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REVIEW

Update on Mayer–Rokitansky–Küster–Hauser syndrome

Na Chen[1], Shuang Song[1], Xinmiao Bao[1,2], Lan Zhu (✉)[1]

[1]National Clinical Research Center for Obstetric and Gynecologic Diseases, Department of Obstetrics and Gynecology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China; [2]Peking Union Medical College, M.D. Program, Beijing 100730, China

Abstract **This review presents an update of Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome on its etiologic, clinical, diagnostic, psychological, therapeutic, and reproductive aspects. The etiology of MRKH syndrome remains unclear due to its intrinsic heterogeneity. Nongenetic and genetic causes that may interact during the embryonic development have been proposed with no definitive etiopathogenesis identified. The proportion of concomitant extragenital malformations varies in different studies, and the discrepancies may be explained by ethnic differences. In addition to physical examination and pelvic ultrasound, the performance of pelvic magnetic resonance imaging is crucial in detecting the presence of rudimentary uterine endometrium. MRKH syndrome has long-lasting psychological effects on patients, resulting in low esteem, poor coping strategies, depression, and anxiety symptoms. Providing psychological counseling and peer support to diagnosed patients is recommended. Proper and timely psychological intervention could significantly improve a patient's outcome. Various nonsurgical and surgical methods have been suggested for treatment of MRKH syndrome. Due to the high success rate and minimal risk of complications, vaginal dilation has been proven to be the first-line therapy. Vaginoplasty is the second-line option for patients experiencing dilation failure. Uterine transplantation and gestational surrogacy are options for women with MRKH syndrome to achieve biological motherhood.**

Keywords MRKH (Mayer–Rokitansky–Küster–Hauser) syndrome; etiology; clinical characteristic; diagnosis; treatment; psychological effect

Introduction

Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, also referred to as Müllerian aplasia or Müllerian agenesis, is a rare congenital condition caused by embryologic underdevelopment of the Müllerian duct (MD) and characterized by hypoplasia of the vagina and uterus [1]. The estimated prevalence of MRKH syndrome is one per 4500–5000 female newborns [2,3]. In 2020, Peking Union Medical College Hospital (PUMCH) conducted a cross-sectional study to investigate the prevalence of female genital tract malformations, consisting of 13 436 ninth-grade female students from three urban and one suburban districts in Suzhou, Jiangsu Province, China. Of these, 7823 female students (mean age: 14.5 ± 0.56 years) voluntarily underwent additional pelvic ultrasound (or pelvic MRI, if necessary) during their routine school physical examinations. Two were diagnosed with MRKH syndrome, indicating a prevalence of MRKH syndrome of 1/3912 in the region (data to be published).

Depending on whether combined with associated extragenital abnormalities (renal, skeletal, and others), MRKH syndrome could be classified into type I (genital abnormalities only) and type II (combined with extragenital abnormalities, mainly including renal, skeletal, cardiac, neurologic, and other rare malformations) [4]. The coexistence of MD aplasia combined with unilateral renal aplasia (URA)/ectopic kidney and cervicothoracic somite dysplasia is called Müllerian aplasia, renal aplasia, and cervicothoracic somite dysplasia syndrome (MURCS) [5].

Etiopathogenesis

The etiology of MRKH syndrome remains unexplained due to its intrinsic heterogeneity. Environmental and genetic causes that may interact during the embryonic development resulting in various phenotypes and severities have been proposed (Fig. 1) [6].

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Correspondence: Lan Zhu, zhu_julie@vip.sina.com

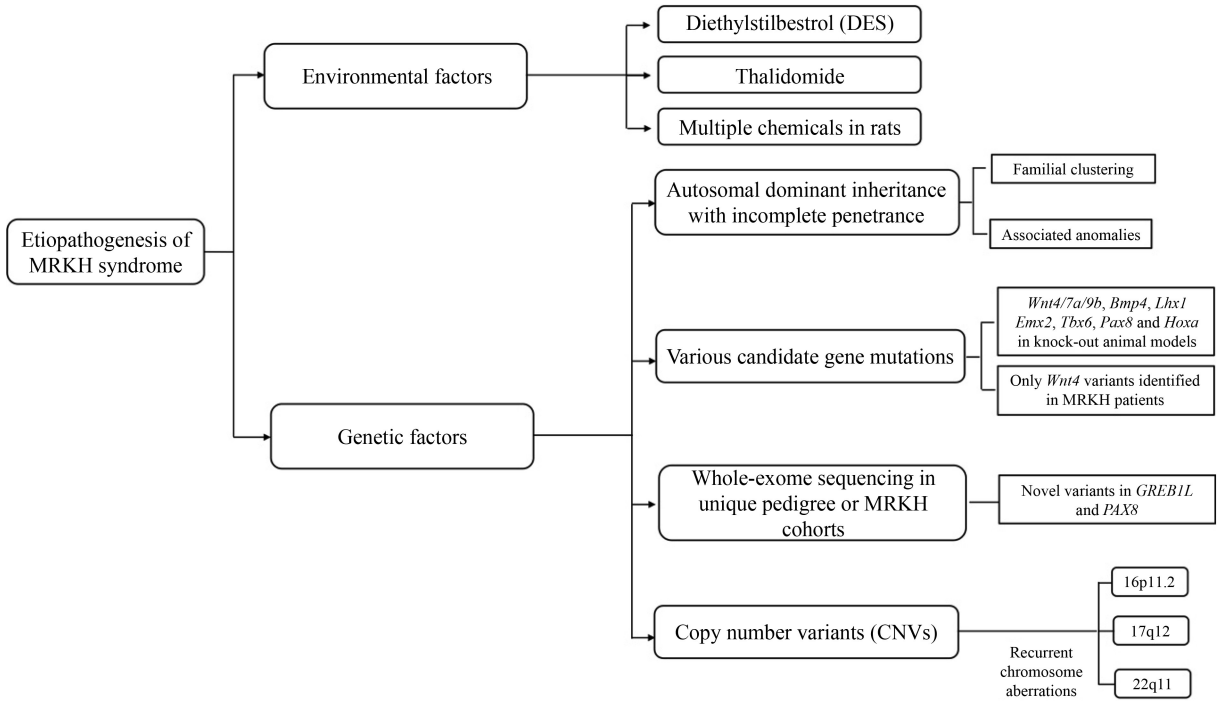

Fig. 1 Etiology of MRKH syndrome.

Although reports of familial occurrence are available [7–9], most cases of MRKH syndrome occur sporadically. Epigenetic and environmental factors have been implicated in the pathogenesis of MRKH syndrome [10]. The identification of monozygotic twins discordant for MRKH syndrome reported in literature suggests a role of epigenetic changes following potential exposure to environmental compounds [11–14]. For example, diethylstilbestrol (DES) is an estrogen agonist once prescribed to prevent miscarriage. Later studies found that fetal exposure to DES increased the risk of fetal genital tract malformations (including MRKH syndrome), possibly by interfering with the *HOX* pathway [15–17]. Fetal exposure to thalidomide could induce phenotypes similar to MRKH syndrome: uterovaginal dysplasia with normal ovarian and fallopian tube development [18]. In rats, fetal exposure to multiple chemicals (e.g., organotin and phthalates) could affect MD development and induce genital malformations, such as MRKH syndrome [16,19,20]. Overall, studies on environmental factors in MRKH syndrome cohort are limited.

While nongenetic factors have been implicated, reports of familial clustering and its associated anomalies suggest the genetic components in the pathogenesis of MRKH syndrome [7,8,21–23]. Herlin *et al.* (2014) reviewed a total of 67 families with familial occurrence of MRKH syndrome; among them, 36 families had ⩾ two members with MRKH syndrome [7]. Chen *et al.* (2021) reported 16 patients with MRKH syndrome from six families with familial occurrence [9]. Studies on familial clustering of MRKH suggest an autosomal dominant inheritance pattern, with incomplete penetrance, variable expressivity, and the possibility of sex-limited (female) expression trait [7,24–25].

Clinical heterogeneity suggests defects occurring in developmental pathways shared by organs closely related (including the genitourinary system, skeletal system, and cardiac system) in the intermediate mesoderm during embryogenesis [26,27]. Candidate causative genes and molecular pathways known to be involved in the development of MD have mostly been elucidated through animal models and genetic analyses in patients with MRKH syndrome [23,28,29]. Molecular defects known to cause genetic diseases that overlap with MRKH syndrome, such as Goldenhaar syndrome, Dandy–Walker syndrome, Holt–Oram syndrome, Bardet–Biedl syndrome, and VATER/VACTERL association [30,31] also contribute to potential candidate genes in the genetic studies of MRKH syndrome.

Knockout of genes expressed along the MD or the Wölffian duct (WD), such as *Wnt4/7a/9b* [32–34], *Bmp4* [35,36], *Lhx1* [37,38], *Emx2* [39], *Tbx6* [40] and *Pax8* [41], leads to MRKH-like phenotypes in mice. In addition, the *Hoxa* gene cluster (*Hoxa9*, *Hoxa10*, *Hoxa11*, and *Hoxa13*), which is expressed along the anterior–posterior axis in a segmental pattern, is required for the correct patterning and differentiation of female MD. Knockout of *Hoxa* gene cluster could cause disruption in the development of the corresponding part of the MD, WD, and spine [42–46]. While numerous candidate genes and

pathways have been identified in knockout animal models, potentially pathogenic mutations in these candidate genes identified in patients with MRKH include a missense mutation in *LHX1* in 1/48 MRKH patients [47], a frame shift mutation in *LHX1* in 1/62 patients with MRKH [48], three missense variants of *LHX1* in 5/112 patients with MRKH [49], a splicing mutation in *TBX6* in 2/112 patients with MRKH [49], a nonsense mutation in *WNT9B* in 1/109 patients with MRKH and four missense mutations in *WNT9B* in 4/109 patients with MRKH [50]. Moreover, none of these candidate gene mutations has a definitive gene–disease association with MRKH syndrome. *WNT4* variants, which are probably involved in androgen regulation, have been identified in four patients with MRKH syndrome with hyperandrogenism [51–54]. To date, only *WNT4* variants have been identified as causal gene mutations for a clinically distinct subtype of MRKH syndrome with hyperandrogenism [51–54].

A whole-exome sequencing (WES) study in a unique three-generation pedigree of two female cousins with type II MRKH syndrome (associated with URA) and two deceased male relatives with URA revealed a novel missense variant in *GREB1L* to be co-isolated with the phenotype of MRKH syndrome in the pedigree [55]. *GREB1L*, as a co-activator for retinoic acid receptors [56], has previously been identified as a candidate gene for congenital anomalies of the kidney and urinary tract (CAKUT) [56–58]. Its relationship to MRKH syndrome was first observed in a WES study of CAKUT cohort (183 cases including 54 fetuses with bilateral kidney agenesis (BKA)) in 2017, in which five female BKA fetuses were identified with heterozygous variants in *GREB1L* and four out of them exhibited the phenotype of uterine agenesis [59].

In a WES study of 592 MRKH syndrome cases (442 from the Chinese Han MRKH cohort and 150 from the multi-ethnic MRKH cohort) and 941 female Chinese Han controls, a total of 26/592 (4.4%) cases were identified with loss-of-function variants in 19 candidate genes essential for MD/WD development, of which *PAX8* (1.2%, 7/592) represented the most significant gene underlying the etiology of MRKH syndrome [23].

Studies of various candidate gene mutations in MRKH syndrome could only explain the etiology of a small percentage of MRKH cases. Copy number variants (CNVs) could also provide clues in the genetic mutational etiology of MRKH syndrome. Recurrent chromosome aberrations at 16p11.2, 17q12, and 22q11 were found in a small proportion of patients with MRKH syndrome in previous studies (Table 1). Sequent analyses have implicated genes located within critical regions of these common CNVs, including *TBX6* in 16p11.2 and *LHX1* and *HNF1β* in 17q12, as possible candidate genes in the pathogenesis of MRKH syndrome [47,49,60–66]. However, with large numbers of genes contained in these genomic regions, determining the exact causative gene(s) has been difficult.

Clinical characteristics

In general, karyotype evaluation of most patients with MRKH syndrome has demonstrated normal 46 XX profiles [1]. Secondary sex characteristics are normally developed due to the normal development of ovaries and normal steroid hormone production [67,68]. Primary amenorrhea is the main complaint of patients with MRKH syndrome, resulting from vaginal and uterine hypoplasia. With a significantly shortened vaginal canal (or a dimple below the urethra), dyspareunia is the second leading complaint in these patients [69]. Over 90% patients have uterine remnants [70,71], which generally present as myometrial nodules without endometrial differentiation and, in some cases, with endometrial differentiation (i.e., functional rudimentary uterus) [71,72]. Tian *et al.* (2021) reported 79 patients with MRKH syndrome who complained of chronic or cyclic pelvic pain and received surgical removal of the rudimentary uterus at PUMCH from January 2009 to January 2020. Of them, 43.0% (34/79) were confirmed to have endometrial differentiation by pathology [73]. Rall *et al.* (2013) analyzed the histologic structure of uterine rudiments from 42 patients with MRKH syndrome and found that 40.4% (17/42) uterine rudiments contained endometrial epithelium and CD10-positive stroma, similar to the proportion reported in Tian's study. The endometrium was predominantly basalis-like with significantly lower proliferation capacity [74]. Subsequently, Brucker *et al.* (2017) reported that the decidualization of endometrial stromal cells from the endometrial tissue of uterine remnants from 39 patients with MRKH syndrome was impaired [75]. Hentrich *et al.* (2020) reported that bulk RNA sequencing of the endometrial tissue from 39 patients with MRKH syndrome showed extensive transcriptomic changes compared with healthy controls [76].

The evaluation for concomitant congenital extragenital anomalies is essential for MRKH syndrome patients because of the close linkage of different organs derived from the mesoderm, such as the urogenital, musculoskeletal, and cardiac systems [77]. Several studies described the phenotype profiles, and the proportion of concomitant malformations varies in different studies [3,9,78–84] (Table 1). In 2021, Chen *et al.* reported the largest MRKH cohort so far, containing 1055 Chinese patients with MRKH syndrome, of which 69.6% were classified as type I and 30.4% as type II [9]. The proportions of type II in European patients with MRKH

Table 1 Reports of patients with MRKH syndrome with CNVs in recurrently affected regions 16q11.2, 17q12, and 22q11.2

Reference	Cases of MRKH	Cases of CNVs	CNVs			Candidate genes	Phenotypes
			Chromosome	Rearrangement	Size		
Sundaram *et al*., 2007, USA [62]	1	1	22q11.2	Deletion	NA		Type II
Cheroki *et al.*, 2008, Brazil [63]	14	1	22q11.2	Deletion	2.6 Mb		Type II
		1	17q12	Deletion	1.2 Mb	*LHX1* and *HNF1β*	Type II
Bernardini *et al.*, 2009, Italy [64]	22	2	17q12	Deletion	1.5 Mb	*LHX1* and *HNF1β*	Type II
Nik-Zainal *et al.*, 2011, Germany [65]	63	4	16p11.2	Deletion	0.55 Mb	*TBX6*	Two type I and two type II
		4	17q12	Deletion	1.4 Mb	*LHX1* and *HNF1β*	One type I and three type II
		1	22q11.2	Deletion	0.39 Mb		Type II
Ledig *et al.*, 2011, Germany [49]	48	1	1q21.1	Deletion	0.4 Mb		Type II
		1	22q11.2	Deletion	0.4 Mb		Type I
		2	17q12	Deletion	1.4 Mb	*LHX1* and *HNF1β*	One type I and one type II
Morcel *et al.*, 2011, France [66]	57	1	22q11.2	Deletion	3 Mb		Type II
Hinkes *et al.*, 2012, Germany [67]	1	1	17q12	Deletion	1.43 Mb	*LHX1* and *HNF1β*	Type II
Sandbacka *et al.*, 2013, Finland [51]	112	5	16p11.2	Deletion	0.53 Mb	*TBX6*	ND
		1	17q12	Deletion	1.7 Mb	*LHX1* and *HNF1β*	ND
McGowan *et al.*, 2015, UK [68]	1	1	17q12	Deletion	1.9 Mb	*LHX1* and *HNF1β*	Type II
Chen e*t al.*, 2021, China [23]	442	4	16p11.2	Deletion	2.36 Mb	*TBX6*	Type II
		2	17q12	Deletion	3.54 Mb	*LHX1* and *HNF1β*	One type I and one type II

NA, not available; ND, not described.

syndrome were reported to be 43.5%–54.4% in six previous studies (Table 2). The discrepancies in the proportions of type II MRKH syndrome between Chinese and European cohorts may be explained by ethnic differences.

Diagnosis

Physical examination of MRKH syndrome could reveal normal external genitalia yet short blind-ending vagina with a lack of cervix and uterus, whereas the growth, including height and hair, and secondary characteristics are usually normal [85].

Ultrasound, as the first-line auxiliary examination due to its high accessibility and low cost [86], demonstrates the absence of uterus or only a primordial uterus and vaginal canal. The development of ovaries is usually unaffected because of their embryonic origin [87]. Three-dimensional ultrasonography shows reliable diagnostic accuracy, with a concordance of 88.9%–96.3% with magnetic resonance imaging (MRI) [88].

Pelvic MRI is the gold standard for diagnosing MRKH syndrome, and it is useful in surgical planning [89,90]. MRI should always be performed when possible because it has better resolution than ultrasound to detect the presence of rudimentary uterine buds and uterovaginal agenesis [71,91]. It has the advantage in showing the evidence of the existence of endometrium (Fig. 2) and a high agreement between endometrium detection by MRI and pathology.

Laparoscopy is not routinely used for diagnosis considering its invasiveness, although it could observe the structures more directly. It is usually performed along with treatment purposes.

Psychological effects

Considering MRKH syndrome is characterized by a 46 XX karyotype and functional ovaries, patients generally develop normal secondary sexual characteristics. Most patients do not seek medical help until puberty since their chief complaint is mainly primary amenorrhea or difficulty in sexual intercourse. The anatomic anomalies of MRKH syndrome could lead to infertility and failure of vaginal intercourse, which bring patients doubts about their female identity and social role, resulting in negative

Table 2 Summary of the phenotypic analysis of patients with MRKH syndrome in previous studies

Reference	Patient number (*n*)	Type II (%)	Unilateral kidney (%)[a]	Scoliosis (%)[b]	Cardiac (%)	Neurologic (%)
Oppelt *et al*., 2006, England [78]	53	52.8	22.6	11.3	5.7	3.8
Creatsas *et al.*, 2010, Greece [79]	200	ND	31.0	5.5	ND	ND
Oppelt *et al.*, 2012, England [80]	282	44.7	18.7	ND	3.5	4.9
Rall *et al.*, 2015, Germany [81]	346	46.8	12.7	11.0	2.6	ND
Kapczuk *et al.*, 2016, Poland [82]	125	54.4	15.2	16.8	ND	ND
Herlin *et al.*, 2016, Denmark [3]	168	43.5	21.6	ND	3.6	1.8
Pan *et al.*, 2016, China [83]	594	7.2	3.9	1.2	0.5	ND
Deng *et al*., 2019, China [84]	274	28.1	6.2	15.7	1.5	0.36
Chen *et al.*, 2021, China [9]	1055	30.4	4.7	20.3	1.8	0.57

[a]Proportion of unilateral renal agenesis in the MRKH cohort studied.
[b]Proportion of scoliosis in the MRKH cohort studied.
ND, not described.

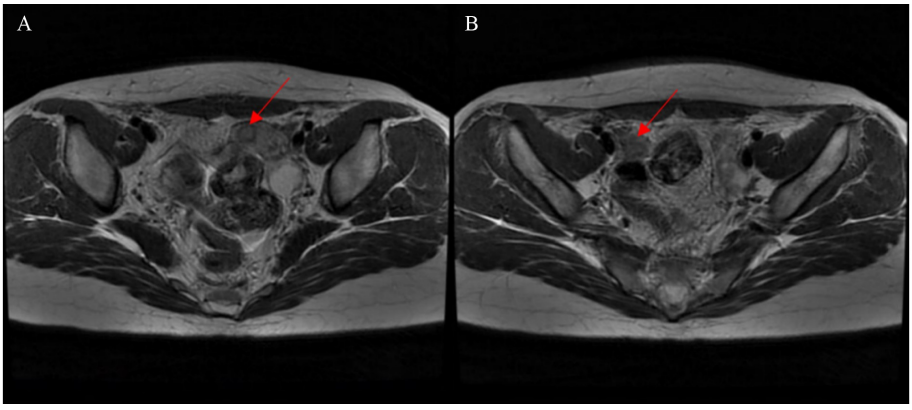

Fig. 2 MR images of the existence of endometrial tissues in rudimentary uterus. (A) Axial fat-saturated T2W1 MR image shows endometrial tissues in the left rudimentary uterus (red arrow) and (B) no endometrium is detected in the right rudimentary uterus (red arrow).

self-evaluation and tremendous emotional burden [92–94]. Several studies discovered that patients with MRKH syndrome had significantly low self-esteem than healthy controls [95–97].

Moreover, MRKH syndrome is generally diagnosed in adolescence, a sensitive and tough period for development and maturity in self-consciousness. Due to cognitive immaturity, dealing with this diagnosis in adolescence often stimulates poor coping strategies, which further exacerbate the negative psychological impact [98,99]. A research conducted by Bargiel-Matusiewicz proved that patients often relied more on emotionally focused coping rather than problem-focused coping, suggesting they were more likely to focus on negative affects [100].

The diagnosis and treatment process of MRKH syndrome often accompany with huge psychological burden, among which depression and anxiety symptoms are common. In several interview studies, some patients used depression, guilt, or even suicidal thoughts to describe their emotional feelings after diagnosis [101]. Some patients admitted concerns about feeling different from peers and managing intimacy relationship. These concerns may cause recurring anxiety symptoms that reach a peak at child-bearing age [102]. Up to now, studies focusing on depression and anxiety of patients with MRKH are limited, and they showed discrepancies in results (Table 3). Heller-Boersma detected that the depression and anxiety subscales of patients with MRKH had a more pathological trend than those of healthy controls [95]. Liao showed that anxiety symptoms increased significantly in patients, especially in patients who underwent vaginal dilation or vaginoplasty [96]. Liao believed treatment could strengthen patients' "illness" and "different from others" cognition, which intensified anxiety experience. Song *et al.* and Chen *et al.* drew the same conclusion in 141 Chinese patients with MRKH, which was the largest sample size up to now [103,104]. However, Weijenborg, Gatti, and Leithner found no difference in depression and anxiety scores between patients with MRKH and healthy controls [97,105,106].

A number of studies have shown that non-surgical and surgical treatments could correct the vaginal structure

Table 3 Depression and anxiety of patients with MRKH syndrome

Reference	Sample size	Measurements	Results
Heller-Boersma *et al.*, 2009 [95]	66 patients with MRKH syndrome 31 healthy controls	SCL-90-R[a]	Trend to anxiety and depression in patients with MRKH syndrome
Gatti *et al.*, 2010 [105]	40 patients with MRKH syndrome 30 healthy controls	BDI[b]	No significant difference observed
Liao *et al.*, 2011 [96]	54 patients with MRKH syndrome	HADS[c]	Higher anxiety scores in patients No difference observed in depression scores
Katharina Leithner *et al.*, 2015 [106]	10 patients with MRKH syndrome 20 controls in PAG[d] unit	PHQ[e]	No significant difference observed
Weijenborg *et al*., 2019 [97]	54 patients with MRKH syndrome 79 healthy controls	SCL-90-R, HADS	No significant difference observed
Song *et al.*, 2020 [107] Chen *et al.*, 2020 [104]	141 patients with MRKH syndrome 178 healthy controls	PHQ, GAD-7[f]	More severe anxiety and depressive symptoms observed in patients

[a]SCL-90-R, the Symptom Checklist; [b]BDI, Beck Depression Index; [c]HADS, Hospital Anxiety and Depression Scale; [d]PAG, pediatric and adolescent gynecology; [e]PHQ, Patient Health Questionnaire; [f]GAD-7, Generalized Anxiety Disorder-7 item scale.

safely and effectively, with satisfied postoperative sexual function [108–110]. However, restoration of anatomical abnormalities alone is not sufficient in the comprehensive treatment of MRKH syndrome. Many studies proved that vaginal dilation or vaginoplasty did not improve patient psychological outcomes [109,111]. The psychological effect of MRKH syndrome is long-lasting. Therefore, psychological intervention and peer support are of great significance for patients with MRKH syndrome. The American College of Obstetricians and Gynecologists (ACOG) guideline for MRKH syndrome states that the psychological effect of the disease cannot be underestimated, and all diagnosed patients should be counseled and encouraged to participate in peer support group [112]. In Chinese expert consensus, providing psychological counseling about intimacy relationships to patients when necessary is also recommended [113].

However, only few studies about psychological intervention on MRKH syndrome were conducted. Heller-Boersma conducted a randomized controlled trial of cognitive-behavioral group treatment (CBT) in patients with MRKH syndrome [114]. The main topics of treatment included key psychological challenges of MRKH syndrome, such as dealing with MRKH diagnosis, dilation therapy, sex and intimacy, and infertility, aiming at helping patients to identify poor psychological coping patterns, correct their misconception about the disease, and improve intimate relationship building skills. After the treatment, the psychological score of the experimental group was significantly improved, and the level of self-esteem increased. In addition, peer support programs among patients have also been shown to significantly reduce anxiety, depression, and oversensitivity in interpersonal communication [115].

Treatments

Creating a functional neovagina is the key to treatment of MRKH syndrome. Though various dilation and vaginoplasty methods have been proposed, they could be generally divided into non-surgical and surgical methods. Table 4 provides an overview of various techniques, including their advantages and disadvantages.

Vaginal dilation is a non-invasive, cost-effective method for MRKH patients with minimal risk of complications. Several options are available to perform vaginal dilation, including Frank's method (place progressive dilator on vaginal dimple manually), Ingram's method (create perineal pressure by dilator on a bicycle stool), and d'Alberton's method (dilate neovagina by regular intercourse) [116,117]. The overall success rate could reach 90%–96% among well-counseled and emotionally prepared patients [118,119]. In addition to vaginal length, the sexual function of patients who underwent vaginal dilation generally had no difference from that of healthy controls [120,121]. Therefore, ACOG has recommended dilation therapy as the first line treatment of MRKH syndrome since 2002 [112,122–124]. The main disadvantages of vaginal dilation are urinary complaints, pain, bleeding, time consumption, and risk of low compliance [1,125]

Vaginoplasty is the surgical procedure to create neovagina, by dissecting a pouch between bladder and rectum and lining various autografts. Many vaginoplasties have been suggested in the past decades, including McIndoe method (split skin graft), Baldwin method (bowel graft), Davydov method (peritoneal graft) and Williams method (labia majora graft) [126]. In general, all these methods mentioned above have quite high anatomical success rate [120]. In terms of postoperative sexual function, patients who underwent vaginoplasty with peritoneal and skin grafts have overall satisfactory sexual function [127–130]. As for vaginoplasty with intestinal graft, though many patients reported normal results measured by Female Sexual Function Index, the subjective sexual satisfaction is limited due to high risks of dyspareunia and unpleasant odor of intestinal discharge [131–133]. Except for autografts, tissue-engineered

Table 4 Advantages and disadvantages of surgical and non-surgical methods

Treatment	Advantages	Disadvantages
Vaginal dilation therapy	Non-invasive Cost-effective Self-controlled Minimal risks of complication	Time-consuming Risk of low compliance Anxiety arousing during dilation Discomfort and pain
Baldwin method	Significant longer vaginal length Satisfactory lubrication Low rate of stricture	Intestinal surgery related complications (postoperative intestinal fistula, obstruction, infection, and stenosis) Relative high risk of vaginal prolapse Unpleasant odor of discharge
Davydov method	Minimally invasive procedure by laparoscopy	Post-operative dilation needed Longer duration for epithelization Risk of bladder and rectum injuries Limited lubrication
McIndoe method	Vaginal approach, no scars in abdomen Simple operation	Donor-site scars Hair growth in neovagina Limited lubrication Post-operative dilation needed
William's method	Simple operation	Hair growth in neovagina Difficulty in penetration during intercourse Risk of hematoma and wound infection Post-operative dilation needed
Tissue-engineered biomaterials	Minimally invasive with no visible scars Simple operation	Expensive Post-operative dilation needed

biomaterial has also been suggested in vaginoplasty [108,134,135]. This method uses acellular dermal matrix as scaffold and small pieces of vaginal vestibule mucosa as "seed" to promote epithelization. It is a minimally invasive procedure with no visible scars on body and has low risks of graft infection and rejection. This procedure also provides satisfactory vaginal length and near normal sexual function post operation [134]. However, the cost is relatively higher than in other procedures. In addition to these features unique to each vaginoplasty methods, surgical methods have the following disadvantages in common: invasiveness, risk of blood loss and anesthesia and risk of postoperative vaginal stenosis. Thus, vaginal dilation is recommended after many types of vaginoplasty. Up to now, many comparative studies have concluded that vaginoplasty surgeries were non-superior to vaginal dilation in anatomical or functional outcomes [125,136–140]. Moreover, patients will take higher risks on invasive procedure, such as bladder and rectal injuries, and graft-related complications. On the basis of this evidence, ACOG recommends to reserve vaginoplasty for patients experiencing failure in dilation therapy.

Except for vaginal dilation and vaginoplasty, the management of functional rudimentary uteri in MRKH syndrome should be emphasized. About 40% of patients with MRKH syndrome were estimated to have functional endometrium, though some of them may have long latent period before showing obstructive symptoms [71,141]. Removal of the rudimentary uteri is the most effective method to relieve obstruction and prevent comorbidities, such as endometriosis. Therefore, laparoscopic hysterectomy should be recommended to symptomatic patients. For asymptomatic patients without resection of rudimentary uteri, physicians should conduct long-term follow-up and careful consultation to inform the possibility of a second time surgery if the obstructive symptoms arise [142].

In addition, the timing of correcting anatomical abnormalities is important. Early intervention could easily lead to a low sense of participation in decision-making procedure of treatment, further increasing psychological burden and decreasing treatment motivation, thereby causing poor compliance and high possibility of treatment failure. Hence, ACOG recommends that surgical and non-surgical treatment should be performed when the patient is emotionally mature and expresses willingness for treatment [112]. In Chinese mainland, the timing for treatment is recommended as psychologically mature and having sexual demands (generally above 18 years old) [113,143].

Reproductive outcome

Uterine transplantation (UTx) has been a growing field of research in recent years [144–147]. In 2014, the world's first livebirth after UTx was delivered by a 35-year-old patient with MRKH syndrome [148]. The grafts could be removed after fertility needs are met, so that patients do not need to be on immunosuppressants and other medications with nephrotoxicity for lifelong time [149]. Till now, nearly a hundred UTx have been performed worldwide [150,151]. Brannstrom *et al*. [152] reviewed all published clinical UTx data up to mid-2021 and showed that the overall surgical success rate, as defined

by a technically successful transplantation with a subsequent regular menstrual pattern, was 76%. The success rates are 78% and 64% for living donor (LD) and deceased donor (DD) UTx procedures, respectively. Twenty-four births (the cumulative live birth rate > 80%) after UTx have been reported, and the results showed a high rate of preterm birth. A notable detail that all three cases of preeclampsia necessitating preterm birth were delivered by patients with MRKH syndrome with single kidney. Considering single kidney is one of the main risk factors of preeclampsia, the high rate of preterm birth could be partly explained as a great majority of the recipients were women with MRKHs [153,154]. In addition, some studies on solid organ transplantation have identified the association between preterm delivery and the use of azathioprine and tacrolimus, which are immunosuppressants also commonly used in UTx [155]. However, whether this finding is a direct consequence of immunosuppression needs to be further proved. Other factors, such as IVF [156] and transplant of less elastic postmenopausal uteri [157], could also be relevant to high preterm rate. However, studies on long-term medical and psychological health of babies, recipients, and donors of UTx are still lacking.

Patients with MRKH syndrome belong to the group of absolute uterine factor infertility (AUFI), who could consider the option of surrogate. AUFI include women with no or non-functional uterus resulting from either congenital malformation, intrauterine adhesion, previous hysterectomy, or any other reasons. These patients have functional ovaries with normal anatomical structures, so their own oocytes and their partners' sperms could be obtained and fertilized *in vitro* and eventually cultured in a gestational surrogate carrier [158–161]. A review aiming to elucidate the reproductive potential of patients with MRKH syndrome reported that out of a cohort of 140 patients with MRKH syndrome, 125 underwent 369 cycles of IVF with gestational surrogacy and delivered 71 newborns, with a 70.6% (149/211) fertilization rate [162]. In a retrospective study on 32 American mothers with MRKH syndrome who underwent surrogacy, 34 children were born, including 17 boys and 17 girls. None of the girls showed congenital malformations, and only one boy presented with hearing loss caused by middle ear defects [10]. Not a single newborn girl with MRKH syndrome to a mother with MRKH syndrome had been reported. However, surrogacy could be complex due to legal restrictions and ethical and moral problems [163–165]. For instance, it is forbidden by the Regulation of Human-assisted Reproductive Technology Law in People's Republic of China. Nevertheless, gestational surrogacy should be addressed to patients as one of the future options according to the ACOG Committee's opinion [112]. Expertise in this area is encouraged to offer counseling and support to patients with MRKH syndrome.

Conclusions

MRKH syndrome is a multifactorial disease caused by genetic and environmental factors that may interact during the embryonic development. The comprehensive evaluation of patients with MRKH syndrome requires the multidisciplinary cooperation of gynecologists, orthopedics doctors, nephrologists, radiologists, and psychologists. Despite the existence of various surgical vaginoplasty, vaginal dilatation should be considered as the first-line treatment for MRKH syndrome. Further attention should be paid to psychological counseling and peer support for diagnosed patients. Appropriate and timely psychological intervention may improve the outcome of patients. UTx and gestational surrogacy are now options for women with MRKH syndrome to achieve biological motherhood.

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Compliance with ethics guidelines

Na Chen, Shuang Song, Xinmiao Bao, and Lan Zhu declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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