Clinical Features and Management of Endometriosis among Patients with MRKH and Functional Uterine Remnants

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Keywords

Mayer-Rokitansky-Küster-Hauser syndrome · Uterine remnants · Endometriosis

Abstract

Objective: This study aimed to determine the clinical features of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome patients with functional uterine remnants and endometriosis in a large cohort of Chinese patients. **Design:** This was a retrospective study. **Participants:** This study had a cohort of 511 MRKH patients. A total of 34 MRKH patients with functional remnant were finally included. **Setting:** This study included a tertiary referring hospital in China. **Methods:** Patients with MRKH diagnosed and treated at Peking Union Medical College Hospital from January 2009 to January 2020 were recruited. A cohort of 511 MRKH patients were retrospectively screened, and a total of 34 MRKH patients with functional remnant were finally included. Relevant clinical data were reviewed retrospectively from medical charts. **Results:** Of 34 patients with MRKH and functional uterine remnants, 23 (68%) had endometriosis. These patients had a

greater mean age at MRKH diagnosis than patients without endometriosis (15.9 ± 3.3 years vs. 13.2 ± 3.5 years; $p = 0.03$). Similarly, these patients experienced a longer time between age at onset of symptoms and age at operation than patients without endometriosis (45.5 ± 39.6 years vs. 19.8 ± 13.2 years; $p = 0.04$). In addition, the CA125 level was significantly higher in patients with endometriosis than in those without it (64.9 ± 85.9 U/mL vs. 25.5 ± 19.1 U/mL; $p = 0.03$). **Limitations:** The number of patients with MRKH analyzed in this study was low as we restricted inclusion to patients with at least 1 functional uterine remnant or endometriosis. **Conclusions:** It is reasonable to monitor the uterine remnant of patients with MRKH closely, regardless of age, to achieve early intervention. The level of CA125 might be helpful to differentiate active uterine remnants with endometriosis and schedule individualized treatments.

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Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (also known as Müllerian aplasia) results from disrupted development of the Müllerian ducts. It is characterized by agenesis or hypoplasia of the uterus and vagina with normal secondary sex characteristics in females. Despite the absence of a normal uterus, approximately 40% of affected patients with uterine remnants have some endometrium [1, 2]. About 50% of these can experience cyclic pelvic pain-like menstrual symptoms but without bleeding [1]. Continuous bleeding in the uterine remnant might form hematometra and lead to reflux of blood to the peritoneal cavity through the ipsilateral Fallopian tube.

Endometriosis is defined as the presence of endometrial tissue outside the internal epithelial lining of the uterine cavity. It is the leading pathologic cause of dysmenorrhea and chronic pelvic pain among adolescents [3]. Several theories have been proposed to account for the pathogenesis of endometriosis, but only retrograde menstruation followed by the endometrial tissue implanting on surfaces in the pelvic cavity is widely accepted as the leading cause [4, 5].

Of note, obstructive Müllerian duct anomalies showed a strong association with endometriosis [6]. The deranged peristalsis and tubal reflux menstruation of obstructive anomalies constitute risk factors for endometriosis [7, 8]. Following the theory of retrograde menstrual flow as an etiology of endometriosis, several studies have demonstrated an increased risk of endometriosis in patients with obstructive genital anomalies [9, 10]. However, in those studies, patients with endometriosis were not stratified based on the types of deformities.

MRKH syndrome with functional uterine remnant is a rare subtype of such obstructive anomalies. During the earliest stages of embryogenesis, failure of Müllerian duct development results in a functioning endometrium that is not connected to a normal outflow tract. Thus, functional remnants causing cyclic pelvic pain might result in endometriosis and severely affect adolescents' quality of life.

Several case studies have presented endometriosis in patients with MRKH [11–13]. However, these case reports with low numbers of patients were not sufficient to capture the features of endometriosis in patients with MRKH. Thus, the exact nature of the relationship between MRKH with functional remnant and endometriosis has yet to be elucidated, and a systematic evaluation is necessary. Here, we systematically analyzed the clinical

features and management of functional uterine remnants and associated endometriosis in a large cohort of patients with MRKH.

Materials and Methods

Study Design and Population

Patients with MRKH diagnosed and treated at the Department of Obstetrics and Gynecology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, from January 2009 to January 2020 were recruited. The inclusion criteria were as follows: (1) normal karyotype of 46, XX; (2) uterovaginal agenesis or uterine remnant verified by pelvic ultrasonography or magnetic resonance imaging; (3) normal female secondary sexual characteristics; (4) undergone surgery for excising uterine remnants because of possible functional remnants or adnexal mass or vaginoplasty; and (5) pathohistological confirmed endometriosis or functional endometrium. The exclusion criteria were as follows: (1) abnormal karyotypes and (2) cervical atresia, vaginal atresia, or transverse vaginal septum with hematometra and hematocolpos.

Relevant clinical data were reviewed retrospectively from charts of recruited patients. Endometriosis diagnosed at the time of surgery was staged in accordance with the revised American Society for Reproductive Medicine (rASRM) guidelines [14]. Follow-up ended with the last inpatient or outpatient contact after surgery.

Statistical Analyses

Statistical analysis between groups was carried out using χ^2 , Fisher's exact, and Student's *t* tests where appropriate. Statistical analyses were performed using GraphPad Prism software version 8.0 (GraphPad Software, San Diego, CA, USA). The significance level for all analyses was set at $p < 0.05$.

Statement of Ethics

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (ZS-1858). All subjects have given their written informed consent for this review of clinical data.

Results

In total, 511 patients were diagnosed with MRKH at PUMCH from January 2009 to January 2020. Of these, 375 were treated with dilation as outpatients and 136 underwent vaginoplasty or excision of uterine remnants because of possible functional remnants or an adnexal mass. Of the 136 charts reviewed, 57 patients underwent peritoneal vaginoplasty without excision of uterine remnants and 45 did not have functional endometrium or endometriosis confirmed by pathology; finally, 34 patients with MRKH conformed to our inclusion criteria (Fig. 1).

All 34 patients underwent excision of uterine remnants and ipsilateral salpingectomy because of possible

Fig. 1. The flowchart of this study. MRKH, Mayer-Rokitansky-Küster-Hauser syndrome.

Table 1. Clinical characteristics of patients with MRKH and functional uterine remnants

<i>n</i>	34
Age at MRKH diagnosis, yr	15.0±3.5 (5–26)
Duration between age at onset of symptoms and age at operation, mo	37.2±35.3 (0.5–144)
VAS score	6.1±2.1 (0–9)
CA125, U/mL	49.4±69.9 (8.8–378.2)
Age at operation	18.1±4.8 (12–29)
Cyclic pain	30 (88)
Site of remnant	
Bilateral	34 (100)
Functional remnant	
Left	14 (41)
Right	9 (27)
Bilateral	11 (32)
Kidney agenesis	8
Skeletal malformations	7
Other malformations	6
Hysterectomy + salpingectomy	34
Vaginoplasty	11
Follow-up, mo	46.3±22.8(15.2–92.5)

Values are presented as mean ± SD (range) or *n* (%). yr, year; mo, month; MRKH, Mayer-Rokitansky-Küster-Hauser syndrome.

functional remnants or an adnexal mass, and 11 (32%) of them received peritoneal vaginoplasty simultaneously. No patients were diagnosed with endometriosis without a functional remnant. The 34 patients had a mean age at MRKH diagnosis of 15.0 ± 3.5 years (range 5.0–26.0) and

a mean age at operation of 18.1 ± 4.8 years (range 12–29). Pelvic pain was common in these patients, with 30/34 (88%) describing their pain as cyclic and 4/34 (12%) as acyclic. The mean visual analog scale (VAS) pain score was 6 ± 2.1 (range 0–9), the mean serum carcinoma anti-

(A)

(B)

Fig. 2. Internal genital organs of patients with MRKH. A patient with left functional remnant but without endometriosis (**a**); a patient with left functional remnant and endometriosis (**b**). MRKH, Mayer-Rokitansky-Küster-Hauser syndrome; U, uterine remnant; O, ovary; F, fallopian duct; E, endometriosis.

gen (CA) 125 level was 49.4 ± 69.9 U/mL (range: 8.8–378.2 U/mL), and the mean time between the patient age at onset of symptoms and that at operation was 37.2 ± 35.3 months (range 0.5–144; Table 1). All 34 patients had bilateral uterine remnants; 11 (32%) patients had 2 functional remnants, 14 (41%) patients had a functional left uterine remnant, and 9 (27%) patients presented with a functional right uterine remnant. Half (17/34) of the patients had various concomitant malformations, including 8 patients with unilateral renal agenesis (2 complicated with skeletal deformities and 2 complicated with anal atresia), 7 with skeletal malformations (4 with idiopathic scoliosis and 3 with limb malformations), and 6 with other malformations (3 cases of anal atresia and 3 of cardiac malformations). The mean follow-up time was 46.3 ± 22.8 months (range 15.2–92.5).

Of the 34 MRKH patients with functional endometrioma, 23 (68%) were diagnosed with endometriosis and 11 (32%) without (Fig. 2). Patients with pelvic endometriosis had a greater mean age at MRKH diagnosis than those without it (15.9 ± 3.3 years vs. 13.2 ± 3.5 years; $p = 0.03$). Similarly, patients with endometriosis experienced a longer time between their age at the onset of symptoms and their age at operation than patients without it (45.5 ± 39.6 years vs. 19.8 ± 13.2 years; $p = 0.04$). In addition, the CA125 level was significantly higher in patients with endometriosis than in those without it (64.9 ± 85.9 U/mL vs. 25.5 ± 19.1 U/mL; $p = 0.03$). The VAS score and the age at operation had no statistical difference between the 2 groups. However, there was a tendency that patients with endometriosis reported a higher VAS pain score (6.2 ± 1.8 vs. 5.9 ± 2.6) and greater age at operation (19.0 ± 5.2 vs.

16.2 ± 3.3 years). There was also no significant difference in the distribution of functional uterine remnants between the 2 groups (Table 2).

Regarding the 23 patients with MRKH and endometriosis, 15 had endometrioma with a mean size of 4.53 cm (range 1–9), 4 had adenomyosis, and 9 presented with superficial peritoneal lesions (of these patients, 5 had endometrioma simultaneously). No case of deeply infiltrating endometriosis was found. All patients with endometriosis had ovarian cysts or adenomyosis ipsilateral to the functional remnant. The mean rASRM score of all patients was 27.4 ± 21.2 (range 1–76), and 14 (74%) patients demonstrated rASRM stage III–IV endometriosis. All patients were discharged uneventfully, and none complained of recurrent pelvic pain or recurrence of endometriosis at the last follow-up (range 15.2–92.5 months).

Discussion

Here, to our knowledge, we report the largest cohort of MRKH patients with functional uterine remnants and related endometriosis. The principal finding was that 68% of the 34 MRKH patients with functional remnants also suffered endometriosis. In addition, these patients had a greater mean age at MRKH diagnosis, experienced a longer time between age at onset of symptoms and age at operation, and had a greater CA125 level than patients without endometriosis.

All the patients in this study had bilateral uterine remnants, but most (68%) of them had only 1 functional remnant. Müllerian duct development during embryogenesis

Table 2. Clinical characteristics of patients with MRKH with functional uterine remnants and associated endometriosis

	With endometriosis	Without endometriosis
<i>n</i>	23 (68)	11 (32)
Age at MRKH diagnosis, yr	15.9±3.3*	13.2±3.5
Duration between age at onset of symptoms and age at operation, mo	45.5±39.6*	19.8±13.2
VAS score	6.2±1.8	5.9±2.6
CA125, U/mL	64.9±85.9*	25.5±19.1
Age at operation, yr	19.0±5.2	16.2±3.3
Cyclic pain	20 (87)	10 (91)
Functional remnant		
Left	8 (35)	6 (55)
Right	7 (30)	2 (18)
Bilateral	8 (35)	3 (27)
Site of endometrioma		
Left	10 (44)	
Right	8 (35)	
Bilateral	2 (9)	
rASRM score (range)	27.4±21.2 (1–76)	
rASRM stage for endometriosis		
I–II	5(26)	
III–IV	14 (74)	
Endometrioma	15 (65)	
Adenomyosis	4 (17)	
Superficial peritoneal lesions	9 (39)	
Size of endometrioma, cm (range)	4.53 (1–9)	

Values are presented as mean ± SD (range) or *n* (%). yr, year; mo, month; MRKH, Mayer-Rokitansky-Küster-Haus-er syndrome; rASRM, revised American Society for Reproductive Medicine. **p* < 0.05 versus without endometriosis.

involves the elongation of paired ducts followed by fusion, canalization, and septal resorption [15]. The varying states of the uterus in patients with MRKH result from aberrations in this developmental process. However, the causes of MRKH syndrome remain poorly understood. Studies showed that about 30% of patients with MRKH demonstrated endometrium confirmed by histological analysis [1, 16]. In our cohort, the proportion of MRKH cases with a functional uterine remnant (25%) was similar to previous studies.

In our cohort, 68% of patients with MRKH with functional remnants were complicated with endometriosis. This proportion is consistent with the reported prevalence of 56% by Marsh et al. [1]. All MRKH patients with endometriosis had a functional uterine remnant, and all had ovarian cysts or adenomyosis ipsilateral to the functional remnant. This is consistent with Sampson's retrograde menstruation theory as one of the etiologies of endometriosis [17]. Although complicated with a functional remnant, the remaining 32% of MRKH patients without

endometriosis suggest that other factors might have influenced the implantation of endometrial remnants in the peritoneum. These potential additional factors include patient-specific immune characteristics, quantity of retrograde flow, or genetic predisposition [9, 18, 19].

Here, MRKH patients with functional uterine remnants and endometriosis experienced a longer period between age at onset of symptoms and age at operation. MRKH patients usually sought medical care complaining of primary amenorrhea or abdominal pain. Although cyclic pain helps diagnose functional uterine remnants, our cohort had 3 patients with functional endometrium but without cyclic pain. Particular attention should be given to patients with MRKH, as amenorrhea lessens the characterization of pain during menses. Awareness of the increased risk of progressive endometriosis among these patients might help improve early diagnosis, prompt early intervention, and prevent morbidity secondary to hematometra and endometriosis, such as pain and distorted anatomy.

The treatment timing and modalities of MRKH can vary depending on whether an activated remnant or potential endometriosis exists. For patients with evidence of functional remnants, removing them is strongly recommended, both for treating pelvic pain and reducing the likelihood of endometriosis [20]. Several case reports have reported management of endometriosis in patients with MRKH. All of them underwent removal of the uterine remnants, and most reported complete remission of pain after surgery and no recurrence of endometriosis [1, 11–13, 19, 21–27]. Similarly, all our patients reported uneventful recovery after the operation, and none complained of recurrent pelvic pain or recurrence of endometriosis in the follow-up.

However, there is no common consensus on dealing with the asymptomatic remnants [28]. Thus, Enatsu et al. [22] reported a patient with MRKH diagnosed with active remnants 8 years after vaginoplasty. Deligeoroglou et al. [23] presented a patient with MRKH who underwent the creation of a neovagina at the age of 21. However, the patient was admitted twice to the hospital because of recurrent pelvic pain and was finally diagnosed with salpingitis and functioning endometrium. The oldest patient with MRKH presenting with functional uterine remnants was reported by Parkar et al. [11]. This asymptomatic patient demonstrated cyclic pelvic pain at the age of 40 and was diagnosed with functioning uterine remnants. Rall et al. [16] showed that the endometrium of uterine remnants in patients with MRKH had significantly low proliferative ability but normal estrogen or progesterone receptor expression levels. Because the hormonal levels are normal, the inadequate proliferative potential of the endometrium might explain the postponed bleeding of uterine remnants. In our cohort, MRKH patients with functional remnants and endometriosis had a greater age at their initial diagnosis of MRKH. Therefore, it is reasonable to monitor the asymptomatic remnants closely regardless of age. We also found that MRKH patients with functional uterine remnants and endometriosis had higher CA125 levels. This biomarker might be helpful to differentiate such active remnants with endometriosis and schedule individualized treatment.

This study had several limitations. First, it was a retrospective one; a prospective design is not feasible when studying such rare reproductive organ anomalies. Second, all patients with MRKH were treated in a tertiary referring center for this disorder, which might have caused some selection bias. Finally, although the number of patients with MRKH analyzed in this study was low as

we restricted inclusion to patients with at least 1 functional uterine remnant or endometriosis, as far as we know, it is the largest cohort ever reported.

Conclusions

Among the 34 MRKH patients with functional endometrium, 23 (68%) also had endometriosis. These patients had a greater mean age at MRKH diagnosis, experienced a longer time between age at onset of symptoms and age at operation, and had a higher CA125 level than patients without endometriosis. Therefore, it is reasonable to closely monitor the uterine remnant of patients with MRKH regardless of their age for early intervention. The level of CA125 might be helpful to differentiate active remnants with endometriosis and plan individualized treatments.

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Statement of Ethics

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (ZS-1858). All subjects have given their written informed consent for this review of clinical data.

Conflict of Interest Statement

The authors declare that no conflicts of interest could be perceived as prejudicing the impartiality of this research.

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Author Contributions

W.J.T. performed the data analyses and drafted and revised the manuscript. N.C. reviewed and corrected the manuscript. L.Z. contributed to the manuscript revision. Z.L., S.S., Y.W., Y.Y., and

J.L.D. helped with data acquisition and performed the analysis with constructive discussions. W.J.T. and N.C. contributed to manuscript preparation. L.Z. supervised and approved the final version of the manuscript.

Data Availability Statement

Data are available upon reasonable request. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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