
CNS	-	Central nervous system
CVS	-	Cardio vascular system

RS	-	Respiratory system
HUN	-	Hydroureteronephrosis
VSD	-	Ventricular Septal Defect
NT	-	Nuchal Thickness
VACTERL	-	**V**ertebral defects, **A**nal atresia, **C**ardiac defects, **T**racheo-**E**sophageal fistula, **R**enal anomalies, and **L**imb abnormalities
OEIS complex	-	**O**mphalocele, **E**xstrophy of bladder, **I**mperforate anus and **S**pinal defects.
COFS Syndrome	-	**C**erebro-**O**culo-**F**acio -**S**keletal syndrome
CHARGE Syndrome	-	**C**oloboma, **H**eart disease, Choanal **A**tresia, **R**etarded growth and anomalies of the central nervous system, **G**enitor-urinary defects and **E**ar anomalies.

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Master Chart

MASTER CHART

S. NO	AGE OF MOTHER	GRAVIDITY	OBSTETRIC HISTORY	COMORBIDITY	GESTATIONAL AGE	SEX OF BABY	USG DETAILS	SUMMARY OF FOETAL AUTOPSY	PLACENTAL EXAMINATION	FINAL DIAGNOSIS
1	24	Primi	nonconsanguineous marriage	Maternal hypothyroidism,oneltroxin	25w2d	F	Grade 0 posterior placenta, severe oligohydramnios, single femur, deformed lower spine, suboptimal visualizationof foetus	Sirenomelia with a 'true tail'. Bilateral renal agenesis. Colonic malrotation, duplication cyst, atresia, imperforate anus. Hypoplasia and failure of fusion of mullerian ducts. Nephrogenic rests in colonic duplication cyst and around mullerian ducts.	Single umbilical artery	SIRENOMELIA.
2	26	G4P0L0A3,	Nonconsanguineous marriage spontaneous abortion.	-	18W	M	Normal study	Distal urethral stenosis with dilatation and hypertrophy of the urinary bladder. Pulmonary hypoplasia.	Placenta: villous edema, retroplacental haemorrhage	BLADDER OUTLET OBSTRUCTION (DISTAL URETHRAL STENOSIS).
3	27	Primi	Consanguinity status not known	-	17w5d	M	Mild oligohydramnios, bilateral ectopic presacral kidneys with bilateral hydronephrosis due to pelvi uretericjunction obstruction, parenchyma of L kidney dysplastic.	Ambiguous genitalia, male pseudo hermaphroditism, persistent mullerian ducts. Anorectal atresia. Bladder outlet obstruction with bilateral hydronephrosis and renal obstructive dysplasia.	Single umbilical artery.	PERSISTENT MULLERIAN DUCT SYNDROME, ANORECTAL ATRESIA AND BLADDER OUTLET OBSTRUCTION.
4	23	Primi	nonconsanguineous marriage	-	23w4d	M	SLIUF of 23-24 w gestation, single umbilical artery, Tetralogy	Tetralogy of Fallot with right aortic arch and left sided patent ductus arteriosus Atresia of distal sigmoid, rectum	Placental hydrops	VACTERL ASSOCIATION

							of Fallot,ectopic hydro nephrotic L kidney, L club footwith absent 2^{nd} to 5^{th} digits	and anus. Fused crossed renal ectopia with hydronephrosis. Left club foot with a single digit.		
5	21	Primi	nonconsanguineous marriage	-	18w1d	M	shows moderate ascites and bilateral pleural effusion- hydrops fetalis.	Hydrops foetalis Bladder outlet obstruction due to urethral stenosis/?posterior urethral valves causing dilated posterior urethra, bladder, ureters and bilateral hydronephrosis Hypoplasia ductus,right and left pulmonary arteries,distal aortic arch and left subclavian artery. Ventriculomegaly, absent corpus callosum, deep posterior fossa.		Non immune hydrops foetalis, bladder outlet obstruction.
6	27	Primi	nonconsanguineous marriage	-	23w4d	F	SLIUF 24 weeks, Pierre Syndrome, left hydronephrosis due to pelviureteric obstruction	Bilateral posterior choanal atresia, lop ears, micrognathia and ?microphthalmia Persistent cloaca Left hydronephrosis	Vilamentousattachment of the cord, medial hypertrophy of decidual arterioles and recanalizing thrombi in placental vasculature	suggestive of CHARGE syndrome.

7	24	Primi	Hypothyroid non consanguinous marriage	-	14w 4d	M	distension of urinary bladder, single umbilical arterybladder outlet obstruction	Megalourethra with megcystis and vesicourachal diverticulum. Absent right kidney and ureter. Micro colon. Single umbilical artery Clinically,14weeks 4days gestation with ultrasound evidence of distension of urinary bladder, single umbilical artery, bladder outlet obstruction.	shows a single artery and single vein	Congenital megalourethra
8	23	G2AI	Oligohydramnios non consanguinous marriage	-	15w	M	Oligohydramnios. Moderate hydroureteronephrosis of right kidney with echogenic parenchyma and a cyst in the upper pole and nonvisualised left kidney and urinary bladder.	Cloacal malformation –male foetus with ambiguous genitalia, smooth / intact perineum(without urethral or anal orifices) and rectal pouch with posteriorly directed anal canal. Absent bladder ,ureters draining into anal canal and renal dysplasia Single umbilical artery	Single umbilical artery	Consistent with cloacal dysgenesis sequence (complete urorectal septum malformation) with absent bladder.
9	26	G2P1L0	1st pregnancy suggestive of urorectal septum malformation (cloacal anomaly)	-	13w3d		Foetus shows omphalocele with exstrophy of distended urinary bladder. The foetal anus is not seen. The nasal bone is seen. Features suggestive of OEIS complex with single umbilical artery.	Female foetus with ambiguous genitalia, intact/smooth perineum(no urethral, vaginal and anal openings) Omphalocele Pelvic pouch ?connecting to ureters and fallopian tubes Colonic atresia	Single umbilical artery and pseudo cyst of umbilical cord	Complete Urorectal septum malformation (cloacal dysgenesis) with omphalocele and pseudocyst of the umbilical cord.

10	27	Primi	nonconsanguineous marriage Oligohydramnios.	-	22w5d	M	Unilateral renal agenesis and ectopic presacral one kidney with gross hydronephrosis.	Esophageal atresia with tracheoesophageal fistula (TEF type-A) Lung hypoplasia Cloacal malformation – male foetus with smooth / intact perineum (without urethral or anal orifices) and absent external genitalia Large intestinal malrotation, vitello intestinal duct remnant with atresia of rectum and anus. Absent right kidney, ureters and urinary bladder. Left renal ectopia with hydronephrosis and dysplasia Bilateral short thigh, short blind ended legs with no feet	chronic hypoxia induced changes and single umbilical artery	Consistent with VATER association / VACTERL association
11	27	G2P1L1	nonconsanguineous marriage.	-	20w	M	features of hypoplastic left heart syndrome.	Heart : hypoplastic left heart with aortic stenosis and mitral atresia Other viscera : bladder – bladder outlet obstruction	Acute chorioamnionitis, maternal inflammatory response Stage2Grade 2.Foetal inflammatory response StageGrade1.	Hypoplastic left heart syndrome with bladder outlet obstruction.

12	26	Primi	nonconsanguineous marriage	-	22w	M	- SLIUF corresponding to 19-20 weeks gestation, with evidence of cleft lip, diaphragmatic hernia on left side and bilateral mild pyelectasis.	Cleft lip and palate Congenital diaphragmatic hernia Pulmonary hypoplasia Membranous VSD with coarctation of aorta Renal cortical cysts with hydroureteronephrosis Remnant of vitellointestinal duct Olfactory bulb agenesis, agenesis of corpus callosum,and hydrocephalus	maternal vascular malperfusion and foetal vascular malperfusion	FRYNS SYNDROME
13	31	G5 P1 L1 A3	multiple congenital anomalies Consanguinity status is not known		26w2d	F	Single umbilical artery,unossifiednasalbone,subaorticmalalignedVSD, right aortic arch withleft ductus, bilateral hydrouretronephros features S/O CLOACAL MALFORMATION Karyotyping revealed 22q micro deletions.	Heart:mild cardiomegaly**,** right aortic arch with left ductus, atrial septal defect, membranous subaortic VSD and sub pulmonary mild stenosis. Single umbilical artery. Bilobed lungs. Bilateral hydroureteronephrosis Enlarged ? labia minora & anteriorly placed anus. Vesico vaginal fistula with a pelvic pouch connects to the external opening through an atretic passage, compatible with partial urorectal septum malformation	cord has 2 vessels no specific pathology.	spectrum of urorectal septum abnormalities S/O persistent urogenital sinus
14	23	G3P1L1	nonconsanguineous marriage	-	21w	F	multicystic dysplasia of both the kidneys.	Multicystic dysplasia, both kidneys Hypoplastic bladder Dilated third ventricles : Brain	Placenta shows marginal cord insertion.	bilateral multicystic renal dysplasia.
15	22	G3A2	3rd degree consanguineou	-	13w1d	M	13weeks gestation showing cystic	Male foetus with intact / smooth perineum (no anal	Placenta : Shows villous	partial urorectal septum

			s marriage.				hygroma and cardiac anomaly	opening)Hydrops foetalis.Anal agenesis with recto-vesical fistula.Cystically dilated bladder with distal urethral stenosis. Bilateral dysplastic kidneys.Transposition of great arteries with VSD Brain : Mild ventriculomegaly.	edema.	malformation sequence (cloacal Dysgenesis sequence)
16	28	G2P2L1	non consanguineous marriage.	-	24w	F	Fetus shows urinary bladder obstruction with bilateral gross hydro ureteronephrosiswith dysplastic parenchyma and patent urachusmost probably urethral atresia.	Female pseudohermaphroditism. Hydrops fetalis Megacystis with hydroureteronephrosis stenosis. Urethral duplication with mid ureteric sternosis of ventral urethra Persistent cloaca Mild stenosis of ductus ateriosus.	Not received	complete urorectal septum malformation sequence (cloacal dysgenesis)
17	21	Primi	marked oligohydramnios		21w6d	F	multiple anomalies	CVC liver Imperforate anus with anal atresia Distal urethral obstruction with hydroureteronephrosis. bicornuate uterus	mild villous edema maternal vascular malperfusion	partial urorectal septum malformation with absent ductus venous
18	28	Primi	non consanguineous marriage	-	18w5d	F	Fetus shows multiple anomalies with single umbilical artery-VACTERL anomaly	Hydrops foetalis Single umbilical artery Left renal agenesis Partial urorectal septum malformation (urogenital sinus) Distal urethral stenosis and	Not received	VACTERL association

								anteriorly placed anus Pre axial polydactyly of right upper limb and lower limb Scoliosis with shortened and deformed left upper limb and right lower limb		
19	31	Primi	secondary consanguineous marriage.	-	13w1d	M	Intrauterine pregnancy with live monochorionic diamniotic twins of about 12weeks 4days gestation arraigned as per CRL. Fetus : Shows features of OEIS (Omphalocele bladder exstrophy imperforate anus) complex.	Fetus : Omphalocoele containing liver and intestines. Extrophy of bladder Anal atresia Hydrocephalous Bilateral renal agenesis Scoliosis	Diamnonic monochorionic placenta with single umbilical arteries in both cord.	FETUS - OEIS COMPLEX
20	31	Primi	Secondary consanguineous marriage.	-	13w1d	M	Intrauterine pregnancy with live monochorionic diamniotic twins of about 12weeks 4days gestation arraigned as per CRL. Fetus : Shows radial ray aplasia with single umbilical artery.	Fetus : Radial aplasia Trachoesophageal fistula with esophageal atresia. Perimembranous ventricular septal defect Hypoplastic right lung Enlarged trilobbed left lung	Diamnonic monochorionic placenta with single umbilical arteries in both cord.	FETUS – VACTERL ASSOCIATION

21	18	G2A1	third degree consanguineous marriage.	G1 - 3MA, spontaneous abortion	24w3d	F	Foetus shows fetal akinesia deformation sequence with multiple anomalies. (Subcutaneous edema, non-visualized stomach, fixed flexion of upper limbs and fixed extension and crossing of lower limbs with plantar flexion of feet, sloppy forehead and micrognathia	Microcephaly, slopping forehead, opaque lens, low set ears, depressed nasal bridge with small nose, small mouth, deviated tongue, micrognathia with very short neck and hirsutism. Hydrops foetalis Hydraencephaly, hypoplastic pituitary, rudimentary posterior fossa and diffuse villous hyperplasia of choroid plexus. Fixed flexion of upper limbs and fixed extension of lower limbs with crossing of left leg over the right leg. Pulmonary hypoplasia, small and flat adrenals and enlarged spleen. Distended bladder, dilated pelvicalyceal system with features suggestive of persistent urogenital sinus.	Hypercoiled cord, intervillous thrombus with some features suggestive of foetal vascular malperfusion.	SUGGESTIVE OF CEREBRO-OCULO-FACIO-SKELETAL (COFS) SYNDROME
22	23	Primi	secondary consanguineous marriage.	-	16w	M	Severe oligohydramnios, fetus show B/l. renal agenesis.	Features of potter sequence. Mild hypocephalous Bilateral renal agenesis with absent ureters. Hypoplastic bladder	Hypercoiled cord.	BILATERAL RENAL AGENESIS
23	35	G7A6	nonconsanguineous marriage	G1 - Spontaneous abortion G2, G6 - Ectopic gestation G3-G5 - Isttrimester	24w	M	Abnormal AC, FL, <1% cable diagnosed to have IUD	FETUS : Ectopic right kidney (pelvic kidney)	Small for gestation Hypercoiled cord with stricture Foetus vascular malperfusion / foetus thrombotic	INTERUTERINE FOETUS DEATH SECONDARY TO HYPERCOILED CORD WITH STRICTURE AND FOETUS VASCULAR MALPERFUSIO

				miscarriageG7. IUD at 14weeks					vasculopathy. Abruptio placenta	N.
24	19	Primi	third degree consanguineous marriage.	-	24w	F	USG evidence of of Joubert's Syndrome (right hand polydactyly, ARPCKD, Gross ventriculomegaly, non visualized vermis and small occipital encephalocele).	Small foetus with microcephaly, depressed nasal bridge, micrognathia, elevated upper lips. occipital meningocele with hydrocephalus. Shallow posterior fossa, small cerebellum and partial agenesis of cerebellar vermis Medullary cystic kidney disease, bilateral Hypertrophied limb muscles with hypoplasia of lungs, heart, liver and brain. Left talipes, postaxial polydactyly - Type B defect (skin tag).	Hyper coiled cord with features of chronic hypoxia.	suggestive of MECKEL – GRUBER SYNDROME.
25	30	Primi	nonconsanguineous marriage	Known case of hypothyroidism	22w	M	Foetus shows features of ARPCKD, cystic lesion posterior to occipital region, crowding of the cranial bones seen . Severe Oligohydramnios.	Microcephaly, folded ear lobules, depressed nasal bride, micrognathia and left Rocker bottom foot Head: occipital encephalocele, ependymal cyst Heart: hypoplastic left heart syndrome(hypoplastic left atrium, ventricle, ascending aorta and arch),right ventricular hypertrophy Lung hypoplasia Mild hepatic fibrosis Bilateral Autosomal recessive polycystic kidney disease(ARPCKD)	Hypocoiled cord, amnion nodosum with features of chronic hypoxia	OCCIPITAL ENCEPHALOCELE, HYPOPLASTIC LEFT HEART SYNDROME AND BILATERAL AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE, THE POSSIBILITY

										OF MECKEL-GRUBER SYNDROME NEEDS TO BE CONSIDERED
26	26	Primi	nonconsanguineous marriage	Known case of hypothyroid	23w	M	SIUG of 18 weeks + 1 D, liquor reduced, AFI - 4 cms. Foetal activity reduced	Distal urethral stenosis with hypertrophy of the urinary bladder.	Placenta : Hypercoiled cord, subchorionic and intervillous haemorrhage. Chronic hypoxia induced changes.	BLADDER OUTLET OBSTRUCTION (DISTAL URETHRAL STENOSIS).
27	25	G3P1L1A 1st pregnancy - Male baby, normal vaginal delivery, 4 years back 2nd pregnancy Spontaneous abortion at 5weeks of conception	nonconsanguineous marriage	Diabetes mellitus	21w	M	Single live intrauterine pregnancy corresponding to 20.3weeks of gestation. Foetus shows scoliosis of spine, curved shortened left femur, talipes deformity of the feet and single umbilical artery	Left foot talipus equinovarus with postaxial polydactyly Mid urethral stenosis with bilateral hydrouteronephrosis	Single umbilical artery Villous edema and intervillous hemorrhage	LEFT TALIPUS EQUINOVARUS WITH BLADDER OUTLET OBSTRUCTION

28	27	G2 A1	non-consanguineous marriage.	-	20w 2d	M	SLIUF at 19weeks, an hydramnios. Foetus shows multicystic dysplasia of both kidneys with pyriform cystic mass in pelvis suggestive of URSM and cardiac anomaly suggested to rule out aneuploidy. Foetal urosonograms multiple dysplasia of both kidneys, pyriform cystic mass in pelvis, suggestive of cloaca. Urinary bladder and anus could not be seen.	Hydrops foetalis, low set ears, bilateral talipes (potter sequence Bilateral autosomal recessive polycystic kidney disease (ARPCKD) ureteral dilatation, obstructive uropathy with mild urethral stenosis. Heart: Enlarged rightatrium, tricuspid atresia (TA), hypoplastic right ventricle, pulmonary atresia and perimembranous ventricular septal defect (VSD). - -	Small for gestational age, Hypercoiled cord, single umbilical artery, maternal vascular malperfusion	CONGENITAL HEART DEFECTS WITH CONGENITAL ANOMALIES OF THE KIDNEY AND URINARY TRACT (CAKUT) AND PULMONARY HYPOPLASIA.
29	25	G2A1	non-consanguineous marriage.	-	19W	M	SLIU 18 weeks. Foetus with increased nuchal thickening, anhydramnios, bilateral renal agenesis with lying down adrenal sign,	Foetus Hydrops fetalis with depressed nasal bridge and low set ears. Abnormal hand with abnormal short fingers, syndactyly and right post axial skin tag. Feet with syndactyly and nail dysplasia. Bilateral renal agenesis with	Hypocoiled cord, amnion nodosum and increased cell islands.	BILATERAL RENAL AGENESIS, PULMONARY HYPOPLASIA AND HAND ABNORMALITIES. THE POSSIBILITY

							absent urinary bladder with cord around the neck is breech presentation.	associated bilateral urethral agenesis and flat, oval adrenals. Elongated, hypoplastic bladder with distal urethral stenosis.Pulmonary hypoplasia.		OF 'ACRO-RENAL SYNDROME' NEEDS TO BE CONSIDERED
30	28	Primi	Non-consanguineous marriage	-	23w	M	Foetus show multiple anomalies with single umbilical artery could be VACTERL association Bilateral mild lateral ventriculomegaly, dilated third ventricle, hypoplastic cerebellum with no visualized cerebral sulci Ventricular septal defect with common arterial trunk. Right renal agenesis, mild hydronephrosis of left kidney with echogenic parenchyma, pyriform urinary bladder with non-	Micrognathia.Left congenital talipes equinovarus. Imperforate anus Large penis with epispadias Intestinal malrotation Anal atresia with rectourethral fistula. Right renal agenesis Mid urethral stenosis. Pulmonary stenosis, Perimembranosis VSD with overriding of aorta (>75%). Bilateral unilobed lungs. Mild right cerebellar hypoplasia. Absent gallbladder and appendix	Normal for gestation Villous edema and intravillous hemorrhage	MULTIPLE CONGENITAL ANOMALIES SUGGESTIVE OF VACTERL ASSOCIATION

							visualized anus. Urorectal, septal malformation sequence.			
31	24	Primi	non-consanguineous marriage	-	22w4d	M	SLIUF 22w Fetus with omphalocele.. Non visualisation of urinary bladder-possibility of bladder extrophy B/L renal pelvic dilatation. Single umbilical artery.	Omphalocele containing portion of liver, gallbladder, small and large intestines including appendix and rectum. Absent external genitalia Imperforate anus with no urethral opening Exstrophy of cloaca Blind ending hindgut (anal atresia) terminating in the cloacal pouch Male foetus with persistent mullerian duct remnants	Small for gestational age, single umbilical artery and subchorionitis.	OEIS COMPLEX
32	25	Primi	non-consanguineous marriage	-	23w6d	M	SLIUF 23w6d single umbilical artery. Persistent left SVC with interrupted IVC. Right ectopic (presacral) kidney. ?closed spinal disraphism/ sacral agenesis	Absent right forearm, right thumb and bilateral talipes Pulmonary hypoplasia with unilobed right lung. Intestinal malrotation, right sided pancreas.Pyloric atresia, anal atresia.Cloacal malformation with no perineal opening.Single, midline, hypoplastic dysplastic kidney (multicystic dysplastic, kidney)Absent ureters and urethra	Single umbilical artery, small for gestational age	VACTERL ASSOCIATION.
33	27	G2A1	non-consanguineous marriage	-	20w2d	M	Anhydramnios . multicystic dysplasia of both kidneys with pyriform cystic mass in pelvis S/O URSM sequence	Hydrops. Cleft palate. Pulmonary hypoplasia with bilobed right lung.Multicystic dysplastic kidneys. Megacystis.Urethral atresia.	Single umbilical artery, small for gestational age	Cleft palate with bladder outlet obstruction

34	25	G2P0L0A1	III degree consanguineous marriage	I st pregnancy missed abortion	20w	M	SLIUF 19w6d. Fetus shows features s/o rhizomelic type of chondrodysplasia puntata and mild pelvi calyceal dilatation (urinary tract dilatation A1)	Foetus : flat facial profile, low set ears,depressed nasal bridge. Short proximal limbs(short arms and short curved thigh) –rhizomelic limb shortening. Posterior urethral valve young classification type I with b/l hydronephrosis and megacystis Pulmonary hypoplasia	Vilamentous cord subchorionitis and villous edema	Rhizomelic limb shortening with flat facial profile and posterior urethral valve
35	29	G3A2	non-consanguineous marriage	BOH 3 abortions G1 : Conceived after ovulation induction, had twin pregnancy MTP done due to decreased cardiac activity. G2. Twin pregnancy IUD of both fetus.	23w3d	M	Single gestation corresponding to a gestational age of 23 weeks + 1 day.Anhydramnios. Bilateral enlarged kidney with multiple cysts, suggestive of polycystic kidneys.	Potter's facies Accessory cervical thymic tissue Autosomal dominant bilateral polycystic kidney disease.	Hypercapillarization	Suggestive of Autosomal dominant polycystic kidney disease.

36	28	G2P2L0	non-consanguineous marriage	1st pregnancy : Baby died at 2.5yrs of age due to AML	22w	F	SLIUG foetus corresponding to 21 weeks + 2 days gestation with IUGR, left renal agenesis, smaller right kidney and cleft soft palate.	Micrognathia Midline cleft hard and soft palate Crossed fused left renal ectopia.	Small for gestation age.Hypercoiled cord. Intervillous space shows sickled RBCs	CROSSED FUSED LEFT RENAL ECTOPIA WITH CLEFT PALATE.
37	28	G2P1L1	-	Diabetes mellitus	20w4d	M	SLIUF 20w with abnormal hands. B/L ventriculomegaly B/L empty renal fossa. Low placed right kidney left pelvic kidney. Cardiac : situs solitus,levocardia, asymmetry of chambers. VSD/ dilated aorta and pulmonary artery	Fetus : Bilateral and 3rd ventriculomegaly secondary to aqueductal stenosis. Asymmetry of cardiac chambers with membranous ventricular septal defect. Horse - Shoe kidneys and bladder hypoplasia. Brachycephaly, hirsutism Hypoplastic left thumb with hypo to aplasia of the palmar creases Bilobed right lung with pulmonary hypoplasia.	Decidual vasculopathy, villous edema	Shows aqueduct stenosis and ventricular septal defect
38	29	G3P2L1	non-consanguineous marriage	-	27w3d	F	SLIUF 27w4d. Mild oligohydramnios. fetus shows bilateral enlarged and echogenic kidneys.	Hirsutism, depressed nasal bridge. b/l enlarged medullary cystic (sponge) kidney. Distended thin walled bladder	Hypercoiled cord focal subchorionicti intervillous hemorrhage with hemorrhagic necrosis	Shows B/Lcystic kidney disease probably medullary cystic (sponge) kidney

39	24	Primi	-	-	22w	M	SLIUF 21w5d. Severe oligohydramnios. Fetus shows posterior urethral valve with urinary bladder outflow obstruction and bilateral gross hydroureteronephrosis.(urinary tract dilatation A2-3)	High arched palate Partial tracheal agenesis and bilobed right lung B/L hydroureteronephrosis with cystic renal dysplasia (obstructive uropathy) Megacystis.Posterior urethral valve (Youngs classification- type 1)	Not received	Shows bilateral hydroureteronephrosis, Megacystis secondary to posterior urethral valve
40	26	G2A1	non-consanguineous marriage	Diabetes mellitus	17w	M	Anomalous fetus-polycystic kidneys with severe oligohydramnios	Right kidney – autosomal dominant poly cystic kidney disease. Left renal agenesis hypoplastic bladder	Villous edema	Right kidney – autosomal dominant poly cystic kidney disease. Left renal agenesis hypoplastic bladder