



MAYER ROKITANSKY KUSTER HAUSER SYNDROME - A REVIEW ARTICLE

Dr. Shweta Thapa K.C* and Prof. Dr. Yi Cunjian

Department of Gynecology and Obstetrics, 1st Clinical Medical School of Yangtze University, Hubei, China.

ABSTRACT

Mayer Rokitansky Kuster Hauser is a rare disorder of female reproductive tract characterized by the congenital hypoplasia or aplasia of uterus, fallopian tube, cervix and upper two-third of vagina. It is either isolated (type I) or associated with a variable abnormalities of renal, skeletal and cardiac system (type II). The MRKH female have normal secondary sexual characteristic, 46XX karyotype and normal functional ovaries. This review contains subtypes, associated anomalies, clinical presentation, current diagnostic tools and treatment modalities of MRKH female. The diagnosis of MRKH female is done by ultrasound and MRI. Both non-surgical and surgical approaches are used to create sexually functional neo-vagina. MRKH female are under emotional stress and fertility issue is a serious problem. So proper counseling and psychosocial support is also important. MRKH patient can achieve parenthood by assisted reproductive technique and gestational surrogacy. This review summarizes the need of further study in genetic abnormalities and advance treatment methods.

Keywords: Primary amenorrhea; Mayer-Rokitansky-Kuster-Hauser syndrome; Ultra sonogram; vaginoplasty; Assisted Reproductive Technique

INTRODUCTION

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is a very rare disorder, characterized by congenital aplasia of the uterus, fallopian tube and the upper two-thirds of the vagina with presence of normal functional ovaries. It is the second most common cause of primary amenorrhea after gonadal agenesis.¹ Affected female usually present with primary amenorrhea, abnormalities of internal genitalia, normal secondary sexual characteristic and have a normal 46 XX karyotype. MRKH females usually have a small vaginal pouch.²

This syndrome was first described by Mayer in 1829 and Rokitansky in 1838.^{1,2} Mullerian or paramesonephric ducts differentiate into fallopian tubes, uterus, cervix and upper part of vagina and any abnormalities during the development results in various malformations.

The incidence of MRKH syndrome is 1 in 4000–5000 births. Sporadic cases of MRKH syndrome are more frequently seen than the familial cases with mode of inheritance as autosomal dominant with incomplete penetrance and variable expressivity.^{3,4}

MRKH syndrome is subdivided into two types: Type I (Isolated) characterized by complete uterine aplasia. Female with MRKH type I present with Mullerian agenesis and short vaginal pouch without any additional congenital anomalies. Type II MRKH (Atypical) or MURCS (Mullerian duct aplasia, Renal dysplasia and Cervical Somite anomalies), characterized by uterine symmetric or asymmetric hypoplasia or cord like rudimentary structures. Female with type II MRKH present with type I characteristic along with either renal, skeletal, hearing and cardiac complications. Type I (isolated) MRKH is less frequent than type II MRKH or MURCS.⁵

Exact cause of MRKH syndrome still remains unclear, genes such as the HOXA7, HOXA9-13, HOXD9-13 and WNT4 are considered to play role in embryonic origin of the female reproductive tract and their altered expression results in various developmental anomalies of female internal genitalia.⁶ The diagnosis of MRKH is made by ultrasound or magnetic resonance imaging, along with underlying normal physiological hormonal levels. Treatment of these patients require multidisciplinary approach, both non-surgical and surgical creation of functional neovagina, psychological support, and fertility care through assisted reproductive technique.⁷

This review aims to provide an overview of MRKH syndrome. It is further subdivided into: types, etio-pathogenesis, clinical presentation, diagnostic methods and management. Treatment of MRKH female includes both non-surgical and surgical intervention.

Presentation of MRKH Female:

The patient with MRKH syndrome always present with primary amenorrhoea with or without cyclic lower abdomen pain. Patients of MRKH syndrome (Type-I) have normal female phenotype with well developed pubic hair and breast of tanner stage 5, normal height with no feature of excessive androgen. They

have normal functional ovaries with normal limit of physiological hormonal levels.⁷

The type II MRKH or MURCS is associated with unilateral renal agenesis (23-28%), ectopic kidneys (11%), renal hypoplasia (4%), horseshoe kidney and hydronephrosis. Skeletal anomalies associated with MRKH type II includes scoliosis(30-40%), vertebral arch disturbances at C4-C5, and asymmetric, fused or wedged vertebrae (Klippel-Feil association).⁸ MRKH type II patients may also present with hearing defects(7-20%) , cardiac malformation that includes aorto-pulmonary window, atrial septal defect and pulmonary valvular stenosis or Tetralogy of Fallot, ⁸ and digital abnormalities like polydactyli , syndactyli etc.⁹ Some patients often present with voiding difficulties, incontinence and recurrent UTI.

The age of patients at time of diagnosis ranges from infancy (gestational anomalies scanning) to early adolescent or adulthood when the female seek medical advice for amenorrhea or infertility.

Etiopathogenesis:

MRKH syndrome is one of the type-1 mullerian anomalies as per AFS (American Fertility Society-1988) classification .¹⁰ Type I MRKH occurs in approximately 44% of MRKH female and type II MRKH occurs in 56% of MRKH patients.⁶ Initially MRKH syndrome was considered as sporadic involving environmental factors like gestational diabetics and teratogenes(e.g. DES, thalidomide) mostly leading MURCS. The teratogenic effect results in failure of approximation of blastemas of the lower cervical-upper thoracic somite arm buds and pronephric buds in the fourth week of fetal life, causing developmental field defect.¹¹ But various hypothesis failed to support non genetic factors due to lower risk of MRKH in first degree relatives. Even the analysis of available pregnancy histories in the past, failed to prove the association of MRKH with any maternal illness ,drugs or teratogenes exposed during pregnancy.^{3,4} The genetic factors involved in MRKH syndrome is also very complex, multiple gene contribute to mullerian development such as Homeobox genes-HOXA, HOXB, HOXC, HOXD and WNT4 gene and their dysregulation results in MRKH syndrome. Hoxa genes are located in chromosome 2,7,12 & 11. ^{3,12} HOXA9 is expressed in the development of the fallopian tube, HOXA7 is expressed for development of uterus, HOXA11 is expressed for development of lower uterus and cervix, and HOXA13 is expressed in the upper vagina, where as HOXA7,HOXA9-13, and HOXD9-13 genes are expressed in kidney and bone development. ¹²

Another gene that contributes mullerian development is WNT4.WNT4 gene is required for the differentiation and regulatory steps in development of female reproductive tract.L12P mutation in this gene reduces the intranuclear level of b-catenin, essential transcription factor for Mullerian duct development. ^{6,13} The WNT4 gene helps to suppress male differentiation by suppressing male gonadal androgen in females. The past study showed majority of MRKH female expressed no mutation for the WNT4 gene and those MRKH female who expressed the mutation also presented hyperandrogenism. So current literature shows WNT4 gene is strongly associated with hypergonadism rather than MRKH syndrome alone.^{13,14,15}

The AMH and its receptor have also been considered as causative factors in MRKH syndrome as AMH initiates MD regression in the 6th gestational week. ^{16,17} But even the mutation analyses of the AMH gene did

not support a link between MRKH syndrome and AMH.

How can we diagnose MRKH syndrome?

The preliminary diagnosis of MRKH syndrome depends upon the detail history of the patient (chief complain of primary amenorrhea),gynecological examination(short vagina and with non-palpable uterus) and normal physiological hormonal profile.

The further confirmation of diagnosis is done by imaging studies, which includes pelvic ultra sonogram (absent of uterus or present of rudimentary uterine horn), magnetic resonance imaging and laparoscopy. The clinical examination and ultra sonogram studies are equally effective as MRI in making the diagnosis of MRKH syndrome.⁷

Abdomino-pelvic ultrasound is a simple, easily available, cost effective and noninvasive method and is the first imaging study done in evaluating the patient with MRKH syndrome. Ultra sonogram can detect any anatomical and structural abnormalities of kidney, bladders, rectum and spine and adequately allows characterizing the uterus and adnexa. It is useful in visualization of normal ovarian structure. It can detect the upper level of vagina, reveals an absence of uterus, and also helps in identification of uterine obstruction and tubal duplication.^{2,18}

MRI (magnetic resonance imaging) is also non invasive, more sensitive and equally efficient imaging tools that can diagnose MRKH syndrome. It often overcomes the limitation of ultra sonogram and provides excellent images of superficial and deep tissue planes. MRI has multi-planar screening capability and is sensitive in discovering other MURSC-associated anomalies such as the skeletal or cardiovascular system, which might remain undetectable in ultrasound.¹⁹ MR urogram (MRU) can be used to visualize both the reproductive and the urinary system and evaluate their functional status.^{2,7,20}

Even though MRI is more accurate and reliable but due to cost factor diagnosis is based on ultrasound findings mostly in developing countries. ²¹

Laparoscopy is the invasive method that helps in the diagnosis of MRKH but is infrequently used as it is highly expensive .Its use is mostly reserves for MRKH patient undergoing surgical intervention (construction of a neo-vagina).²² Since laparoscopy provides only indirect assessment of uterine cavity so other anomalies associated with MRKH may not be visible. ²

Laboratory Studies:

Chromosomal analysis of MRKH is essential to differentiate it from androgen sensitivity syndrome (presence of intra abdominal testis). The karyotype of MRKH is always 46XX and that of androgen insensitivity syndrome (AIS) is 46XY. ^{23,24} The lab investigations of LH, FSH, Testosterone and 11 b estradiol are always within normal limits , indicating appropriate ovarian function and thus rule out any pituitary abnormalities. ²⁴

Other additional investigations carried out in MRKH patients are: CT-abdomen, intravenous pyelogram and spine radiography. CT-abdomen provides information regarding the associated renal and spine anomalies, and intravenous pyelogram assess renal collecting system. Spine radiography may show spine deformity such as short spine, congenital fusion of vertebrae at different levels, degenerative and osteoarthritic changes and variable degree of sacral agenesis.^{2,20}

Treatment Modalities and Psychological support:

Patients with MRKH syndrome are under anxiety, acute depression and emotional stress due to lack of menstruation and inability to conceive. There should be multi-disciplinary approach from various departments like reproductive endocrinologist, adolescent gynecologist, geneticist, orthopedic specialist, urologist, psychiatrist and audiologist for their diagnosis and further management.^{23,26}

The main goal of treatment is to provide emotional and psychosocial support, non surgical and surgical creation of neo-vagina, to regain functional sexual satisfaction including orgasm and natural lubrication.

Non surgical intervention in creation of neo-vagina:

The most common nonsurgical procedure used in creation of neo-vagina is (Frank Technique) the first line of therapy. Frank's Method uses vaginal dilators that stretch the short vagina into a greater diameter and length. Dilators size are gradually increased until the satisfied vaginal functional length of greater than 6 cm is achieved.²⁵ The procedure takes prolong duration ranging from 6 weeks to months and need of daily dilatation. Since the success rate is 78%-92%, so great motivation is required for successful completion.^{26,27}

Another nonsurgical process used to lengthen vaginal size is Ingram's Method. Similar to frank's methods, vaginal dilators is put in the saddle of bicycle stool. The patients are asked to sit on the stool, slightly leaned forward, for at least 15-30-minute, for about two hours per day. This method slowly increases the length and diameter of vagina. The treatment is continued for six months or more until sexual satisfaction is achieved.²⁸

Both frank's and ingram's procedure of neovagina creation has similar drawbacks of discontinuity because female experience fatigue, lack of comfort, lack of privacy, or even a lack of time to dilate, need of repetitive use leading to shame and embarrassment.^{21,28}

Surgical interventions in creation of neovagina:

Surgical creation of neo-vagina includes Creatsas vaginoplasty, the Vecchietti procedure, Davydov procedure, McIndoe procedure, and sigmoid vaginoplasty.

The Creatsas vaginoplasty is a simple and successful method and there are no any post-operative complications.

The Vecchietti operation is considered as surgical version of frank's method.^{26,29} This is open

procedure, neo vagina is created by a traction device attached to the abdomen, then sutures are placed subperitoneally with plastic olive placed in the vaginal dimple. When the tension on the traction device is increased, it pulls the thread, thus stretches vagina upto 1–1.5 cm per day to create a neovagina. This surgically created neo-vagina gives sexual satisfaction in about 94% of MRKH female and vaginal dilatation is more successful compare to frank's and ingrams methods.³⁰

Davydov procedure:

This is a laproscopic procedure. Peritoneal flap is used to create neo-vaginal lining. Initially vaginal dimple is located and is opened by giving H-shaped incision, then probe is inserted into the vagina, lastly peritoneal edges are pulled down to forms new vaginal lining and sutured to the vaginal opening. The outcome of this process is unsatisfactory leading to painful sexual activity. ³¹

McIndoe procedure:

During this procedure, skin graft is taken from the thigh or gluteal region and wrapped around an acrylic mold. Both molds and grafts are then inserted into the neo-vagina which is created by giving incision in vaginal fovea and dissecting vesico-rectal space. Thus molds are left for about 2 weeks, and later dilated daily by vaginal dilators. ³²

Sigmoidal vaginoplasty:

The neo vagina is created by grafting a 12-18 cm long segment of sigmoid colon. Various literature review, showed success rate of vaginoplasty about 66-70%.^{7,32} Some MRKH female who underwent surgical vaginoplasty experienced complications like-urethrovaginal fistula, hemorrhage, infection, graft failure, excessive skin scarring and vaginal stenosis, discharge and dyspareunia.

Role of counseling:

The MRKH female should be well counseled regarding the diagnosis, different therapeutic measure and fertility issues. MRKH female experience reactive depression, isolation, anxiety, confusion and fear of partner rejection. Unable to conceive by natural methods cause serious impact in patient well-being. However today's modern technology, assisted reproductive technique (ART) with gestational carrier have helped MRKH women to achieve genetic offspring and enjoy parenthood. Uterine transplantation can be the other options but is still under experiment, so the women with uterine agenesis can have child either through adaptation or gestational surrogacy. There are centers worldwide that offers services for gamete donation, IVF, surrogacy and adoption. The quality of life of MRKH women can be improved by proper procedural intervention, psychological counseling, and support from family members and support groups. ^{33,34}

CONCLUSION

MRKH syndrome is rare disease, it is one of the most likely diagnoses in patients presenting with primary amenorrhea. Burden of MRKH is still underestimated due to late diagnosis, unknown etiology and lack of study. MRKH female are under serious psychosexual and psychosocial problems. Therefore, detail knowledge of different therapeutic interventions and their complications is needed to provide adequate satisfaction. The management of MRKH female is very crucial, collaboration of gynecologist, endocrinologist, fertility expert, counselor and other professional is required to provide optimal care and increase quality of life.

Further research into the etiology of MRKH syndrome is required in future to uncover the underlying genetic and molecular factors association. These females need multidisciplinary approach from nonsurgical or surgical creation of functional neo-vagina to psychosocial supports.

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