Review Article

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Association of the rectovestibular fistula with MRKH Syndrome and the paradigm shift in the management in view of the future uterine transplant

Yogesh Kumar Sarin

Director Professor & Head Department of Pediatric Surgery, Lady Hardinge Medical College, New Delhi, INDIA

Correspondence*: Dr. Yogesh Kumar Sarin, Director Professor & Head Department of Pediatric Surgery, Lady Hardinge Medical College, New Delhi, India, **E-mail**: yksarin@hotmail.com

KEYWORDS

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ABSTRACT

Uterine transplantation in Mayer-Rokitansky-Küster-Hauser (MRKH) patients with absolute uterine function infertility have added a new dimension and paradigm shift in the management of females born with rectovestibular fistula coexisting with vaginal agenesis. The author reviewed the relevant literature of this rare association, the popular and practical classifications of genital malformations that the gynecologists use, the different vaginal reconstruction techniques, and try to know what shall serve best in this small cohort of these patients lest they wish to go for uterine transplantation in future.

INTRODUCTION

In a female newborn, a single perineal opening with shorter appearing introitus suggests cloaca. If instead, there are three openings in the introitus with the rectal opening appearing as a fistula in the posterior vestibule, outside of the hymen, it is diagnostic of a rectovestibular fistula (or simply, vestibular fistula as per Krickenbeck classification).[1] However, if two openings are seen in the introitus with an absent anus, then we would have a differential diagnosis of three entities- i) imperforate anus with no fistula [commonly seen in patients with trisomy 21], ii) anorectal agenesis with rectovaginal fistula and iii) rectovestibular fistula with vaginal atresia, cervicovaginal atresia or uterocervicovaginal atresia, popularly known as Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome.[2] The majority of these patients with such anorectal malformations would present in the neonatal period. But, in a developing country like India where there are still home deliveries happen in remote villages, there may be some girls with wide rectovestibular fistula who may be decompressing stools relatively well and may present as late as in early adolescence.

The presence of two openings in the introitus is probably the least common presentation of the anorectal malformation in a female newborn. Traditionally, it has been said that if there are two orifices in the perineum of a girl with an imperforate anus, then the malformation is most likely a rectovaginal fistula with a reported incidence in literature varying widely from 0% to 84%.[3,4] These false high reported incidences have been attributed to the indiscriminate inappropriate labeling of rectovestibular fistula and cloaca as rectovaginal fistula. [5,6] The true incidence of this variant is probably less than 1%.[7]

Though anorectal agenesis without fistula is known to constitute 2-4% of all anorectal malformations, it is much less common in females as compared to their male counterparts.[8,9] Male-female ratio has been quoted around 5:1 in one large series.[8] The associated presence of Down's Syndrome is a pointer and has been quoted to coexist in 40-95% subjects.[8,9] These neonates would obviously not been able to decompress the meconium and would present as surgical emergencies.

The author of this review article has not encountered a single case of anorectal agenesis with or without rectovaginal fistula in his entire professional career spanning over 3 decades but has treated 14 patients (few unreported) of the third unusual variant of the rectovestibular fistula with vaginal atresia, the major-

ity being MRKH Syndrome; each of them had some or the other form of bowel vaginoplasty.[2,10,11]

The focus of this review article is on the management strategies of the rectovestibular fistula with vaginal atresia. Robert Gross described two cases of vaginal atresia among 507 patients with anorectal malformation, but without a description of a surgical repair.[12] The exact frequency of vaginal agenesis in patients with rectovestibular fistula is unknown. The reported incidence has been anywhere between 0.5% to 16.3%.[13,14] The incidence seen in tertiary referral base with high workloads is around 10%.[10,15] De la Torre et al. in 2016 [14] and Skerritt et al. in 2017 [16] did two historic metanalyses; adding few more cases from the literature, at least 113 patients of rectovestibular fistula associated with vaginal atresia could be searched in published literature (Table 1). So, it will be fair to label it as a rare variant in the Krickenbeck classification. The 15 patients reported by Ahmed et al. in 2020 [17] from Cincinnati Children's Hospital Medical Center, Cincinnati enrolled from 1991 to 2017 have not been included as it was difficult to find out if there was any overlap of this cohort with the patients earlier reported by Levitt from the same institution in 2009.[18]

We, pediatric surgeons, are usually involved in the management as far as the creation of neovagina and the neo-anus, but do not get to follow these children in their post-pubertal period or when they grow up as adults, ready to cohabit with a male partner or marry. The transplant surgeons have added a new dimension by venturing into uterine transplantation (UTx) in these subjects. This has led to a paradigm shift in the management. Earlier, the debate used to resolve around vaginal replacement using bowel vis a viz other neovagina creation methods (non-surgical as well as surgical using skin grafts/flaps, peritoneum, buccal mucosa, etc.) and their pros and cons. But in the futuristic scenario, we have to evaluate the neovagina creation methods and their potential impact on subsequent UTx.[50] Most importantly, any surgery that would entail a laparotomy and result in adhesions in the lower abdomen and pelvis has to be avoided as this would prohibit future uterine transplantation. Further, we must equip ourselves to accurately record the different components of associated Mullerian/ uterovaginal anomalies as per the classifications devised by the American and European Associations so that we are on the same page and avoid any miscommunication with the surgeons who are going to undertake subsequent surgeries in later adult lives of these subjects.

MRKH Syndrome and the various classifications

The MRKH syndrome is regarded as an inhibitory malformation of the Mullerian (paramesonephric) ducts. Clinically, this malformation of the female genital organs presents as a rudimentary solid bipartite uterus with a solid vagina. Mayer and Rokitansky described one case each of the 'bipartite uterus' in the years 1829 and 1838, respectively.[51,52] Küster in 1910, for the first time, summarized and collected individual cases of 'rudimentary solid septate uterus with solid vagina' from the literature in a review paper.[53] It was only in 1961 that the 'rudimentary solid septate uterus with a solid vagina' was first given its current name, 'Mayer–Rokitansky–Küster syndrome' by the gynecologist Hauser,[54] later being extended to 'Mayer–Rokitansky–Küster–Hauser' syndrome.

MRKH patients have normal development of the female phenotype, with normal thelarche and pubarche, and a female karyotype (46 XX) with primary amenorrhea. In its typical form or isolated type, there is a septate, rudimentary uterus, aplasia of the cervix and upper 2/3rd of the vagina, and normal or hypoplastic bilateral adnexa. The ovarian function is intact, as evident by development of pubarche and thelarche and the presence of a biphasic basal temperature curve, and also that hormonal secretion does not differ from that in normal individuals.

Schmid-Tannwald and Hauser in 1977 described an atypical form of MRKH syndrome associated with various additional malformations of ovaries and kidneys.[55] Two years later, in 1979, Duncan et al. described the most severe form of MRKH syndrome, the MURCS association that comprised of Mullerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia.[56] Some authors describe typical and atypical MRKH syndrome anomalies as type 1 and type 2 MRKH and include all patients having associated extra-genital anomalies, including MURCS association as Type 2.[57]

Oppelt et al. in 2006 reported in their large series of 53 MRKH patients that the typical form, atypical form, and those with MURCS association existed in 64%, 24%, and 12% patients respectively; or in other words, associated extra-genital congenital malformations were present in more than a third of cases.[58] However, the spectrum of types 1 and 2 of the MRKH syndrome is known to vary across different races and geographical locations; the incidence of MURCS association was only 3% in a large cohort of 274 Chinese subjects with MRKH syndrome.[59]

Oppelt et al. recommend sets of essential and desirable investigations that are required for work-up of MRKH syndrome.[59] Essential investigations included chromosomal analysis (to rule out the differential diagnoses of testicular feminization and adrenogenital syndrome), MRI of abdomen/pelvis, and hormonal status (LH, FSH, estradiol) to rule out non-functional ovaries. The desirable investigations included an ultrasound of the vaginal vestibule and rectum, diag-

Table 1: Analysis of reported patients with vaginal atresia with rectovestibular fistula.

Author	Year	Country	N	RVF	Sigmoid	Vagina	Ileum	Skin/ mucosa flaps	Dilatation	PC	PF	No vaginal Replacement	NM	Functional uterus	Uterus preserved (Y/N)
Gross [12]	1953	USA	2										2		
Cohn [19]	1956	Canada	1	1											
Ein [20]	1971	Canada	2	2											
Fujiwara [[21]	1974	Japan	1	1										1	N
King [22]	1977	USA	1									1			
Tolete-Velchek [23]	1989	USA	4	1	1			1					1	3	Y in 3
Digray [24]	1999	India	1	1											
Okoye [25]	2000	UK	1									1			
Adejuyigbe [26]	2002	Nigeria	1			1									
Sarin [2]	2002	India	4		1		1	1				1			
Gunsar [27]	2003	Turkey	1		1										
Tei [28]	2003	Japan	2	2											
Deshpande [29]	2003	India	1	1											
Patankar JZ [30]	2004	Singapore	1				1								
Patankar SP [31]	2004	India	1									1			
Banu [32]	2006	Bangladesh	5	1		2			1				1	1	Y in 1
Wester [33]	2006	Sweden	1							1					
Sarin* [10]	2006	India	6	2	2	1									
Komura [34]	2007	Japan	1									1			
Matignas [35]	2008	Philippines	1	1										1	Y
Chatterjee [36]	2008	India	2										2		
Wakhlu [13]	2009	India	6										6		
Levitt [16]	2009	USA	26	13	8	3	2								
Wang [37]	2010	China	3						1		1#	1			
Mane [38]	2010	India	1												
Wester [39]	2012	Sweden, Finland, Spain	7		4	3								3	3
Yamataka [40]	2012	Japan	1												

Jessel [41]	2012	USA	1												
de Blaauw [42]	2013	Netherlands, USA	2		2										
Kisku [43]	2014	India	7	2	5									3	Y in 3
Kapczuk [44]	2014	Poland	1					1							
Pandya [45]	2015	USA, Japan	5	1	1	3									
Teo [46]	2015	Singapore	1									1			
De la Torre [13]	2016	USA, Mexico	8				6					2			
Gupta [47]	2016	India	1	1											
Bjørsum-Meyer [48]	2016	Denmark	2							1			1		
Tiwari [49]	2017	India	1	1											

RVF=Rectovestibular Fistula, NM= Not Mentioned, PF= Peritoneal Flaps, PC= Pouch Colon

*duplication of rectum (N=1)

laparoscopic Davidov procedure

nostic laparoscopy, and ovarian biopsy. The ovarian biopsy is recommended because of the possibility of detecting 'streak gonads' in MRKH patients. Depending on the presence of specific associated anomalies, other recommended supplementary examinations that may be required include urodynamics, echocardiography, myography, imaging for skeletal malformations, and audiography.

In view of the variability in the genital malformations and the presence of associated anomalies, Oppelt et al. suggested VCUAM (Vagina Cervix Uterus Adnex–associated Malformation) classification in the same year 2005.[60] The external and internal female genital organs were divided into the following subgroups in accordance with the anatomy: vagina (V), cervix (C), uterus (U), and adnexa (A). Associated malformations were assigned to a subgroup (M) relative to each specific organ (Table 2).

So, using VCUAM classification, the different genital anomalies depicted in Fig. 1 (a), (b), and (c) below could be designated as V5b,C2b,U4b,A1b,M#; V5b,C2b,U0,A0,M#; and V+,C0,U0,A0,M#. One of the limitations of this classification is that distal vaginal atresia is not included.

Table 2: VCUAM classification of genital malformations- Description of the individual malformations relative to the organ. (Reproduced with permission from Oppelt et al. Fertil Steril. 2005;84:1493-7)[60]

Vagina (V)	0 Normal 1a Partial hymenal atresia 1b Complete hymenal atresia 2a Incomplete septate vagina _50% 2b Complete septate vagina 3 Stenosis of the introitus 4 Hypoplasia 5a Unilateral atresia 5b Complete atresia S1 Sinus urogenitalis (deep confluence) S2 Sinus urogenitalis (middle confluence) S3 Sinus urogenitalis (high confluence) C Cloacae + Other # Unknown
Cervix (C)	0 Normal 1 Duplex cervix 2a Unilateral atresia/aplasia 2b Bilateral atresia/aplasia + Other # Unknown
Uterus (U)	0 Normal 1a Arcuate 1b Septate<50% of the uterine cavity 1c Septate>50% of the uterine cavity 2 Bicornate 3 Hypoplastic uterus 4a Unilaterally rudimentary or aplastic 4b Bilaterally rudimentary or aplastic + Other # Unknown
Adnexa (A)	0 Normal 1a Unilateral tubal malformation, ovaries normal 1b Bilateral tubal malformation, ovaries normal 2a Unilateral hypoplasia/gonadal streak (including tubal malformation if appropriate) 2b Bilateral hypoplasia/gonadal streak (including tubal malformation if appropriate) 3a Unilateral aplasia 3b Bilateral aplasia + Other # Unknown
Associated Malformation (M)	0 None R Renal system S Skeleton C Cardiac N Neurologic + Other # Unknown

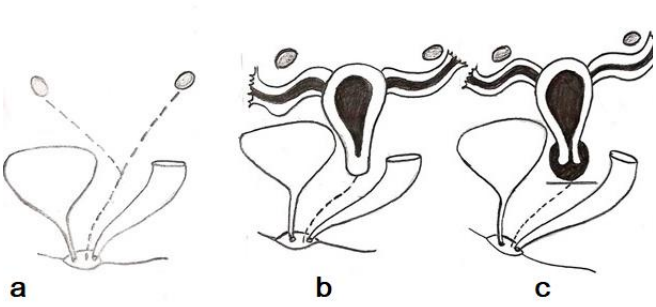


Figure 1: Rectovestibular fistula associated with- a) MRKH (vaginal agenesis with varying degrees of uterine agenesis/ hypoplasia, b) Cervicovaginal atresia (vaginal and cervical agenesis with the normal functioning uterus), c) Distal vaginal atresia (atresia of the distal vagina, hematocolpos of the proximal vagina)-(Adapted with permission from Kisku et al. Int Urogynecol J. 2015;26:1441-8.)[61]

There is one more classification that is often used.[62] The new European Society of Human Reproduction and Embryology–European Society of Gastrointestinal Endoscopy (ESHRE/ESGE) classification system incorporates all cases of uterine aplasia under Class U5 or aplastic uterus, defined as a formation defect characterized by the absence of any fully or unilaterally developed uterine cavity (Fig. 2). The further classification includes Class U5a or aplastic uterus with rudimentary (functional) cavity and Class U5b without a rudimentary (functional) cavity. This may come with co-existent subclassification of the cervical and vaginal anomaly, which is C4 (cervical aplasia/dysplasia) and V4 (vagina aplasia). The co-existence of other anomalies of non-Mullerian origin is reported separately.

To explain further, the findings of seven patients of the rectovestibular fistula with vaginal atresia reported by Kisku et al. are tabulated [40] and then the anomalies have been cataloged the two aforesaid classifications (Table 3).[60,62]

Besides the VCUAM classification and ESHRE/ESGE classification, there are two more classifications in vogue these days- American Fertility Society classification and the clinical and embryological classification of the malformations of the female genital tract by Acien et al.[63,64] The limitation of the AFS classification lies in the impossibility of assigning variations of a malformation to precise organ subgroups.

Treatment of rectovestibular fistula associated with vaginal atresia

Traditionally, the main goal of treatment of the vaginal atresia was considered to create an appropriate vaginal cavity in order to facilitate sexual intercourse and egress of menstrual blood (in case of vaginal or cervicovaginal atresia, where functional endometrium and uterus is present). Throughout the years, a lot of non-surgical and surgical interventions have been developed. Currently, the best management method remains controversial due to the lack of longitudinal studies and prospective evaluation of the interventions undertaken.[65]

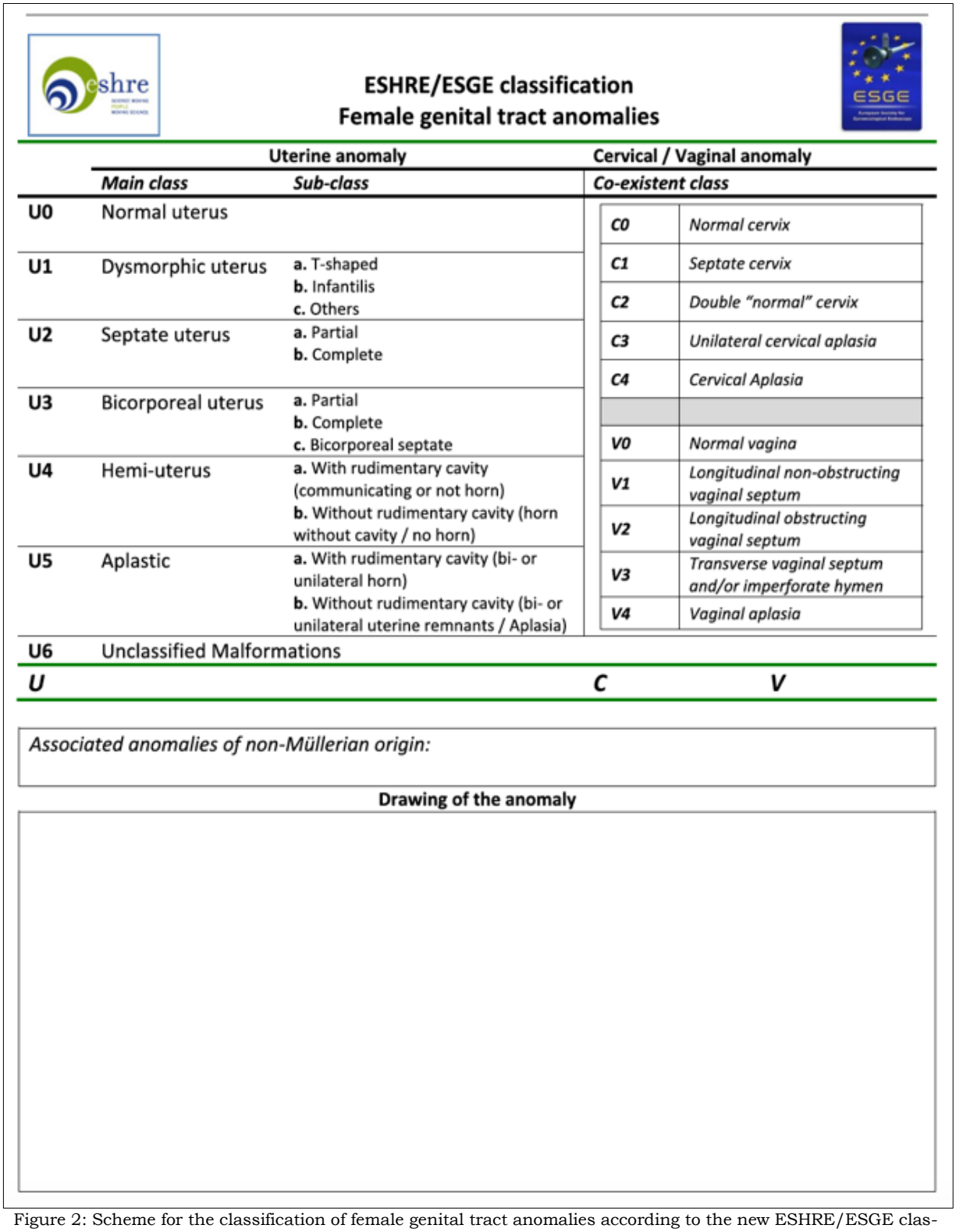
Non-Surgical treatment

According to the American Committee of Obstetricians and Gynecologists (ACOG) recommendations, the first-choice treatment should begin with non-surgical methods based on dilation.[66] A recent multicenter study showed that surgery was not superior to non-surgical methods.[67] Non-surgical options are reserved for those patients who are motivated and psychosexually mature because the success rate depends mainly on the patient's compliance and attitude.[68] Multidisciplinary care involving social workers, trained nurses, psychologists, and physicians plays a key role in the success rate.[69]

First described by Frank in 1938, the dilators of increasing sizes are placed inside the vaginal dimple, and intermittent, progressive, manual pressure is applied to deepen it over a period of 6-12 months.[70] In 1981, Ingram modified Frank's technique to avoid some inconveniences by installing a dilator on a bicycle seat, allowing the patient to perform other activities during the sessions such as doing homework or practicing a musical instrument.[71] It is recommended that the dilators are used 3 times a day for 15-20 min each; some advice dilation for up to 2 hours a day.[69,72] Both methods are cost-effective procedures, with a low complication rate, allowing the creation of a functional neovagina as long as >6 cm in depth.[73,74] Adjuvant treatment, such as estriol cream, lidocaine ointment, paracetamol, naproxen, diazepam, nitrous oxide, and oxygen have been known to improve outcomes of these dilation methods by minimizing discomfort and anxiety during progressive dilation.[75]

But an extensive review of MRKH patients with rectovestibular fistula, including the published case reports/series and even metanalyses, barely revealed a couple of patients who received the dilatation technique (Table 1); the reason could lie in the fact that unlike the MRKH syndrome, subjects without the associated rectovestibular fistula, this cohort of patients does not have a vaginal dimple, reminiscent of the lower 1/3rd-1/5th of vagina derived from the urogenital sinus; instead, there is the anorectal opening of variable size present there. Hypothetically assuming that a particular patient has a wider introitus and even a vaginal dimple anterior to the anorectal opening, it is still hard to believe if the subject or her partner could have sexual gratification, as an inversion of an epithelial lined tissue achieved by these measures would lack

lubrication for intercourse. Second, she could have a problematic vaginal prolapse as the apex of the neovagina is not anchored. So, the assertions made by many obstetricians and gynecologists regarding these non-surgical measures do not break the ice with the pediatric surgeons.



ESHRE/ESGE classification
Female genital tract anomalies

	Uterine anomaly		Cervical / Vaginal anomaly	
	Main class	***Sub-class***	***Co-existent class***	
U0	Normal uterus		***C0***	*Normal cervix*
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	***C1***	*Septate cervix*
U2	Septate uterus	**a.** Partial **b.** Complete	***C2***	*Double "normal" cervix*
U3	Bicorporeal uterus	**a.** Partial **b.** Complete **c.** Bicorporeal septate	***C3***	*Unilateral cervical aplasia*
U4	Hemi-uterus	**a.** With rudimentary cavity (communicating or not horn) **b.** Without rudimentary cavity (horn without cavity / no horn)	***C4***	*Cervical Aplasia*
U5	Aplastic	**a.** With rudimentary cavity (bi- or unilateral horn) **b.** Without rudimentary cavity (bi- or unilateral uterine remnants / Aplasia)		
U6	Unclassified Malformations		***V0***	*Normal vagina*
			V1	*Longitudinal non-obstructing vaginal septum*
			V2	*Longitudinal obstructing vaginal septum*
			V3	*Transverse vaginal septum and/or imperforate hymen*
			V4	*Vaginal aplasia*
U			***C***	***V***

Associated anomalies of non-Müllerian origin:

Drawing of the anomaly

Figure 2: Scheme for the classification of female genital tract anomalies according to the new ESHRE/ESGE classification system (Reproduced with permission from Grimbizis et al. Hum Reprod. 2013;28:2032-44.)[62]

Table 3: Classification of seven patients of the rectovestibular fistula with vaginal atresia as per the anomalies (adapted with permission from Kisku et al. Pediatr Surg Int. 2014;30:6333-9).[43]

No.	Anomalies of Mullerian origin		Associated extra-genital malfor-mations/ anoma-lies of non-Mullerian origin	MRKH-Typical/ atypical/ assoc. with MURCS	VCUAM clas-sification [56]	ESHRE/ESGE classification [62]
	Vaginal mal-formation	Associated genital mal-formations				
1	Vaginal atresia	Left rudimentary uterine horn. Right uterine horn hypoplastic with small cavity and cervical Atresia	NIL	Typical	V5b,C2b,U4b, A#,M0	U5a,C4,V4
2	Vaginal atresia	Hypoplastic uterus, chocolate cysts in the sigmoid mesentery, endometriosis noted	Absent left kidney; segmental thora-columbar spine scoliosis	MURCS	V5b,C#,U3,A# ,MR+	U1c,C4,V4
3	Vaginal atresia	Absent uterus	Absent right kid-ney	Atypical	V5b,C#,U4b,A #,MR	U5b,C4,V4
4	Vaginal atresia	Cervix absent uterus distended with hematometra	VSD closed at 6 years. Bilateral external and mid-dle ear anomalies		V5b,C2b,U0,A #,M+	U0,C4,V4
5	Vaginal atresia	Bicornuate uterus, cer-vix hypoplastic with left adnexal chocolate cyst	Bilateral ectopic ureters. Left poor-ly Functioning kid-ney	Atypical	V5b,C+,U2,A1 a,MR	U3,C3,V4
6	Vaginal atresia	Rudimentary uterus	Absent left kidney	Atypical	V5b,C#,U4b,A #,MR	U5b,C4,V4
7	Vaginal atresia	Rudimentary hemiuteri	Absent left kidney	Atypical	V5b,C#,U4b,A #,MR	U5b,C4,V4

Surgical treatment

Surgical methods should be reserved for patients who refuse the dilation technique as well as for those after unsuccessful non-surgical management. There are a number of surgical techniques used to create an artificial vagina.

Bowel vaginoplasty

Sneuguireff in 1892 had utilized rectum for neovaginal reconstruction; while mentioning this, Baldwin had described intestinal vaginoplasty using ileum in 1904.[76] He performed the same 3 years later in 1907. Wallace performed the first sigmoid colon vaginoplasty in 1911. Subsequently, these procedures were abandoned because of a high mortality rate in the pre-antibiotic era, only to be revisited after half of a century or so.[77] Today, the sigmoid colon is favored for vaginoplasty for its larger diameter close proximity to the perineum and easily mobilized vascular pedicle. Ileum, as a vaginal replacement, has been also used, [10] but is known to be associated with a higher risk of stenosis.[78] In addition, ileal segments produce copious mucous, which is not as lubricating as the colonic mucous, leading to dyspareunia. Post-coital bleeding also occurs with the ileum owing to a more fragile mucosal lining.[77] Cecum and jejunum segments have also been used but have never become popular due to associated high morbidity and mortality. A blind duplicated rectum has also been used as a vaginal replacement.[10] An eight-centimeter-long sigmoid colon in a child and a little longer (up to 12 cm) in case of adolescent/ adult, with its own blood supply, is mobilized to the introitus. There are a number of advantages of this method, e.g., it provides an epithelial-lined, lubricated passage as a conduit for menstrual flow and coitus, and no dilators are usually required after the surgery.[10,61,79] In a recent study, 43 cases of sigmoid vaginoplasty were reviewed, and the overall success was reported, both anatomical (the mean length of a neovagina was 11.7 ±1.2 cm) and functional (97% of patients rated their sexual intercourse as satisfactory).[80] The most concerning flaws are excessive odorous secretions in the beginning, donor site morbidity, defecation problems, postoperative ileus, anastomotic leaks, the development of inflammatory bowel disease, ulcerative colitis, diversion colitis, potential neoplasia and carcinoma in the grafts, neovaginal prolapse, and stenosis.[61,81,82] The laparoscopic modification has been gaining more and more popularity, with fewer postoperative pelvic adhesions, less intraoperative blood loss, a better cosmetic effect, a shorter hospital stay, and faster recovery.[83] Robotic approaches are also evolving, but due to high costs, they still remain limited.[84]

In the presence of vaginal atresia with recto vestibular fistula itself, the latter itself has been often used as neovagina for infants with MRKH, and the rectosigmoid pulled down as the neoanus; Cohn and Murphy were the first to report this surgical correction using this procedure of combined anovaginoplasty in 1956.[19] Ein and Stephens also similarly operated through the abdominal route in 1971.[20] Levitt and Pena (1998) later, however, chose to operate through an incision that they use for the posterior sagittal anorectoplasty.[15] Levitt et al. and Kisku et al. also reported retaining rectovestibular fistula for vaginoplasty in such patients initially,[15] but subsequently advised against it owing to the delay in toilet training.[18,61] Levitt et al. even mentioned the need for further augmentation of the neovagina when the patient became sexually active.[18] However, we had good short-term results with this procedure; the time consumed for surgery was significantly reduced, and the final cosmetic appearance was extra-ordinary.[10] Unfortunately, our patients were not available for follow up, so we don't know how they fared in their adult lives. Levitt et al. and Kisku et al. felt that it would be better to use the rectovestibular fistula as the neoanus. Stressing at the psychological implications of delaying the genital reconstruction, we propagate that the neovagina and neoanus be created at the same operation in infancy or any time later at the presentation by the procedure shown in Fig.3,[10,61] but Kisku et al. propagated that the neoanus be created in infancy, but the creation of neovagina using sigmoid colon should be deferred till puberty when the uterine structures can be assessed for anastomosis with the bowel segment.[43] In their series of 7 patients, 4 of them had a uterus or its remnants. Delayed surgery allowed them to assess the growth of the rudimentary uterus/hemiuteri. At puberty, the functioning uterus was anastomosed to allow for menstruation (Fig. 4).[43] Non-functioning ones may be excised. They felt that this distinction might be difficult in the neonatal period. They also pondered if the delayed operation would allow the use of non-operative treatment to create a neovagina![44]

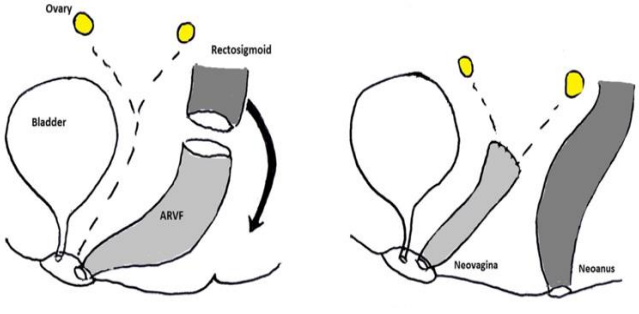


Figure 3: Using the rectovestibular fistula as the neovagina (Reproduced with permission from Kisku et al. Int Urogynecol J. 2015;26(10):1441-8.) [61]

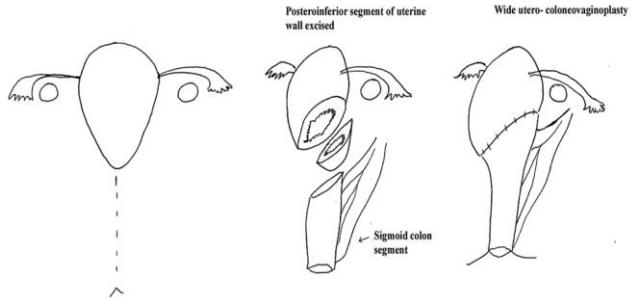


Figure 4: Uterocoloneovaginoplasty (Reproduced with permission from Kisku et al. Pediatr Surg Int. 2014;30:633-9.)[43]

The merits of both techniques were debated in a recent paper published in 2015; the data included were that of 15 patients with vaginal anomalies and atresia associated with imperforate anus (5 were rectovestibular fistula)- 10 operated in the USA where it was believed that the distal rectum should be used for neoanus, be created with proximal colon and 5 operated in Japan where the distal rectum was used as neovagina and the proximal colon was pulled through as neoanus. The Japanese technique did not leave a colon anastomosis after reconstruction, while the USA technique used a potentially better-vascularized segment of the colon for the neovagina. This study couldn't detect a difference in the continence outcomes between the two approaches and concluded that it was difficult to know if there was a long-term continence advantage to pulling through the more distal rectum for the correction of the imperforate anus.

Table 1 shows that though there may not be a universal consensus in favor of one approach or the other, creating neovagina using the rectovestibular fistula is the favored technique.

Performing such UTx in the future should be taken into consideration while choosing the method for neovagina creation. Gauthier et al. advised against bowel vaginoplasty fearing the high risk of infections from intestinal flora under immunosuppressive therapy, with potential endometritis or thrombosis and failure of UTx.[85]

Vecchietti vaginoplasty

One of the most popular types of surgery in those patients presenting in adulthood is the laparoscopic Vecchietti vaginoplasty, first described in 1965 as a laparotomy.[86,87] A unique hybrid of surgical and non-surgical techniques, it involves continuous upward traction on a plastic olive placed in the vaginal dimple that is attached to sutures that pass through the vesicorectal space into the abdominal cavity, through then extraperitoneal space, and later traverse the anterior abdominal wall with attachment to a

traction device. Continuous upward pressure on the vaginal vestibule stretches the mucosa, leading to elongation of the cavity to a 7cm to 10cm functional neovagina, after several weeks.[88] This method preserves natural vaginal tissue and avoids stenosis complications and excessive mucus production. The procedure can be accomplished in less than one hour.[73] However, these have never been performed in children.[89] Some alternatives to Vecchietti's procedure have been proposed, using balloons or a Foley catheter instead of acrylic olives, or applying a different approach, avoiding vesicorectal tunneling. It is considered a safer, shorter, more effective, and less traumatic procedure, with a very low complication rate.[90,91] Kolle et al. from Germany have given the verdict in favor of the laparoscopic-assisted Vecchietti procedure as the most ideal functional vaginoplasty from the point of a later UTx.[50]

Since this procedure requires very careful dissection, so it is done in only surgically naive tissue and is not possible in subjects with rectovestibular fistula and vaginal atresia.

McIndoe Procedure

The McIndoe procedure, very popular with gynecologists, involves creating a neovaginal space postpuberty between the rectum and the urethra-bladder through the perineal route by inserting an inlay graft.[92,93] Graft methods require the postoperative use of molds or frequent vaginal dilations in order to prevent possible graft contraction and stenosis. McIndoe modifications with different types of grafts have been proposed, e.g., with split-thickness skin grafts and full-thickness skin grafts, an amnion, autologous vaginal tissue cultured in vitro, and artificial grafts. Injury to the neighboring organs, such as the rectum and bladder, is the most serious complication. Complications include lack of vaginal length, inadequate lubrication, resulting in dyspareunia, a high rate of stenosis, and excessive hair growth.[94] External visible scars from the usual graft harvest sites – the buttock, groin, or thigh – may not be acceptable to the patients. The molds need to be carefully changed to avoid the shearing of the graft, as the secondary healing of lesions is connected with unfavorable long-term results.[95] According to McQuillan and Grover, graft techniques require the longest hospital stay after the surgery.[96] There have been case reports of squamous cell carcinoma and squamous papillomas arising in skin grafts used for vaginal construction.[97-99]

Given the risk of transplant rejection and high infection rates, the McIndoe technique cannot be considered a suitable first-line treatment before UTx, considering the mandatory immunosuppression that UTx involves.[50]

Williams vaginoplasty

Williams vulvovaginoplasty and its modification by Creatsas et al. are procedures in which the vulvoperineal flaps are sutured to form a vertically-oriented neovagina that subsequently requires regular dilation or frequent sexual intercourse.[100,101] It would be impossible to raise the vulvar tissues because of the adhesions caused locally due to the prior dissection of the rectovestibular fistula, so probably would not be possible in the cohort of patients that is being discussed. The unnatural axis and the aforementioned complications associated with natural skin grafts render these techniques unsuitable for subsequent UTx, however.

Wharton–Sheares–George vaginoplasty

In the Wharton–Sheares–George vaginoplasty procedure, [102,103] the rudimentary Müllerian ducts were dilated incrementally by pushing Hegar dilators in the direction of the pelvic axis, and the resulting median raphe was then intersected using diathermy. Subsequently, a vaginal mold is inserted into the newly created cavity and held in position by two sutures. A mean vaginal length of 8.3 cm and a width of 3.3 cm was achieved. No major Intraoperative and postoperative complications or prolapse were reported to date. Overall, it was concluded that the Wharton-Sheares-George method of vaginoplasty is a minimally invasive, quick, and safe surgical option that does not require allogenic or autologous transplants, nor does it require traction devices or specialized surgical equipment and provides anatomically and functionally successful outcomes.

Davydov procedure

In the Davydov procedure, an autologous peritoneal graft is used for vaginoplasty. Laparoscopically, peritoneum graft from the pouch of Douglas is dissected and mobilized. After creating vesicorectal space, the peritoneum is reached and then the mobilized peritoneal sac is opened and fashioned to form the future neovagina.[104] The procedure is known to result in a good anatomic and functional vagina and has low Intra- and postoperative risks.[105] The peritoneal pouch gets laid with vaginal epithelium in 6 months that could be documented by vaginoscopy and biopsy.[106] The complications include bladder or intestinal injury, postoperative infections, vaginal prolapse, postoperative vaginal vault granulation, and vaginal stenosis.[65]

With regard to later UTx, the suitability of the Davydov method is limited. In the case of postoperative failure, reoperations are difficult and are associated with intra-abdominal adhesions.[50] The feasibility of uterus transplantation may be impaired by the altered pelvic anatomical structures.

Acellular porcine small intestinal submucosa (SIS) graft for vaginal reconstruction

Vaginoplasty using SIS graft has been successfully achieved in women with MRKH, and the anatomical and functional outcomes of this procedure are comparable to the laparoscopic Davydov procedure.[107] Combined laparoscopic and Wharton-Sheares George cervicovaginal reconstruction using SIS graft have also been reported in MRKH patients.[108]

Jejunal free graft

Free jejunal graft has also been used for vaginal replacement in one case of vaginal atresia in 2011; 2 years later, she underwent deceased donor UTx.[109]

Vaginoplasty procedures and their potential impact on subsequent UTx

There is as yet no consensus in the medical literature as to which of the surgical options for the creation of a neovagina provides the best UTx results.[51] According to Kolle et al.,[50], the following requirements should be met to ensure successful UTx :

i. Candidates must have normal ovaries with good ovarian reserve

ii. Candidates must not previously have undergone major intra-abdominal surgery or intestinal neovagina creation

iii. Candidates must get a neovagina that has the following features

   a. High elasticity

   b. Natural anatomical axis

   c. Sufficient dimensions- length (≥8 cm) and width (≥2 cm)

   d. Lined with natural epithelium, and

   e. No need for lifelong dilation.

   f. 4 cm wide anastomosis between donor's uterus and neovagina

They concluded that the Vecchietti-based laparoscopically assisted method of neovagina creation provides ideal functional conditions for later UTx. Frank's non-surgical self- dilation method and the Wharton–Sheares–George vaginoplasty appear to provide further suitable options for neovagina creation prior to uterus transplantation. However, these authors had not accounted for the presence of the opening of the rectovestibular fistula in the vulva. For the cohort under discussion, i.e., patients with rectovestibular fistula and vaginal agenesis, it would be appropriate to leave the rectovestibular fistula as neovagina, and the colon should be pulled down to create neonaus, but it is important to perform through these procedures concurrently either laparoscopically, or through the posterior sagittal route with which we neonatal/ pediatric surgeons are well conversant with.

Uterine transplantation

Though the MRKH cohort represents only ~3% of women with absolute uterine factor infertility (AUFI), the vast majority of UTx attempts have been performed in this cohort only.[110] Women with MRKH syndrome usually have functioning ovaries that can produce viable oocytes. While advances in assisted reproductive technologies are significant, women with AUFI cannot carry a pregnancy, which leaves adoption and the use of in vitro fertilization (IVF) with gestational or surrogate carriers as the only methods for parenting. While many patients find these alternatives to be satisfactory, adoption and surrogacy may be impossible for some patients due to personal, religious, legal, financial, or ethical reasons.[111] Similar is the case of a woman who has undergone a hysterectomy or who has a uterus that is in situ but has been damaged by infection or surgical instrumentation. UTx has added a novel treatment to the existing armamentarium options for all such women.

The first human unsuccessful living-donor UTx procedure was reported in 2002 by physicians in Saudi Arabia and involved a 26-year-old recipient with AUFI due to a prior hysterectomy.[112] There have been no subsequent attempts by this group. The next human uterine transplant did not take place until nine years later, in 2011. The 2011 transplant was performed by a Turkish team and was novel in the first-ever use of a deceased donor. This transplanted uterus showed evidence of menstrual function, but despite several early failed pregnancies, no successful live births have resulted from the graft to date.[113]

During the intervening 9-year period, Brännström and his team in Sweden built many successful animal models in different species, including swine, rodent, and non-human primates.[114] In 2014, they published the results of their first clinical trial of 9 living related donor human UTx, 8 of whom had AUFI due to MRKH.[115] Of the nine transplants performed, seven remaining grafts were successful and recovered menstrual function within months of the transplant without any need for hormonal support. Multiple live births have since been reported from Brännström's group.[116] All births have been via the planned Cesarean section. This clinical trial is the first that demonstrated that uterine transplantation can achieve the ultimate endpoint of a healthy live birth. This remarkable achievement attracted major attention worldwide and caused many countries to prepare for UTx, including countries in Asia. To date, three groups have performed UTx in humans in Asia, and many others are aiming for the clinical application of

UTx with the accumulation of basic experimental data.[117] Following Sweden, USA, Brazil, and Serbia, India became the 5th country to have a live birth after a successful UTx on October 18th, 2018; the credit goes to a 12-member team headed by surgeon Dr. Shailesh Puntambekar in Galaxy Care Hospital, Pune who had performed UTx in a lady who suffered from AUFI due to Asherman's Syndrome. Till April 2020, 16 post-UTx live births have taken place worldwide.[118]

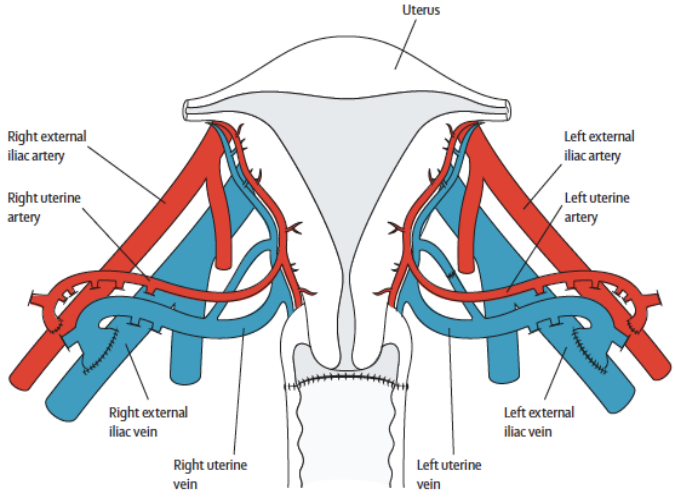


Figure 5: Schematic representation of the major steps of UTx. (Reproduced from Brännström et al. Lancet. 2015;385(9968):607-16.)[126]

The details like recipient factor, donor considerations (live as well deceased), surgical considerations, ischemia times, postoperative management, immunosuppression are beyond the scope of this review article; only a schematic representation of major steps of UTx is given in Fig. 5. The readers are advised to refer to some of the representative articles published in the last 6-7 years.[110,119-125] There are three factors that may be worth highlighting here. One is about the short vaginal length of the blind vagina typically found in women with MRKH, especially those who received the non-surgical treatment. Even with patients who report regular intercourse, the vaginal length may be as short as 2–4 cm, and the routine use of dilators prior to surgery or even vaginal augmentation surgical procedures should be considered in such women. The uterine transplanted patients need to have cervical biopsies to monitor the immunosuppressive therapy and the subsequent IVF procedures, so the vagina and the uterovaginal anastomosis should be wide enough to allow instrumentation. Second, the embryo transfer to the transplanted uterus must wait at least for 6 months; most UTx surgeons would rather wait for even a year.[124] Third, UTx is presently the only ephemeral transplant to remain in situ for a limited time in the recipient [109], so every UTx recipient would need to essentially undergo 3 surgeries: the transplant surgery, Cesarean section for delivery, and finally, removal of the uterus after 6 months of successful delivery; some surgeons may allow a second pregnancy before excising the transplanted uterus.

CONCLUSION

Rectovestibular associated with vaginal atresia is a rare variant of anorectal malformations in females with little more than 100 cases have been reported globally. The vaginal atresia is usually part of MRKH syndrome. Although a lot of literature is available about non-surgical and surgical treatment of vaginal atresia associated with MRKH syndrome, it is a different scenario when it coexists with rectovestibular fistula. Bowel vaginoplasty has been the favored reconstruction for this association. Of the two philosophies, whether the distal rectovestibular fistula should be retained as neovagina or neoanus, although there is no consensus, the majority of surgeons believe in retaining the distal rectovestibular fistula as the neovagina and performing pull-through of the proximal colon as neoanus via the posterior sagittal route. The advent of uterine transplants in MRKH patients with normal ovarian function has added a new dimension to the surgical management of this association of anomalies. Clearly, all described procedures should be performed by pediatric surgeons with extensive experience in vaginal reconstruction and laparoscopic surgery. Though there is not a single specific mention in the available literature related to uterine transplantation of the association of vaginal atresia and rectovestibular fistula, a review of the various neovagina reconstruction techniques in this context gives a fair idea of the ideal management. The neonatal/pediatric surgeons and gynecologists should work in tandem for such rare cases and learn from each other. The rectovesical space and the lower abdomen/pelvis should be treated as sacrosanct; any gross violation of these areas would lead to adhesions that would preclude any future uterine transplantation. It would be appropriate to leave the distal rectovestibular fistula as neovagina, and the colon be pulled down to create neoanus; it is important to perform these procedures concurrently either laparoscopically or through the posterior sagittal route with a lot of diligence.

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