ROLE OF MRI IN EVALUATION OF MRKH SYNDROME

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ABSTRACT: MRKH Syndrome is one of diverse spectrum of congenital mullerian duct anamolies ranging from complete absence to hypoplasia of uterus and upper 2/3rd of vagina owing to their embryological origin. This is the second most common cause of primary amennorhoea in young females who shows normal development of secondary sexual characters and endocrine profile with essential normal female phenotype & genotype (46 XX). Our study is to emphasis the role of MRI in diagnosis of this syndrome non-invasively without exposure to radiation. The excellent soft tissue anatomical details by MRI provides the diagnosis with accuracy along with information of adjacent viscera and other associated systemic anamolies.

KEYWORDS: Magnetic Resonance Imaging (MRI), Mullerian agenesis, Mayer Rokitansky Kuster Hauser Syndrome (MRKH syndrome).

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INTRODUCTION: MRKH Syndrome is the most common example of Class I mullerian duct anamolies (American fertiltity society classification 1988). The basic knowledge of embryogenesis of female reproductive system is important in evaluating the severity of anamoy, its systemic associations. The diversity of uterine anamolies range from complete agenesis of uterus, proximal vagina to presence of rudimentary uterus and vagina. This hypoplastic uterus may be a single or paired uterine buds owing to their formation from paired mullerian ducts or it may mimic a post pubertal uterus. The varying degree of zonal differentiation from single to three layers, their functioning status and pathologies associated with them are better delineated by MRI. Relatively high position or ectopic ovaries, (upto 40%), constant caudal relation of uterus with ovaries is well answered by MRI as compared to Ultrasound. The accuracy and specificity are comparable to laparoscopic findings. Our study is to emphasis the role of MRI in establishing the diagnosis, differentiation into subtypes, recognition of associated anamolies, guiding the clinician during fertility workup and treatment.

METHODOLOGY: PATIENT SELECTION CRITERION: Our institutional review board approved this study and waived the requirement of informed consent. We reviewed MR images pertaining to female pelvic studies in patients presenting with primary amenorrhoea during past three years with a suspicion of this syndrome during October 2012 to October 2015.

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The final cohort consisted of 12 patients (age range 14 to 25 yrs, mean age 19.5 years). Basis for selection is clinical history with physical examination, endocrine profile and pelvic ultrasound is performed in all these cases. Transvaginal sonography has not been performed as they are unmarried. Detailed evaluation of bilateral inguinal regions is done to exclude the presence of ectopic rudimentary testis. None of the pt had a medical history regarding urologic symptoms (pain, hypertension, pyelonephritis) or testicular feminization syndrome which was confirmed clinically and by ultrasound evaluation.

Mr Imaging Technique: MR imaging has been performed on all these patients using body coil on 0.35 T XGY OPER MRI machine (Ningbo Xingaoyi Magnetism Co-Ltd-China) In supine position after a localizer, T1SE (TR/TE 360/18), T2 FSE (9TR/TE 3000/105), IRFSE (TR/TI/TE 3400/70/105) sequences in axial, coronal and sagittal planes, 3-5mm slice thickness with 1or 1.5 mm intersection gap, 30 or 36 cm FOV, NEX is 2or 3, matrix is 256X182 Scan is performed with optimally distended urinary bladder. As no additional information could be added by contrast study in this particular context, contrast enhanced MR imaging is not performed. For all patients screening of spine and abdomen has been performed to evaluate associated anamolies.

MR Image Analysis: Two experienced radiologists (reader 1 with 5yr of experience and reader 2 with 10 years of experience rendered the consensus analysis of MR Images for following:

Presence or absence of uterus, vagina, ovaries, presence or absence of endometrial cavity formation, ovarian volume and relationship with uterus. Evaluation of urogenital and vertebral system is done as these are the most common associated anamolies that we come across in MRKH syndrome.

RESULTS: Out of 12 patients, complete absence of uterus is noted in one patient (8.3%). Uterine hypoplasia is noted in 11 (91.6%). Ovaries seen bilaterally in 10 patients. In one patient single left ovary is seen. Visualised ovaries are normal in size and signal intensity with tiny follicles, inspite of their relative high position. All the cases have vaginal hypoplasia. Vaginal agenesis is not encountered in any patient. One showed ectopic low lying left kidney with malrotation of axis. Other abnormalities in literature like vertebral segmental defects, MSK abnormalities, renal agensesis, hearing defects or other cardiac problems are not encountered in our study. From this analysis, 10 are classified as MRKH type I and two are classified as MRKH type II.

For all the patients endocrinal profile consisiting of FSH, LH, HCG, Testosterone has been performed in our institution and they are in normal physiological limits. Four patients underwent karyotyping and confirmed to be as normal female karyotyping i.e., 46XX. Diagnostic Laporaotomy which is done in two other patients confirmed the same diagnosis. Other patients are not affordable for these investigations.

	Present (n%)
Bilateral ovaries	11(91.6%)
Single ovary	1(8.3%)
Hypoplastic uterus	11(91.6%)
Absent uterus	1 (8.3%)
Hypoplastic vagina	12(100%)
Associated anamoly	1(8.3%)

Table 1

In only one case ectopic left kidney in lower lumbar region

DISCUSSION: MRKH Syndrome accounts for 15% of cases presenting with primary amenorrhea and is the second most common cause for it. Incidence is 1 in 4000 to 4500 female live births.[1] The cause is still unknown and it is believed to be polygenic, multifactorial with variable penetrance. Most cases are sporadic, although few familial cases have reported. The disorder is congenital which will not be detected until early adolescence. The affected females are genotypically normal (46XX) phenotype, endocrine status will be normal because of normal ovarian function though uterus and upper 2/3rd of vagina shows variable size and development. In extremely rare conditions, vaginal atresia or agenesis can occur. There will be no signs of androgen excess. This condition has been described by Mayer (1829), Rokitansky (1838) along with other associated anamolies of renal, vertebral and MSK system. Hauser & Schreiner (1961) emphasised the importance of distinguishing this syndrome from androgen insensitivity syndrome which also shows feature of vaginal atresia.[2]

Synonyms and associations of MRKH Syndrome are Mullerian aplasia, GRES (genital,renal, ear syndrome) CAUV(congenital absence of uterus and vagina).

The Sub Types Constitutes: Type I or Typical, also known as Rokitansky sequence, Type A or Isolated MRKH form, in which only mullerian duct anamolies are noted. Symmetrical uterine buds or hypoplastic uterus and fallopian tubes are present. Ovaries are normal. No other associated systemic abnormalities are noted.

Type II or Atypical or MRKH Type B Variety constitute mullerian as well as other anomalies of urological, skeletal, vertebral and cardiac systems.[3] MURCS (Mullerian, Renal, Cervical Somite) is the most severe form in this.[2,4]

Here asymmetrically developed uterine buds or fallopian tubes are present.[5] Urological abnormalities like renal ectopia, horse shoe kidney and in rare cases, renal agenesis, vertebral sementation defects like block vertebra, hemivertebra, transitional vertebra, scoliosis musculoskeletal abnormalities like radius, carpel, phalangeal abnormalities, femoral epiphyseal abnormalities are seen in association with MRKH Type II. Owing to their similar embryological origin from mesoderm, association of urological, mullerian and skeletol system anamolies is noted in type II syndrome.[6] Discrimination between these two types MRKH syndrome and with androgen insensitivity syndrome is essential for treatment planning.

The primordia for female internal reproductive system are paired mullerian ducts.[7] Arrest of mullerian duct development seven weeks after fertilization results in MRKH syndrome during embryogenesis.

Paired Mullerian ducts give rise to uterus, cervix, fallopian tubes, ans upper 2/3rd of vagina. The severity of disruption of normal development can range from complete absence or partial absence with double or single uterus or uterine buds variable or absent uterine zonal differentiation or cavitation with or without evident opening into introitus. Upper 2/3rd of vagina may be completely atretic or hypoplastic.[8]

Absence of broad ligaments and utero-ovarian ligaments is a consistant feature in this patients. This will lead to relatively high positioning of ovaries in relation to uterus. Embryologically ovaries develop from mesoderm and migrate to pelvis as the fetus grows. Though normal development of ovaries is seen, as utero-ovarian ligments are not formed in MRKH Syndrome, they are placed in high pelvic position.[2,9]

Normal FSH, LH, 17β Estradio levels are noted representing the normal function aiding for development of female secondary sexual characteristics. Hyperandrogenism is not seen.

Lower 1/3rd vagina is always seen as it develops from ecto dermal cells This can present as short blind ending pouch or a dimple in perineum.

Sometimes due to functioning endometrium there can be cryptomenorrohea and haematometra with pt presenting with cyclical abdominal pain. Few cases with formation of leomyoma s in hypoplastic uterus or uterine buds has been reported.[10,11,12]

MRI because of its multiplanar capability, excellent soft tissue resolution aids in establishing this diagnosis

noninvasively without radiation as compared to laporoscopy and CT imaging. Diagnostic dilemmas in ultrasound regarding the length of uterus, cervix, corpus body ratio, zonal anatomy, extent of vaginal development are better answered by sagittal MR Imaging. Presence, location of uterus /uterine buds, ovaries, their size, volume, follicular presence, relation of ovaries to uterus are better seen by axial imaging. Vagina is best assessed by sagittal and axial MR imaging and is seen as intermediate signal intensity tubular structure in between bladder base, urethra anteriorly and anal canal posteriorly[13] Associated renal, vertebral and other systemic abnormalities can be better detected by MRI with high specificity.

A vestigeal lamina located beneath peritoneal folds, itself situated transversly posterior to bladder where utero-sacral ligamens as a quadrangular retrovescical structure mimics hypoplastic or juvenile uterus. It is difficult to differentiate this vestigial lamina from hypoplastic uterus by ultrasound where the MRImaging comes to rescue the situation. This vestigial lamina will not have central mucosal line as uterus have.[14,15]

Associated systemic anamolies are better delineated and aid to differentiate this syndrome into MRKH TYPE I & TYPE II which has the key role in treatment planning an management.

The main Differential Diagnosis to be Considered are

A. Androgen insensitivity syndrome also called as testicular feminization syndrome.

This is a X-linked recessive trait that is caused by mutations of androgen receptor gene resulting in end organ resistance to androgen in blood stream. Therefeore the typical post receptor events that mediate the harmonal effect on tissues does not occur. This results in antenatal undervirilisation of external genitalia resulting in female phenotype of baby. In due course, there will be development of female secondary characterstics of growth and absence of male type. Very few cases can be diagnosed at birth by identification and analysis of inguinal masses as undescended testis. As the individual is genotypically male (46 XY), testis will be present in variable position of their normal path of their descent. This will promote normal production of testosterone and its conversion into dihydrotestosterone. Also, mullerian inhibition factor is produced resulting in inhibition of development of uterus, fallopian tubes, and proximal 2/3rd of vagina. Sometimes androgen insensitivity syndrome can be Complete or Partial depending upon the residual receptor function. Complete androgen insensitivity syndrome individuals have normal labia, clitoris and vaginal introitus. Partial androgen insensitivity syndrome phenotype may range from mildly virilised female external genitalia to mildly undervirilised male external genitalia.[2,16,17]

B. WNT4 Syndrome also known as MRKH–like Syndrome.

This is also known as Biason-Lauber syndrome. This is caused by mutations in WNT4 gene. This is a rare disorder that affect genetically female. Ovaries in embryonic life undergo partial virilisation resulting in both oestrogen and androgen secretion. There will be abnormal high levels of androgens in blood stream causing mullerian inhibition factor recruitment resuting in non-formation of uterus and proximal 2/3rd of vagina. Under the influence of estrogens, breast and pubic hair growth like that of female phenotype is developed.[2]

C. In very rear cases, isolated vaginal hypoplasia or atresia may be seen or it seen as a part of larger syndromes like MRKH Syndrome, Mc Kusick-Kaufmann syndrome, Winter syndrome and Fraser syndrome.[18] In these cases, individuals are genotypically female (46 XX) with normal uterus, ovaries but with variable development of vagina. No signs of hyperandrogenism is seen. Normal development of secondary sexual characterstics noted.

With this knowledge, once the diagnosis is established, along with associated malformation identification and work up, main focus is directed towards social, psycho-social condition of patient. Treatment requires coordinated efforts of team of various departmental specialists. Depending on age of diagnosis, paediatrician, gynecologist, plastic surgeon, endocrinologist and psychiatrist and other health care professional guidance can be sought for comprehensive health care approach to treatment.

When the individual is emotionally mature, ready to start sexual activity, creation of neo-vagina by various nonsurgical techniques like usage of vaginal dilators or surgical techniques like vaginoplasty is recommended.[19,20] As the functional uterus is absent, assisted reproductive techniques like harvesting their own eggs, invitro-fertilisation and surrogate pregnancy can be offered. Psychological support and counseling both professionally and through support groups is recommended for affected females and their families.

CONCLUSION: MRI has become the key diagnostic tool in diagnosing this condition when there is a diagnostic dilemma in ultrasound. There will be no radiation exposure and better soft tissue resolution and better delineation of pelvis anatomy as compared to CT, noninvasiveness with less morbidity, less expensive and hospital stay as compared to laparoscopy and diagnostic accuracy is on par with laparoscopy findings. Not only that, MRI can accurately assess the uterine morphology, zonal differentiation and vaginal length and other systemic associations, this provides complete diagnostic information for treatment planning and follow up making it a unique, helpful diagnostic tool.

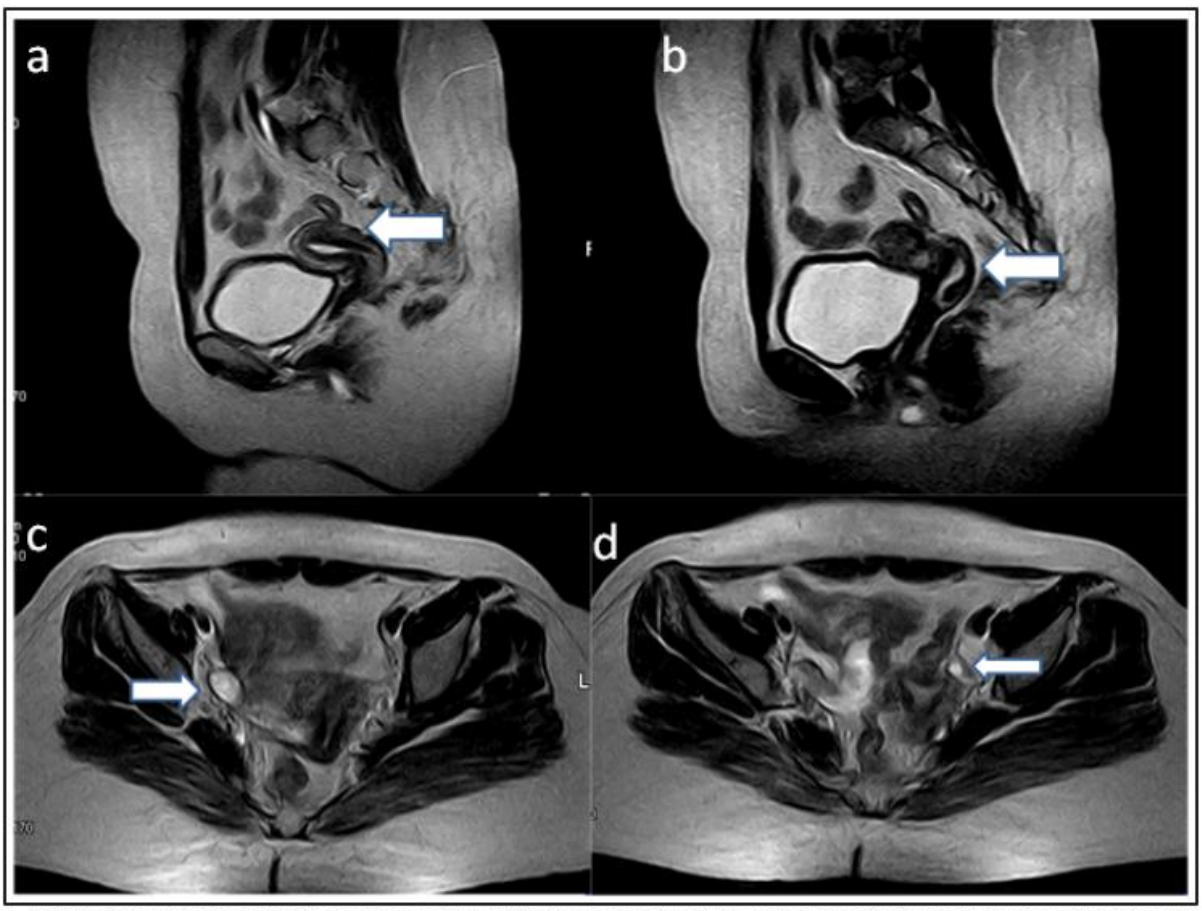

Fig. 1: (a,b) Serial T2W sagittal images of a normal female pelvis showing normal sized uterus with normal volume, zonal differentiation with normal cervix and whole length of vagina. (c,d) serial T2W axial images in the same case, right and left ovaries are noted in normal expected anatomical location because of presence of broad ligament and utero-ovarian ligaments. Normal volume and follicular pattern ovaries is noted.

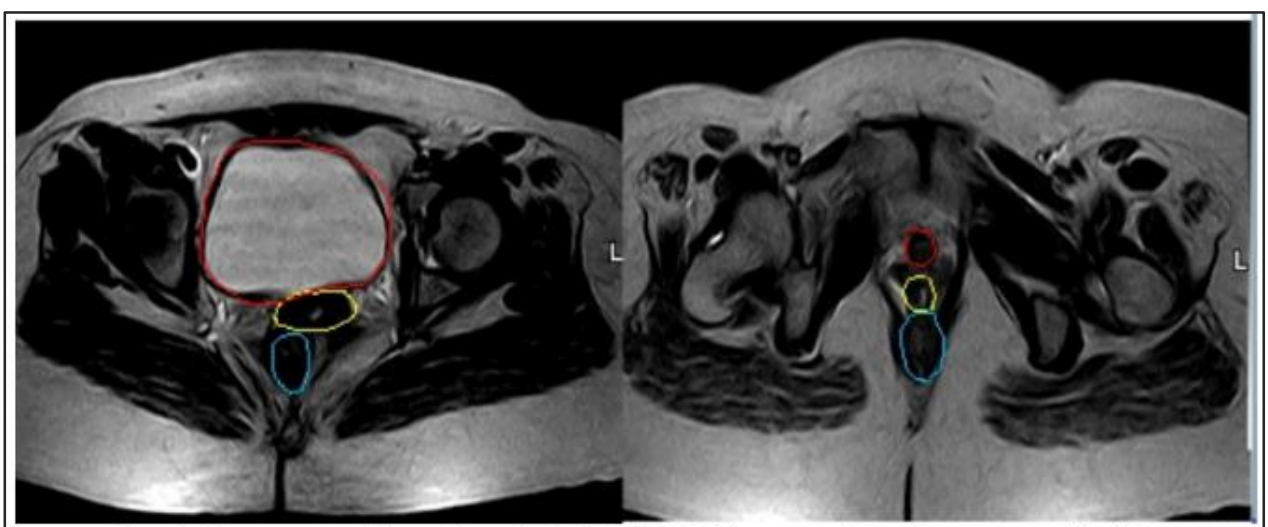

Fig. 2: In a normal female pelvis, T2W Axial images showing urinary bladder, urethra (red outline), cervix, vagina (yellow outline) and rectum, anus (blue outline)

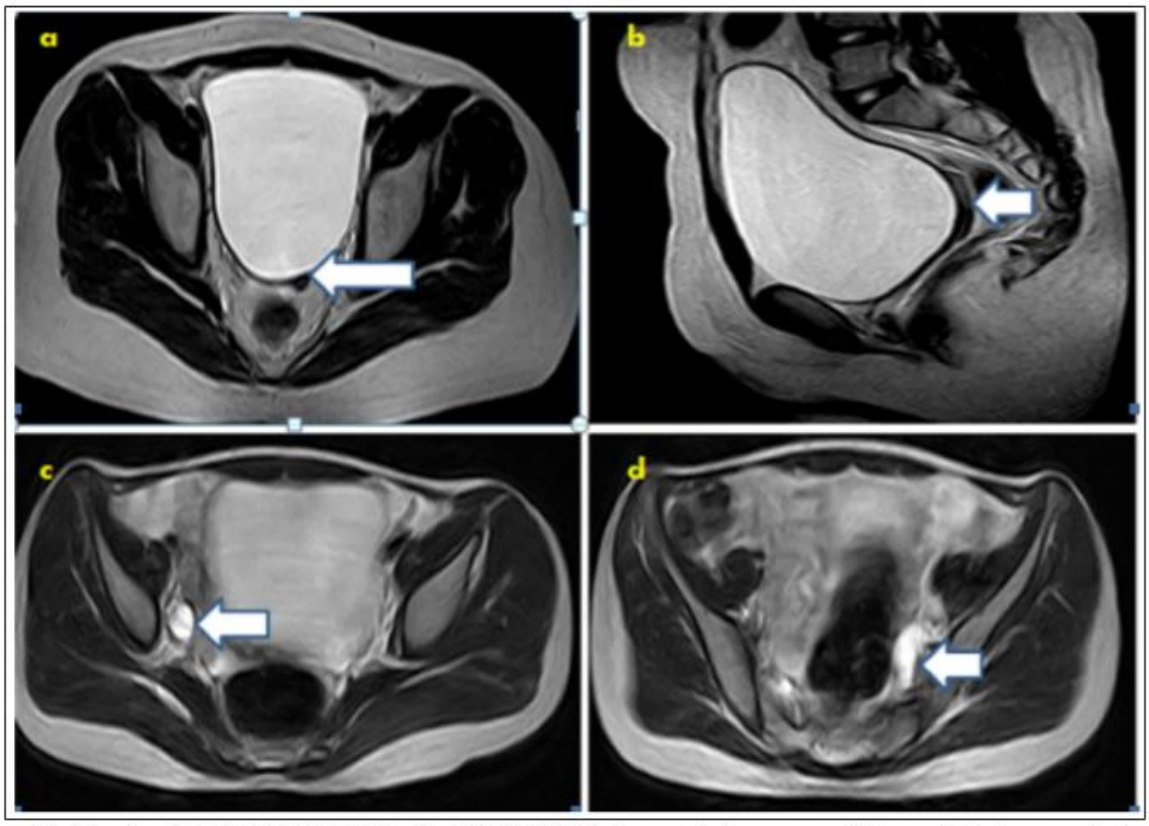

Fig. 3: a,b,c & d, Axial T2WI & Sagittal T2WI (a&b) shows uterine remnant (arrows) in its expected location posterior to urinary bladder with absent zonal anatomy. Axial T2WI (c&d) shows normal sized Right ovary and left ovary with normal signal intensity and follicles suggestive of normal physiological function

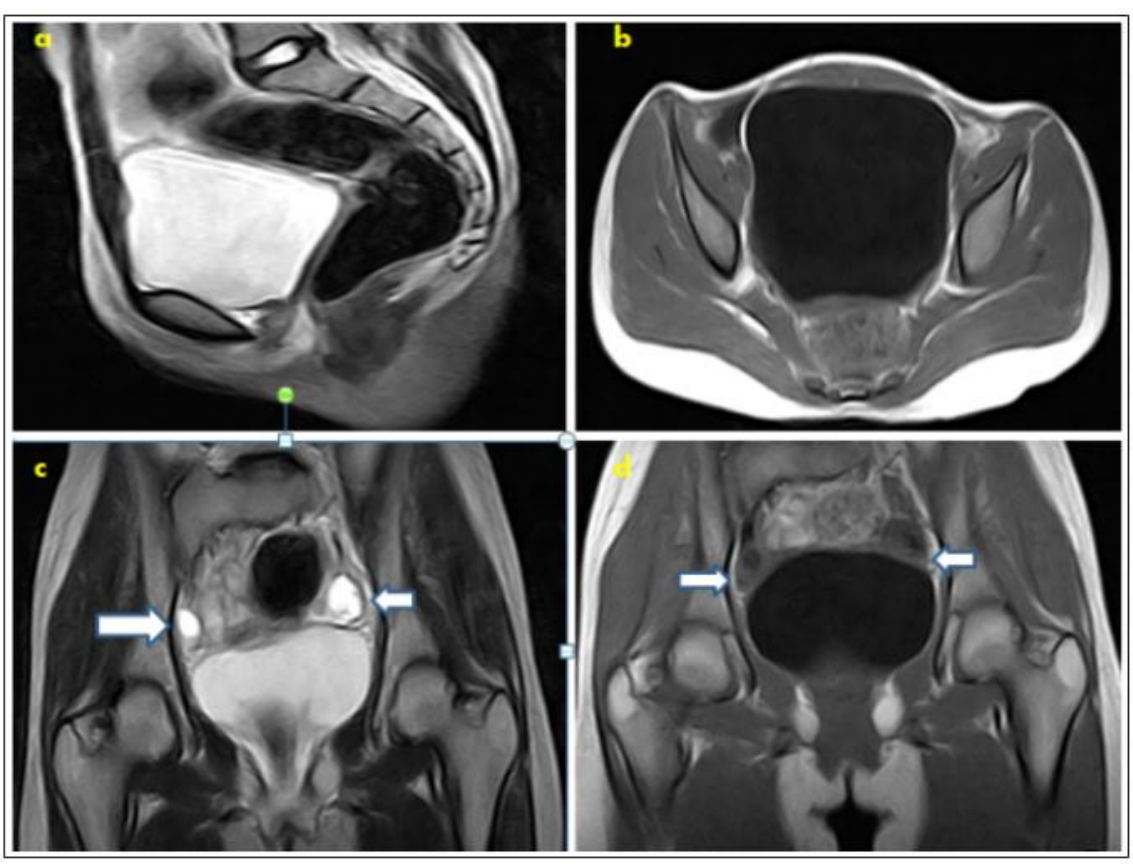

Fig. 4: a,b,c,& d – Sagittal T2WI & Axial T1WI (a&b) reveals absent uterus. Coronal T2WI & Coronal T1WI (c&d) reveals high placed both ovaries and are normal in size, signal intensity with normal follicular pattern

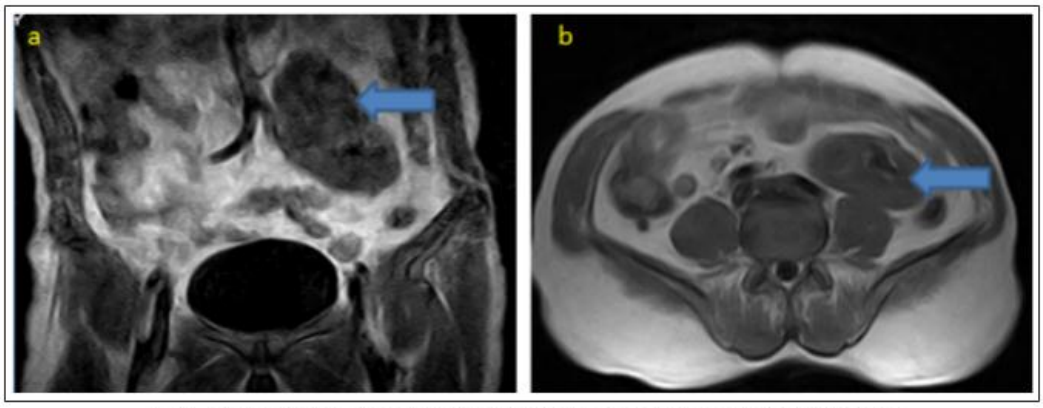

Fig 5. Coronal (a) and sagittal (b) T1WI reveals ectopic low lying left kidney in left lower lumbar region (arrows) in MRKH syndrome individual

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