



HAL
open science

Optimizing care for MRKH patients: From malformation screening to uterus transplantation eligibility

A. Cospain, Ludivine Dion, Maud Bidet, Krystel Nyangoh Timoh, Chloé Quélin, Isis Carton, Alinoë Lavillaureix, Karine Morcel, Paul Rollier, Laurent Pasquier, et al.

► To cite this version:

A. Cospain, Ludivine Dion, Maud Bidet, Krystel Nyangoh Timoh, Chloé Quélin, et al.. Optimizing care for MRKH patients: From malformation screening to uterus transplantation eligibility. *Acta Obstetricia et Gynecologica Scandinavica*, 2024, 10.1111/aogs.14985 . hal-04767398

HAL Id: hal-04767398

<https://hal.science/hal-04767398v1>

Submitted on 5 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.



L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

ORIGINAL RESEARCH

Optimizing care for MRKH patients: From malformation screening to uterus transplantation eligibility

Auriane Cospain^{1,2}  | Ludivine Dion^{3,4} | Maud Bidet⁵ | Krystel Nyangoh Timoh³ | Chloé Quelin^{1,6} | Isis Carton³  | Aline Lavillaureix¹ | Karine Morcel^{7,8} | Paul Rollier¹ | Laurent Pasquier¹ | Bénédicte Nouyou² | Sylvie Odent^{1,9} | Daniel Guerrier¹⁰ | Erika Launay² | Marc-Antoine Belaud Rotureau^{2,4} | Mélanie Fradin¹ | Sylvie Jaillard^{2,4} | Vincent Lavoué^{3,4}

¹Clinical Genetics Department, CLAD Ouest CRDI, ERN ITHACA, Rennes University Hospital, Rennes, France

²Cytogenetics and Cell Biology Department, Rennes University Hospital, Rennes, France

³Gynecology Department, Rennes University Hospital, Rennes, France

⁴Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), Rennes, France

⁵Medically assisted reproduction Department, Clinique Mutualiste La Sagesse, Rennes, France

⁶Anatomy and Pathological Cytology, Rennes University Hospital, Rennes, France

⁷Department of Obstetrics and Gynecology, CHU Brest, Brest, France

⁸Univ Brest, INSERM, UMR 1304, Brest, France

⁹Univ Rennes, CNRS, INSERM, IGDR (Institut de génétique et développement de Rennes)-UMR 6290, ERL U1305, Rennes, France

¹⁰IGDR CNRS UMR 6290, University of Rennes, Rennes, France

Correspondence

Auriane Cospain, Clinical Genetics Department, CLAD Ouest CRDI, ERN

Abstract

Introduction: Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome with utero-vaginal aplasia is the most severe form of the Müllerian duct anomalies and can be associated with extra-genital abnormalities such as renal or skeletal anomalies, hearing loss, or cardiac defects. The past two decades have witnessed significant advances both in understanding the etiologies of MRKH and in the development of fertility treatments such as uterine transplantation. The present work aimed to determine the rate of women with MRKH syndrome who underwent optimal initial management (after comprehensive malformation assessment) and to establish the rate of patients eligible for uterine transplantation (i.e., those with a vaginal length ≥ 7 cm without reconstruction using a bowel segment, and an anti-Müllerian hormone level >1.5 ng/mL before 35 years).

Material and Methods: Cohort study of 85 women with MRKH syndrome consulting in our tertiary center.

Results: 62.4% of women with MRKH syndrome had an exhaustive malformative evaluation according to the French guidelines (Protocole National de Diagnostic et de Soins [PNDS]), of which 76.5% had associated malformations (MRKH type II). Pedigree, when available, showed a family history of infertility or a urogenital tract spectrum anomaly in 60% of cases. Concerning the uterine transplantation selection criteria, when evaluated, 22.6% of women had an anti-Müllerian hormone level <1.5 ng/mL and 36% a vaginal length <7 cm. On the 21 women with complete evaluation of both primary and secondary outcomes, 14 of them would be eligible for a uterine

Abbreviations: AMH, anti-Müllerian hormone; DES, diethylstilbestrol; ESGE, European Society for Gynaecologic Endoscopy; ESHRE, European Society of Human Reproduction and Embryology; MDA, Müllerian duct anomalies; MRI, magnetic resonance imaging; MRKH, Mayer-Rokitansky-Küster-Hauser; PNDS, Protocole National de Diagnostic et de Soins; UTx, uterine transplantation.

Sylvie Jaillard and Vincent Lavoué contributed equally to this work.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Author(s). *Acta Obstetrica et Gynecologica Scandinavica* published by John Wiley & Sons Ltd on behalf of Nordic Federation of Societies of Obstetrics and Gynecology (NFOG).

ITHACA, Rennes University Hospital, 16 Boulevard de Bulgarie, Rennes 35200, France.
Email: auriane.cospain@chu-rennes.fr

transplantation program at the time of consultation according to the main inclusion criteria of uterine transplantation program.

Conclusions: Women with MRKH syndrome are often inadequately explored for associated malformations. Early assessment and monitoring of the ovarian reserve is key for fertility preservation, especially in the era of uterine transplantation.

KEYWORDS

fertility preservation, MRKH syndrome, Müllerian duct anomalies, uterine transplantation

1 | INTRODUCTION

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (Online Mendelian Inheritance in Man database [OMIM] number %277000) is a severe form of Müllerian duct anomalies (MDA) and is estimated to affect approximately 1 in 4000–5000 female individuals.¹ The syndrome is characterized by a congenital absence or severe hypoplasia of the uterus and of the upper two-thirds of the vagina, with normal functional ovaries. Women affected by MRKH syndrome present normal female secondary sexual characteristics, apart from primary amenorrhea, and have a 46, XX karyotype.

MDA may be associated with other extra-genital abnormalities such as renal anomalies (renal agenesis, ectopic kidneys), skeletal anomalies (spine, limbs, ribs, scapulae), hearing loss, or cardiac defects. Isolated MRKH is classified as type I following extensive evaluation of malformations and as type II when extra-genital comorbidities are present (OMIM %601076).

Women presenting with primary amenorrhea, referred to gynecologists specializing in disorders of sex development, typically undergo a routine diagnostic work-up established in France in 2021 by the Reference Center for Rare Gynecologic Pathologies ([PNDS]²). This includes a physical examination and a hormonal evaluation (follicle-stimulating hormone, luteinizing hormone, estradiol, and testosterone), complemented by transperineal or transabdominal ultrasonography and pelvic magnetic resonance imaging (MRI) to determine absence of the uterine and the presence and position of the ovaries. An MRKH diagnosis is retained if the woman has an utero-vaginal aplasia, and a 46, XX karyotype excluding differential diagnoses such as complete androgen insensitivity (OMIM #300068). Evaluation of extra-genital malformations should encompass kidney and urinary tract ultrasonography, skeletal x-rays (covering the cervico-dorso-lumbar spine or the entire skeleton), screening for hearing loss, and cardiac ultrasound. After this evaluation, the genital malformation is classified according to the European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecologic Endoscopy (ESGE) guidelines.³

The past two decades have witnessed significant advances both in understanding the etiologies of MRKH and in the development of fertility treatments such as human uterine transplantation (UTx).^{4–6}

Key messages

38% of women with MRKH syndrome are inadequately explored for associated malformations. Early assessment of ovarian reserve is necessary at diagnosis in women with MRKH syndrome. MRKH syndrome may have a familial and hereditary dimension.

As part of a multidisciplinary research endeavor at the Rennes Hospital Center (France) focusing on UTx in women with MRKH syndrome, we set out to describe the genital and extra-genital phenotype of a cohort of women consulting at our center.

The primary outcome was to determine the rate of women with MRKH syndrome who underwent optimal initial management (after comprehensive malformation assessment). The secondary outcome was to establish the rate of patients eligible for UTx, i.e., those with a vaginal length of ≥ 7 cm without reconstruction using a bowel segment and an anti-Müllerian hormone (AMH) level >1.5 ng/mL according to the inclusion criteria for UTx recipients described in the UTx project at Rennes University Hospital (TULIpE project is available on [ClinicalTrials.gov](https://clinicaltrials.gov)⁷ [no NCT05726305]).

2 | MATERIAL AND METHODS

2.1 | Design

This was a single-center cohort study.

2.2 | Patients

We included all women with MRKH syndrome ≥ 18 years, or < 18 years with informed consent of the patient and their legal guardians.

Recruitment was conducted at the Center for Rare Gynecological Diseases of Rennes University Hospital between 2004 and January 2024. For individuals included before 2020, data were collected retrospectively, and the women were recontacted whenever possible

and offered an updated genetic consultation. For women included in 2020 and after, data were collected prospectively.

Gynecological and genetic consultations were offered to all patients, and included an extensive malformation evaluation including renal imaging, a spine x-ray, and an echocardiography. An audiogram was ordered for all women who reported hearing loss. Any dysmorphic features were analyzed, comorbidities were explored, and a three-generation pedigree carried out.

2.3 | Data collection

Medical history included the diagnostic circumstances, vaginal agenesis management (surgical technique of vaginoplasty or vagina creation by dilatation complications, maintenance dilation), and gynecological history (age at first intercourse, dyspareunia, medical follow-up). A standardized pelvic examination was performed with patient consent, inserting two digits, then using dilators (Amielle, Owen-Mumford Ltd) to increase the diameter (2–3.5 cm). The length and width of the vagina were determined by painless maximal insertion of the dilator. Data about the assessment of associated malformations were collected. Women were offered psychological follow-up (as they wish, with a hospital or private practice psychologist) and hormonal evaluation of the ovarian reserve was performed (AMH level).

Clinical and genetic data at our center are stored in a local secure database, designed specifically for this project and accessible only with a validated login and password from the Rennes University Hospital intranet to ensure confidentiality.

2.4 | Outcomes

The primary outcome was the number of women who underwent comprehensive associated malformation assessment including abdominal ultrasonography and pelvic MRI to determine the absence of a uterus and the presence and position of the ovaries, kidney, and urinary tract ultrasonography, skeletal x-rays (covering the cervico-dorso-lumbar spine or the entire skeleton), screening for hearing loss, and cardiac ultrasound before consulting at our center.

The secondary outcome was the number of women with a vaginal length ≥ 7 cm (without reconstruction using a bowel segment) and an AMH >1.5 ng/mL, which are the two main eligibility criteria for an UTx (ClinicalTrials⁷ no NCT05726305), and assessed systematically in women who consulted as from 2020.

2.5 | Statistical analyses

The patients' characteristics and their medical history were described overall. Data are reported as mean or median [range] for quantitative variables and as frequencies (%) for qualitative variables.

3 | RESULTS

3.1 | Patient general characteristics

3.1.1 | Initial diagnosis

The demographic characteristics and gynecological assessments of the 85 women included in the cohort are set out in Table 1. Primary amenorrhea should classically be explored after the age of 15 years old: 15/85 patients (17.6%) in the cohort were diagnosed before this age. The primary complaint at referral was primary amenorrhea for 69/85 patients (81.2%), followed by abdominal pain and dyspareunia.

A blood karyotype was performed in 81/85 patients (95.3%) revealing a normal 46, XX formula in all but two who had the following: 46, i(X) (q10)[1]/45, X[25]/46, XX[34] (monosomy X mosaicism) which could at least partially explain the MDA syndrome^{8,9}; and 47, XX, +mar (small supernumerary marker chromosome corresponding to an isochromosome 15, inherited from a healthy mother and considered as secondary data unrelated to MDA). For four patients, no blood sample was available for genetic analysis.

3.1.2 | Genital phenotype and gynecological data

Pubertal development was considered normal in 82/85 women (96.5%) in the cohort. Three patients had clinical hirsutism. One

TABLE 1 Characteristics of the cohort and gynecological assessment.

	Number of individuals	% of all individuals (N = 85)
Demographic data		
Number of individual	85	
Median age at first complaint	16 [0; 25]	
Gynecologic assessment		
Mullerian derivatives gynecologic malformations		
Aplastic uterus and cervical aplasia	85	100%
Bi- or unilateral uterine horns	32	37.6
Vaginal 2/3 sup aplasia	77	90.6
Non mullerian derivatives gynecologic anomalies		
Surgical ovarian hernia	1	1.2
Ectopic ovarian position	2	2.4
Unilateral ovarian agenesis	1	1.2
Labia minora hypertrophy	3	3.5
Urinary meatus gap	2	2.4
Other gynecological anomaly: Ovarian cyst	5	5.9

of these women had an elevated testosterone level at 1.89 ng/mL for a norm below 1.85 ng/mL (data not available for the other two).

Based on the ESHRE/ESGE classification,³ the 85 women were classified U5C4 (aplastic uterus, cervical aplasia, 100%), with bi- or unilateral uterine horns for 32/85 (U5b, 37.6%). Vaginal aplasia was associated in 77/85 women (V4, 90.6%) and 8 women presented with isolated uterine aplasia at the time of genital malformation diagnosis. Complex genital malformation with non-Müllerian derivative anomalies was described in 8 women: four with ovarian anomalies (ectopic position ($n=2$), surgical ovarian hernia ($n=1$), and unilateral agenesis ($n=1$)), and four with vulvar anomalies (labia minora hypertrophy and urinary meatus gap ($n=1$), only labia minora hypertrophy ($n=2$), only urinary meatus gap ($n=1$)). Moreover, ovarian cyst were reported in five women.

3.1.3 | Family history

A three-generation family pedigree was established for 80 families. A relevant family history was noted in 48/80 case (60%), as detailed below. Two families were identified with two or more relatives having MRKH syndrome. Two patients reported parental consanguinity. Infertility, of non-malformative or undetermined cause, was reported in a relative in 15 cases (see [Figure S1](#), family 1-15), and genital anomalies (including male genital malformations) were reported in 9 relatives (see [Figure S1](#), family 1, family 3, family 16 to 21). Nine patients had a relative with renal agenesis and four a relative with cardiopathy. Exposure to diethylstilbestrol (DES, Distilbene®) was reported in two families. In the first family, the father of the index case with MRKH syndrome was reportedly exposed to DES in utero. In the second family, proband's mother had in utero exposure to DES.

3.2 | Primary outcome ([Table 2](#))

In this cohort of 85 women, 51 (62.4%) underwent an exhaustive evaluation of malformations according to the PNDS French guidelines and were consequently classified as having type I or type II MRKH syndrome based on the following rules: if the morphological evaluation was not complete (absence of renal, cardiac or spinal evaluation, normal hearing), classification as type I was not possible, but the patient could be classified as having MRKH type II if a malformation had been identified on one of the examinations performed. Type I or II MRKH classification was possible for 68/85 (80%) patients in our center. For the remaining 20%, at least one medical examination was missing meaning that the syndrome could not be classified. Of the 68 patients with a classified MRKH syndrome, 16 had type I and 52 type II.

3.2.1 | Extra-genital assessment with renal, skeletal, and cardiac-associated malformations ([Table 2](#))

Renal imaging data, by ultrasound or MRI, were available for 83/85 patients (97.6%) and reported to be normal in 50 cases. The 33 abnormal cases had one or more renal malformations. Unilateral renal agenesis was the most frequent renal condition, affecting 12 patients. Other renal anomalies reported were ectopic pelvic kidneys ($n=8$, for one or both kidneys), fused or horseshoe kidneys ($n=3$), renal malrotation ($n=3$), ureteral duplicity ($n=3$), renal hypoplasia ($n=2$), parenchymal atrophy ($n=1$), unilateral renal fluid cyst ($n=1$), bilateral renal microcysts ($n=1$), asymmetric kidney size ($n=1$), and unilateral dilation of excretory ducts ($n=1$).

Spine x-ray data were available for 76/85 patients (89.4%) and reported to be normal in 37 cases. The 39 abnormal cases had one or more skeletal malformations. Scoliosis was reported in 24 patients. Other skeletal abnormalities were segmental anomalies ($n=6$), spina bifida ($n=6$), hip or pelvis anomalies ($n=6$, with pelvis tilt, agenesis of bilateral ischiopubic branches, coxa vara hips), fused vertebrae ($n=4$), rib anomalies ($n=3$, with agenesis/hypoplasia of the first or last pairs of ribs), scapular asymmetry or Sprengel deformity ($n=2$), anomalies in the number of vertebrae (absent vertebrae, $n=2$). One patient had unilateral radial aplasia and aplasia of the thumb, one unilateral hypoplasia of the fibula, and one syringomyelia from T4 to the terminal cone.

Echocardiography was performed in 53/85 patients (62.4%) and was normal in all but two: one who presented a ventricular septal defect; and another presenting dilation of the ascending aorta at the Valsalva sinus (Z score +3.5 DS) and tubular aorta (Z score +3.5 DS).

3.2.2 | Extension of the phenotype

Each woman was asked whether she had any hearing difficulties. If the answer was positive, an otorhinolaryngology consultation with audiometry was carried out. Eight patients presented hearing loss, mostly unilateral. Earlier audiometric tests were rarely available and could not determine whether the hearing loss was congenital or acquired. Hearing loss was reported by the patients as occurring during childhood in six cases, and acquired during adulthood in one (information not available for one case).

Cognitive abilities and an inquiry about psychiatric comorbidities were assessed for 79/85 woman (92.9%). Seven women had psychiatric disorders: depressive syndrome ($n=2$), anxiety disorder ($n=2$), anorexia nervosa ($n=1$), bipolarity ($n=1$), psychiatric follow-up in childhood without a diagnosis ($n=1$).

Other clinical associations reported were one patient with a VACTERL association (esophageal atresia, unilateral radial aplasia, scoliosis, unilateral renal agenesis, ventricular septal defect), and another with anal imperforation, vertebral fusion, unilateral renal

TABLE 2 Primary outcome: Extra-genital assessment and associated malformations.

	Number of individuals	% of subgroup ^a	% of all individuals (N=85)
Individual with kidney assessment	83		97.6
Individual with abnormal renal assessment	33	39.8	38.8
Unilateral renal agenesis	12	14.5	14.1
Ectopic kidney	8	9.6	9.4
Renal malrotation	3	3.6	3.5
Horseshoe kidney	3	3.6	3.5
Ureteral duplicity	3	3.6	3.5
Renal hypoplasia or asymmetric kidney size	3	3.6	3.5
Parenchymal atrophy	1	1.2	1.2
Renal cyst	2	2.4	2.4
Unilateral dilatation of excretory ducts	1	1.2	1.2
Individual with spine x-ray	76		89.4
Individual with abnormal skeletal assessment	39	51.3	45.9
Scoliosis	24	31.6	28.2
Segmental anomalies	6	7.9	7.1
Spina bifida	6	7.9	7.1
Hip or pelvis anomalies	6	7.9	7.1
Fused vertebra	4	5.3	4.7
Absent ribs	3	3.9	3.5
Scapular asymmetry (Sprengel deformity)	2	2.6	2.4
Absent vertebrae	2	2.6	2.4
Individuals with cardiac ultrasound	53		62.4
Individual with abnormal cardiac assessment	2	3.8	2.4
Ventricular septal defect	1	1.9	1.2
Aortic dilatation	1	1.9	1.2
Deafness	8		9.4
MRKH type I^b	16	23.5	18.8
MRKH type II^b	52	76.5	61.2

^aSubgroup: correspond to the number of patient how undergone the adequate evaluation (abdominal ultrasound or MRI for renal assessment, x-ray for spinal assessment, audiogram for deafness, echocardiography for cardiac assessment).

^bClassification was available for 68 individuals following the criteria: the morphological evaluation is complete and normal for type I, or incomplete but showing at least one malformation for type II.

agenesis, and epilepsy onset at 23 years. One patient had a craniopharyngioma at 11 years and pituitary insufficiency. Two other patients had biological hyperprolactinemia.

3.3 | Secondary outcomes (Table 3)

3.3.1 | Management of aplasia of the upper two-thirds of the vagina

Of the 77/85 patients with vaginal aplasia, data concerning the management were available for 60 (Table 3): 33 underwent progressive dilation only (manually or with Franck's method using

dilatators) and did not require surgery. Vaginal length was reported for 25 patients on clinical examination and was ≥ 7 cm in 16/25 patients (64% of the evaluated patients). Twenty-seven patients underwent surgery, using the Davydov procedure to create a neovagina ($n=19$), the Vecchietti procedure ($n=2$), or using a bowel segment ($n=4$). The surgical procedure was not described in two cases.

3.3.2 | Ovarian reserve assessment

An assessment of ovarian reserve for fertility preservation was proposed for 31 patients under 36 years of age by AMH level. AMH was

TABLE 3 Secondary outcome: Ovarian assessment and management of vaginal aplasia.

	Number of individuals	% of subgroup ^a
AMH dosage	31	
Median age at AMH dosage (years)	27 [16; 36]	
Average AMH value (ng/mL)	3.5 [0.6; 11]	
Number of individuals with AMH dosage <1.5 ng/mL	7	22.6
Median age for individuals with AMH dosage <1.5 ng/mL (years)	30 [21; 33]	
Vaginal hypoplasia therapy with natural reconstruction or de Frank's method (only)	33	
Vaginal length reported	25	75.8
Vaginal length not reported	8	24.2
Vaginal length <7 cm at last evaluation	9	36
Vaginal length ≥7 cm	16	64
Surgical vaginal reconstruction	27	
Davydov procedure	19	70.4
Vecchietti procedure	2	7.4
Using a bowel segment	4	14.8
Evaluation of the secondary outcome	21	
AMH >1.5 ng/mL + vaginal length ≥7 cm without bowel segment	14	66.7
AMH >1.5 ng/mL + vaginal length <7 cm without bowel segment	4	19
AMH <1.5 ng/mL + vaginal length ≥7 cm without bowel segment	3	14.3

^aSubgroup: correspond to the number of individual how undergone adequate evaluation data was available.

below 1.5 ng/mL in 7/31 patients (22.6% of the evaluated patients), at a median age of 28 years [21; 33], suggesting diminished ovarian reserve in these women (see Appendix S1).

3.3.3 | Eligibility for UTx

In view of the UTx program, 21 women of our cohort evaluated for malformative assessment additionally underwent a vaginal length evaluation along with an AMH level. Among these 21 women, 14 were eligible UTx recipients (i.e., vaginal length ≥7 cm without using bowel segment and an AMH level >1.5 ng/mL). Relative to the entire cohort since 2004, this small selection of patients represented 16.5% (14/85).

4 | DISCUSSION

The present report constitutes a comprehensive clinical description of 85 women with MRKH syndrome who underwent an extensive malformation assessment. 38% of the women were under-assessed

for associated malformations according to the French national recommendations PND5 of 2021.² This highlights the crucial role of expert centers, where patients with suspected MRKH syndrome should be referred to benefit from the most advanced technical facilities and up-to-date knowledge.

Recommendations regarding malformation assessments in the context of MRKH and UTx: In France, the evaluation for associated malformations in women with uterovaginal aplasia must include an ultrasound of the kidneys and urinary tract, and an x-ray of the skeleton (cervico-dorso-lumbar spine ideally which reduces exposure to x-rays technology). An audiogram and a cardiac ultrasound are recommended based on medical history and clinical examination. In the family, additional investigations may also be proposed depending on the family history. A renal ultrasound for the parents and siblings is at least recommended. These recommendations are similar to those established by the American College of Obstetricians and Gynecologists (ACOG) in 2018.¹⁰ Renal anomaly is the most prevalent condition associated with uterovaginal aplasia. In our cohort, kidney malformations were found in 38.8% of the all cases which is with a little higher than previous descriptions: 29.6% of renal malformations were found in a German cohort of 284 women,¹¹ 24% in another German cohort of 346 women,¹² 34.2% in a Danish cohort of 168 women,¹ and 13.1% in a Chinese cohort of 244 women.¹³ Skeletal anomalies are also reported in around 30% of cases,^{6,12,13} and in up to nearly 40%, depending on the cohort.¹³ In this cohort, radiographic anomalies of the skeleton or spine were found in 45.9% of cases, including six cases of spina bifida. This condition has previously been reported in some cases of MRKH.^{11,14,15} VACTERL association has also been reported in women with MRKH syndrome, suggesting a potential co-occurrence of these two rare syndromes.^{1,14} The frequency of associated malformations appears to be influenced by several factors, including ethnicity,¹⁶ genetic background,^{6,17} and the extent of the malformation assessment performed. These findings confirm the importance of systematically performing renal imaging and spinal radiography in women diagnosed with uterovaginal aplasia. Thus, we cannot classify as MRKH type I if morphological assessment is incomplete. In a UTx project, it is essential to thoroughly assess the overall health of the recipient woman to avoid overlooking any malformations or conditions associated with uterovaginal aplasia that could compromise the surgical procedure or result in a high-risk pregnancy. For example, kidney malformation could lead to UTx contraindication. We have to distinguish two situations: (1) kidney place in pelvis, which is a surgical contraindication because of potential problem of volume or place in pelvis for transplanted uterus plus pelvic kidney and also anatomy modification of pelvic vessels. (2) Alone kidney that could lead to decrease clearance of creatinine, which is a contraindication for UTx because of nephrotoxicity of immunosuppressive treatment that could lead to kidney insufficiency, but only one kidney with normal creatinine clearance is not a contraindication to UTx. Published data showed pre-eclampsia and HTA complications in UTx, with higher rate than general population but lower rate than pregnant renal transplanted

women. This higher rate of HTA complications is probably due to calcineurin inhibitor.¹⁸

For the 21 women with complete evaluation of both primary and secondary outcomes, 66.7% would have been eligible for a UTx at the time of consultation according to the main inclusion criteria of the UTx program¹⁹ (16.5% of the total cohort).

Ovarian reserve in women with MRKH syndrome and recommendations for monitoring: Impaired ovarian reserve with low AMH levels was observed in 22.6% of the tested women who had consulted since 2020. In the literature, the hormonal profile of women with MRKH syndrome did not appear to be altered,²⁰ as evidenced by the onset of thelarche and pubarche at a normal age. However, in a cohort of 30 women with MRKH syndrome, three had elevated AMH levels, suggesting a non-ovulating state.²¹ In a cohort of 50 women with MRKH type I and 50 with MRKH type II, no significant decrease in ovarian reserve was found compared to a control cohort.²² Comparing in vitro fertilization outcome in 27 women with MRKH syndrome, a better response to ovarian hyperstimulation was found in women with type I MRKH.²³ As these studies were conducted on small sample sizes, larger cohort studies would be valuable to improve knowledge in this field. We suggest that ovarian reserve should be assessed systematically at the time of initial diagnosis of MRKH or from the age of 18, to offer oocyte preservation and thus maintain eligibility for UTx (or gestational surrogacy if available in the country). Furthermore, it would be worth monitoring ovarian endocrine function over time in these women to identify the development of premature ovarian insufficiency and consequently initiate hormone replacement therapy, as the average age of menopause is unknown in this condition.

Importance of family history: The fact that 60% of women presented a significant family history potentially related to MRKH syndrome (infertility or anomaly of the urogenital tracts) strongly supports the role of genetics and the need for family genetic investigation, which might suggest a variable penetrance or variable expressivity of certain genes of interest. Our findings show that MRKH is not a sporadic or isolated disease in many cases. This is an important element in the context of UTx, as women can expect to have offspring with their genetic heritage. It is therefore essential to provide them with appropriate genetic counseling whenever possible. Few studies have been conducted on very small cohorts of children born from UTx. These studies have not identified any syndromic associations in the offspring, although isolated malformations have occasionally been observed (caudally displaced urethra, cryptorchidism²⁴).^{5,25} However, the genetic basis of MRKH syndrome is still under investigation.^{17,26,27} When a Mendelian inheritance of MRKH is known, the risk of transmission to the child can be estimated, taking into account the incomplete penetrance and variable expressivity of certain genetic syndromes. In other cases, if MRKH syndrome is of indeterminate etiology, the evaluation of the risk of malformations in the offspring would require studies on very large cohorts and could only be assessed through

appropriate methodologies and statistical associations. We suggest a careful follow-up of children born from UTx, in order to track the potential transmission of malformations.

Weaknesses of study: First, the recommendations have evolved since the first women included in the cohort were met in 2004, and the additional assessments could not be updated for all women. This introduces variability into the cohort. Second, the cohort contain a small group of women who had an AMH level and a vaginal length estimation. As a result, conclusions regarding the secondary outcome are based on a small number of women.

5 | CONCLUSION

In the era of the development of UTx programs, national and international guidelines for women with MRKH women should integrate initial ovarian function evaluation and longitudinal follow-up. Extensive assessment of the patients is essential for a UTx program and centralized management has become necessary to generate accurate data. Furthermore, due to the significance of family history in many cases, genetic investigations and a careful follow-up of children born from UTx should be proposed, to enhance understanding of MRKH and UTx issues.

AUTHOR CONTRIBUTIONS

Auriane Cospain and Ludivine Dion: Conceptualization, formal analysis, investigation, methodology, validation, writing of original draft, review and editing. Sylvie Jaillard and Vincent Lavoué: Conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, writing of original draft, review and editing. Maud Bidet; Investigation and validation, writing of original draft, review and editing. Bénédicte Nouyou: Data curation and methodology. Krystal Nyangoh Timoh, Chloé Quelin, Isis Carton, Alinoe Lavillaureix, Karine Morcel, Paul Rollier, Laurent Pasquier, Sylvie Odent, Erika Launay, Marc-Antoine Belaud Rotureau and Mélanie Fradin: investigation and validation.

ACKNOWLEDGMENTS

We would like to thank all the healthcare professionals involved in patient data collection and in the French PRAM network (Programme de Recherches sur les Aplasies Müllériennes). We would like to thank the French association "Syndrome de Rokitansky".

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

All patients were informed and consented to this observational research. The research received a favorable opinion after review by the ethics committee of the University Hospital of Rennes (opinion No. 24.75) on July 7, 2024.

ORCID

Auriane Cospain  <https://orcid.org/0000-0002-0007-4195>

Isis Carton  <https://orcid.org/0000-0003-4587-3828>

REFERENCES

- Herlin M, Bjørn AMB, Rasmussen M, Trolle B, Petersen MB. Prevalence and patient characteristics of Mayer-Rokitansky-Küster-Hauser syndrome: a nationwide registry-based study. *Hum Reprod.* 2016;31:2384-2390.
- Haute Autorité de Santé [Internet]. [cité 16 févr 2024]. Aplasies Utero-Vaginales-Syndrome de Mayer-Rokitansky-Küster-Hauser. Disponible sur. https://www.has-sante.fr/jcms/p_3300390/fr/aplasies-utero-vaginales-syndrome-de-mayer-rokitansky-kuster-hauser
- Grimbizis GF, Gordts S, Di Spiezo SA, et al. The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies. *Hum Reprod.* 2013;28:2032-2044.
- Georgopadakos N, Manoli A, Passia G, Skandalakis PN, Filippou D. Uterus transplantation as a therapy method in Mayer-Rokitansky-Küster-Hauser syndrome. *Cureus.* 2019;11:e6333.
- Jones B, Saso S, Bracewell-Milnes T, et al. Human uterine transplantation: a review of outcomes from the first 45 cases. *BJOG.* 2019;126:1310-1319.
- Herlin MK, Petersen MB, Brännström M. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome: a comprehensive update. *Orphanet J Rare Dis.* 2020;15:214.
- Home | ClinicalTrials.gov [Internet]. [cité 30 mai 2024]. Disponible sur. <https://clinicaltrials.gov/>
- Brakta S, Hawkins ZA, Sahajpal N, et al. Rare structural variants, aneuploidies, and mosaicism in individuals with mullerian aplasia detected by optical genome mapping. *Hum Genet.* 2023;142:483-494.
- Meena A, Daga MK, Dixit R. Unusual association of turner syndrome and Mayer-Rokitansky-Küster-Hauser syndrome. *BMJ Case Rep.* 2016;2016:bcr2015212634.
- Committee on Adolescent Health Care. ACOG committee opinion no. 728: Müllerian agenesis: diagnosis, management. *And Treatment Obstet Gynecol Janv.* 2018;131:e35-e42.
- Oppelt PG, Lermann J, Strick R, et al. Malformations in a cohort of 284 women with Mayer-Rokitansky-Küster-Hauser syndrome (MRKH). *Reprod Biol Endocrinol RBE.* 2012;10:57.
- Rall K, Eisenbeis S, Henninger V, et al. Typical and atypical associated findings in a group of 346 patients with Mayer-Rokitansky-Küster-Hauser syndrome. *J Pediatr Adolesc Gynecol.* 2015;28:362-368.
- Deng S, He Y, Chen N, Zhu L. Spectrum of type I and type II syndromes and associated malformations in Chinese patients with Mayer-Rokitansky-Küster-Hauser syndrome: a retrospective analysis of 274 cases. *J Pediatr Adolesc Gynecol.* 2019;32:284-287.
- Orstavik KH, Steen-Johnsen J, Foerster A, Fjeld T, Skullerud K, Lie SO. VACTERL or MURCS association in a girl with neurenteric cyst and identical thoracic malformations in the father: a case of gonosomal mosaicism? *Am J Med Genet.* 1992;43:1035-1038.
- Goryaeva M, Sykes MC, Lau B, West S. Unusual association between cardiac, skeletal, urogenital and renal abnormalities. *BMJ Case Rep.* 2016;2016:bcr2016215281.
- Kauffman RP. Mayer-Rokitansky-Küster-Hauser syndrome (müllerian agenesis): a wider window into ethnic phenotypic diversity. Where to from here? *Fertil Steril.* 2021;116:363-364.
- Herlin MK. Genetics of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome: advancements and implications. *Front Endocrinol.* 2024;15:1368990.
- Barragan-Wolff M, Espinosa-Cervantes MS, Acevedo-Gallegos S, Rodriguez-Sibaja MJ, Lumberras-Marquez MI, Ito-Esparza MJ. Uterus transplantation: a scoping review focused on obstetric outcomes. *Int J Gynaecol Obstet.* 2024. Advance online publication. doi:10.1002/ijgo.15752
- Rennes University Hospital. Transplantation of Uterus for Uterine infertility From Living Donor or Deceased Donor. [clinicaltrials.gov](https://clinicaltrials.gov/study/NCT05726305); 2024 janv [cité 1 janv 2024]. Report no: NCT05726305. <https://clinicaltrials.gov/study/NCT05726305>
- Friedler S, Grin L, Liberti G, Saar-Ryss B, Rabinson Y, Meltzer S. The reproductive potential of patients with Mayer-Rokitansky-Küster-Hauser syndrome using gestational surrogacy: a systematic review. *Reprod Biomed Online.* 2016;32:54-61.
- Oppelt P, Strissel PL, Kellermann A, et al. DNA sequence variations of the entire anti-Müllerian hormone (AMH) gene promoter and AMH protein expression in patients with the Mayer-Rokitansky-Küster-Hauser syndrome. *Hum Reprod.* 2005;20:149-157.
- Henes M, Jurow L, Peter A, et al. Hyperandrogenemia and ovarian reserve in patients with Mayer-Rokitansky-Küster-Hauser syndrome type 1 and 2: potential influences on ovarian stimulation. *Arch Gynecol Obstet.* 2018;297:513-520.
- Raziel A, Friedler S, Gidoni Y, Ben Ami I, Strassburger D, Ron-El R. Surrogate in vitro fertilization outcome in typical and atypical forms of Mayer-Rokitansky-Küster-Hauser syndrome. *Hum Reprod.* 2012;27:126-130.
- Schulz P, Testa G, York JR, Johannesson L. Children after uterus transplantation: 2-year outcomes from the Dallas UtErus Transplant Study (DUETS). *BJOG.* 2022;129:2117-2124.
- Ejzenberg D, Andraus W, Baratelli Carelli Mendes LR, et al. Livebirth after uterus transplantation from a deceased donor in a recipient with uterine infertility. *Lancet.* 2018;392:2697-2704.
- Williams LS, Eksi DD, Shen Y, et al. Genetic analysis of Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) through ascertainment of a large cohort of families. *Fertil Steril.* 2017;108:145-151.e2.
- Triantafyllidi VE, Mavrogianni D, Kalampalikis A, Litos M, Roidi S, Michala L. Identification of genetic causes in Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome: a systematic review of the literature. *Children.* 2022;9:961.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cospain A, Dion L, Bidet M, et al. Optimizing care for MRKH patients: From malformation screening to uterus transplantation eligibility. *Acta Obstet Gynecol Scand.* 2024;00:1-8. doi:10.1111/aogs.14985