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Varied presentation of female external genitalia – a record analysis

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Summary

Ambiguous genitalia, a cluster of varied presentations classified as disorders of sexual development (DSD), involves a spectrum of manifestations affecting both internal and external genital organs. Diagnosing and treating these disorders is complex and requires a multidisciplinary approach. This article aims to explore the complexities and challenges of diagnosing and managing DSD. These cases highlight the importance of genetic, phenotypic, and biochemical evaluations in achieving accurate diagnosis and treatment plans, which may include surgical interventions and psychological support. The cases presented include individuals with 46,XY and 46,XX DSD, highlighting conditions such as MRKH syndrome, recto-vaginal fistula, and persistent urogenital sinus, androgen insensitivity syndrome each with unique clinical presentations and treatment challenges. Treatment options, such as McIndoe vaginoplasty, and considerations regarding psychological counselling and legal gender assignment further complicate the management of DSD, emphasizing the need for a comprehensive, individualized care approach.

Key words

DSD – ambiguous genitalia – vaginoplasty – sexual differentiation

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Introduction

Ambiguous genitalia is a cluster of varied presentation. There is different classification which describe these disorders. The classification based on etiology is described as disorders of sexual development [1]. The presentation of these disorders is a spectrum of manifestation involving both internal and external organs. The deformities are identified mostly by the radiological investigations like ultrasonography or MRI. The ESHRE/ESGE consensus provides the most descriptive classification [2]. Many times, the diagnosis is not straight forwards and hence, the diagnosis needs a multidisciplinary approach. The treatment aspect of these disorders is equally challenging. To achieve a near normal appearance, proper diagnosis and treatment plan is much needed. The aim of the study is to highlight the intricacies and challenges in the diagnosis and treatment aspects.

Case series

The patients who had presented to the Department of Plastic Surgery were assessed for the complaints and the type of DSD. The type of management used are also analyzed.

Case 1

The patient was reared as a female for 22 years, visited a gynecologist with complaints of primary amenorrhea. On examination, the patient had minimally developed breasts. External genitalia were phenotypically female with a small opening to the vagina, which was 1 cm deep, with the absence of clitoris. On palpation, the patient testis was noted in the inguinal region. The patient's USG revealed absent uterus and ovaries, classified U5/C4/V3 as per ESHRE/ESGE consensus. Further evaluation revealed a 46,XY karyotype. The patient was in a psychological dilemma. After thorough counseling, the patient underwent diagnostic laparoscopy and bilateral orchiectomy. The vagina was reconstructed using McIndoe vaginoplasty. The patient underwent all legal formalities to change the phenotypical sex to female. Post-operatively, hormone replacement therapy was initiated (Fig. 1A–C).

Case 2

The patient was phenotypically a female for 26 years and visited a gynecologist with a history of primary amenorrhea. On evaluation, all female secondary characteristics were well developed. The external genitalia were phenotypically female but the vagina was absent. Abdominal USG showed that the uterus and ovaries were absent, too. On karyotyping, the patient was 46,XX and belonged to U5/C4/V4 according to ESHRE/ESGE consensus classification.

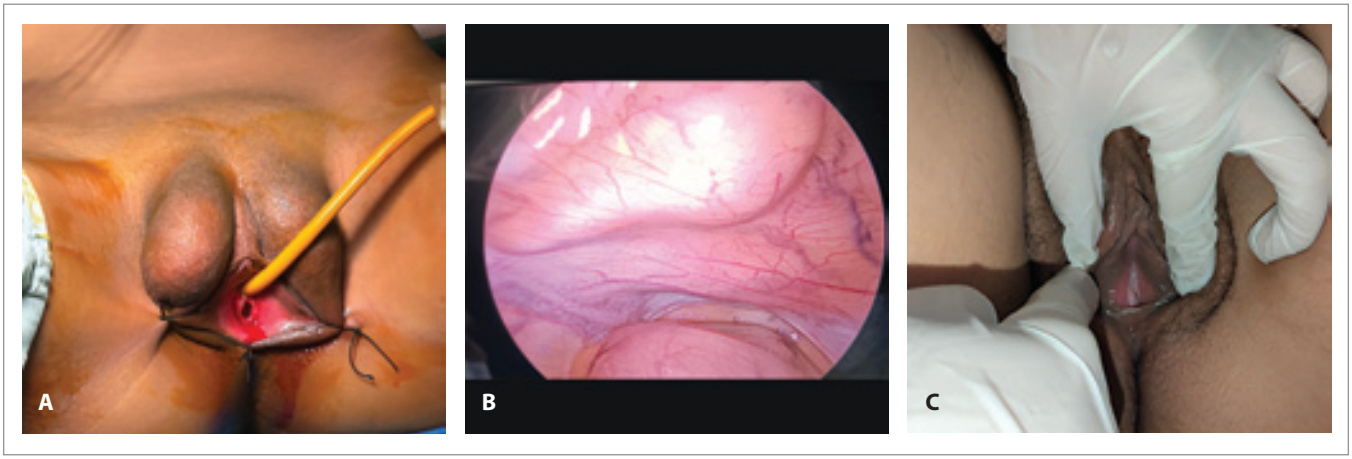

Fig. 1. A) Pre-op image – absent vagina and testicular bulge in the right labia; B) intra-operative laparoscopy showing absent uterus and ovaries; C) post Mc Indoe's vaginoplasty.

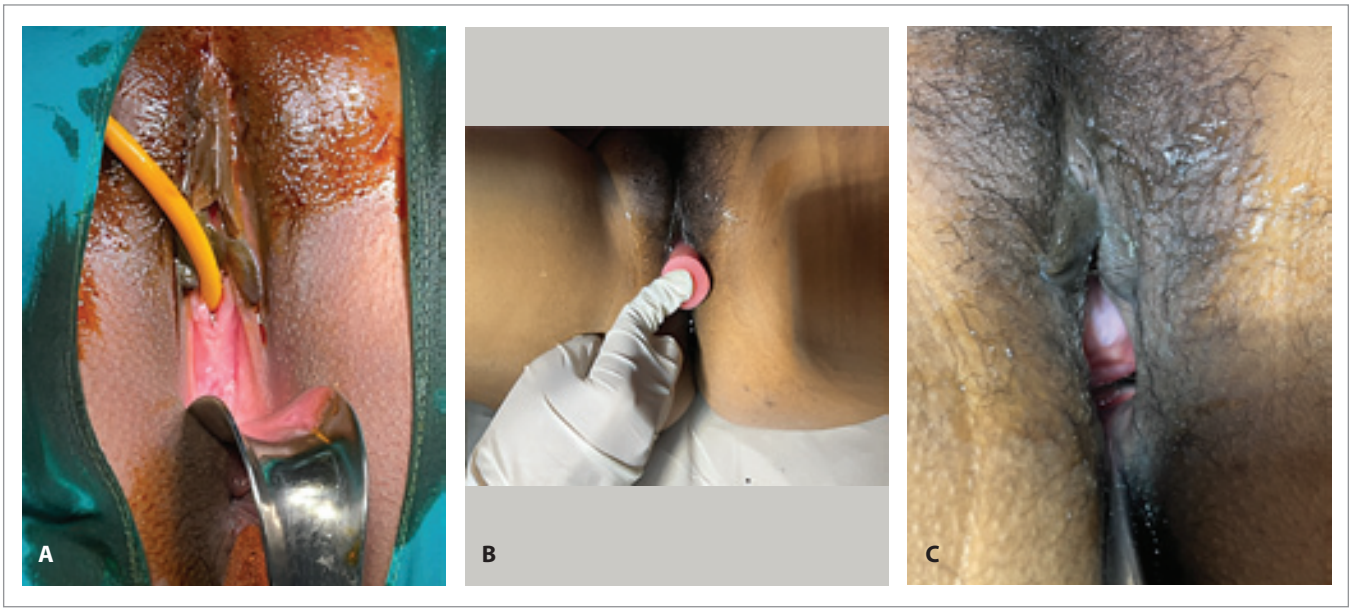

Fig. 2. A) MRKH type 1: pre-operative image showing no vaginal opening; B) post-operative image showing reconstructed vagina with adequate dilatation; C) late post-operative image.

The diagnosis of type I Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome was made. The patient counseled about the reproductive limitation and was advised vaginoplasty. The McIndoe vaginoplasty was performed to create a vaginal cavity (Fig. 2A–C).

Case 3

This patient had all features similar to case 2 (type I MRKH). However, the urethral opening was very wide. The patient had no vaginal opening and was unaware of it. This patient also belonged to U5/C4/V4 as per ESHRE/ESGE consensus classification. The patient counseled accordingly and McIndoe vaginoplasty was done.

Case 4

This patient had an interesting presentation. A 23-year-old female, married for 3 years, was brought by her husband to the Department of Urology with the complaints of fecal staining of his genitalia after each sexual intercourse. On further inquiry, the patient was otherwise healthy. The patient had neither attained menarche, nor consulted any clinician since her childhood. The parents have hidden the above history from the husband prior to the wedding. There were no bowel or bladder complaints. After the initiation of her sexual life, she started to notice leakage of urine through the rectum and perianal staining, upsetting her day-to-day activities. Recently, the husband also complained of a small quantity of blood staining his genitalia after the act of intercourse, which subsided on its own, but was significant (Fig. 3A–C).

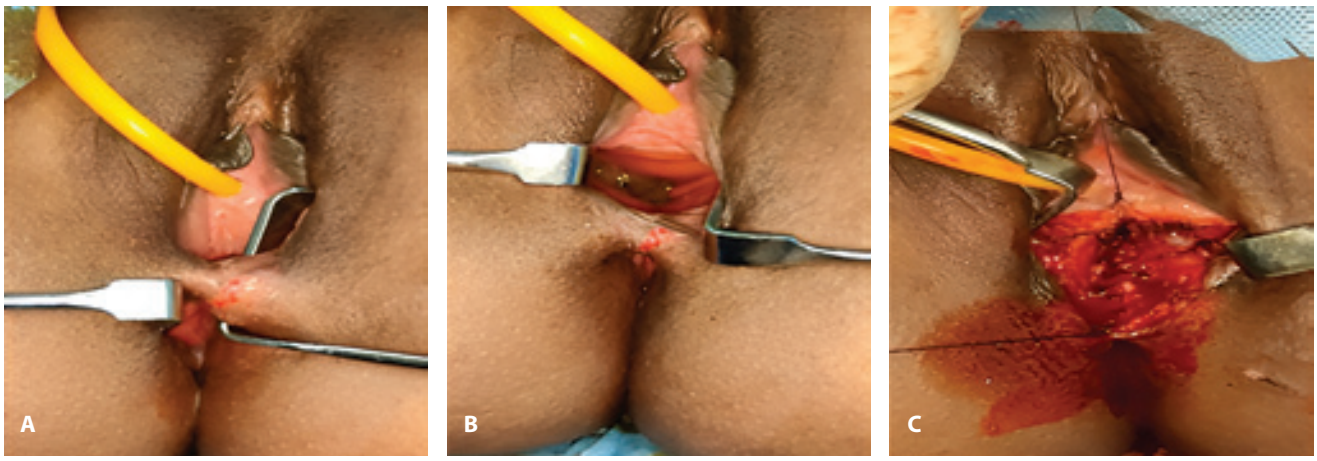

Fig. 3. A) MRKH type 1: pre-operative image showing vaginal opening; B) pre-operative image showing recto-vaginal fistula; C) intra-operative image showing separation of vaginal as well as rectal wall.

On examination, all secondary sexual characters were normal. The per speculum examination revealed a fistulous opening seen in the posterior vaginal wall, about 2–3cm from the vaginal opening. The vaginal walls were shortened and the urethral opening was in a normal position. The per rectum examination evidently showed a defect seen in the anterior rectal wall, easily admitting 2–3 fingers. The proximal level of the fistula could be visualized at 4 CMS above the anal verge. The rest of the rectal examination was unremarkable. Only a band of tissue connecting the distal end of the fistula and the rectal opening was seen. An abdominal and pelvic USG showed agenesis of the uterus, only thin tubular structures were noted, and both ovaries were normal. In the right ovary, a simple cyst was noted. A pelvic MRI was done to integrate the USG findings. The sagittal view demonstrated a hypoplastic uterus and the absence of upper vagina. This patient belonged to U5/C4/V3 according to ESHRE/ESGE consensus classification. Coronal images confirmed the presence of normal ovaries with a cyst in the right ovary and absence of the vaginal wall between the rectum and the bladder. MRI also revealed a communication between the mid-third of the vagina and the rectum, 4 cm above the anal verge, suggestive of a fistula. The kidneys were unremarkable. She also underwent i.v. urogram that was negative for renal abnormalities. The chromosomal study showed a normal karyotype of 46,XX. The patient also had a low anti-Müllerian hormone (AMH) level (0.70). All the above mentioned features suggested MRKH syndrome.

The treatment was aimed at closing the fistulous tract and create a vaginal cavity. The fistulous tract identified as a rectal opening was closed from the per rectum side. The fistulous tract was well epithelized and roomy, so it was included in the vagina and the proximal end was closed in layers, creating the vaginal canal.

Case 5

The patient was a 24-year-old female patient, with absolutely no complaints. She had normal menstruation, however, during her hemorrhoidectomy surgery, the surgeon noticed she had no vaginal opening and was referred to a gynecologist. The examination revealed that the patient had fused labia. MRI was suggestive of indistinct distal vagina and urethra at the introitus with normal uterus and ovaries. To know the confluence of both openings, the patient was referred to a urologist and a micturating cystourethrography (MCU) was performed. According to ESHRE/ESGE consensus classification, the patient had U0/C0/V2 deformity. The MCU revealed persistent urogenital sinus with communication between the middle part of the vagina and the urethra with a common length of the tract of 2 cm and absent lower third of vagina and external vaginal opening. The patient was treated with cystoscopy to identify both openings and then labial flap vaginoplasty was done (Fig. 4A–C).

Discussion

The development of the genital system and differentiation into male and female is a complex process. The process involves various steps including gene expression and various chemical pathways. Any abnormality in even one step would lead to abnormal genital phenotype.

Normal 46,XY inheritance will have the SRY gene which is the trigger factor for the development of male gonads [3]. Once the male gonads are formed due to active Sertoli cells and Leydig cells, there is a regression of the Müllerian ducts because of AMH effect (female genital organ) and stabilization of the Wolffian duct, which eventually leads to male external genitalia. The deficiency

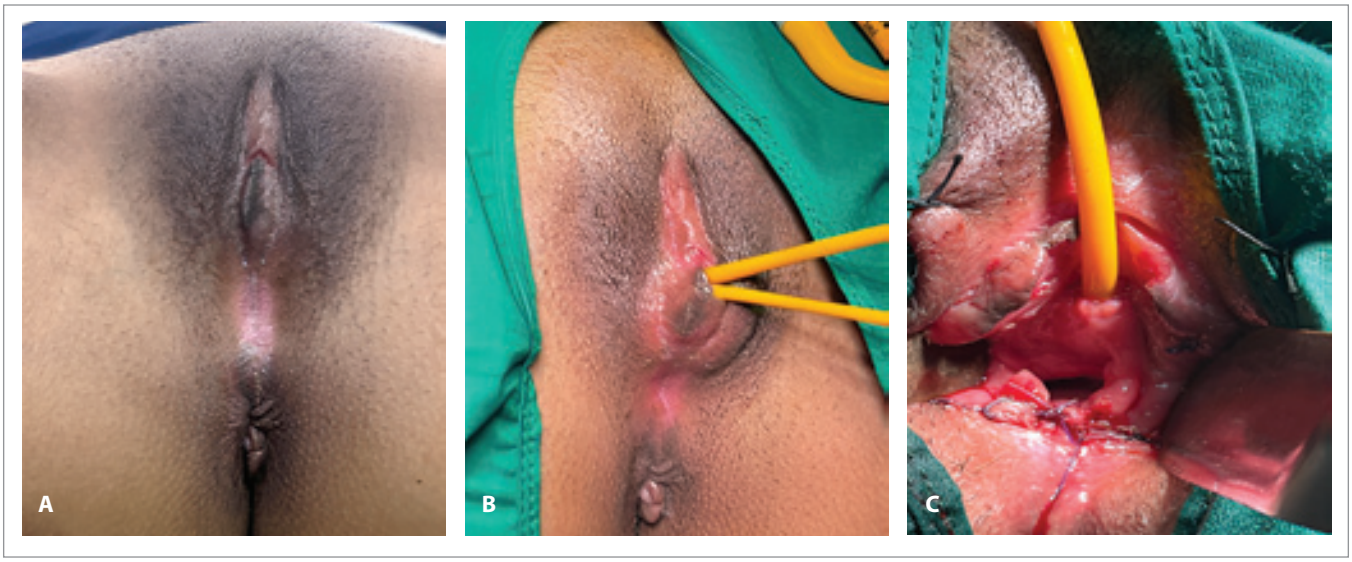

Fig. 4. A) Patient with persistent urogenital sinus; B) post- cystoscopy catheterization of urinary and vaginal tracts; C) post-operative image after labial flap vaginoplasty.

of AMH will lead to abnormal male external genitalia with persistent Müllerian duct structures in 46,XY males [4]. Similarly, in 46,XX inheritance, the paired Müllerian ducts develop due to the presence of female gonads. Later, they fuse in the midline and develop into the uterus, cervix, and upper third of the vagina which form the internal reproduction organs [5]. Caudal two thirds of the vagina are formed by the uterovaginal primordium along with the urogenital sinus [6]. The classification of these disorders is based on morphology as well as etiology. The ESHRE/ESGE consensus classification provides the most comprehensive diagnosis. The other diagnosis mainly depends on the etiology (Tab. 1)

46,XY DSD

The spectrum of these cases ranges from mild versions of lower virilization to severe versions caused by androgen insensitivity. As the latter can be complete or partial, clinical presentation can include mild or severe types [3]. The majority of these patients present with ambiguous genitalia [7]. Although the genital sex cannot be clearly defined, about two thirds of patients are reared as males [8]. Many other case series also suggest the same. However, our patient was reared as a female. The patient consulted a gynecologist only at the age of 20 years with complaints of virilization (hirsutism and deepening of voice) and primary amenorrhea. On examination, the patient's genital phenotype was female. Swyer 's syndrome describes the similar condition where the patient has streak gonads with a potential to develop into malignancy. However, this patient had well developed testis as well but they were undescended [9]. Postoperatively, this patient's testis were sent to histopathology to rule out a malignancy. These gonads were present in the labia, giving it a bulk and appearance of labia majora. The patient had both urethral and vaginal opening but the vaginal opening was 1 cm deep and 1 cm wide only. On radiological evaluation, the patient had no female internal organs. All these were suggestive of absent Müllerian duct structures, but karyotyping nailed the diagnosis as 46,XY DSD. The patient was counseled regarding the same, mainly for the inability to reproduce. The patient as well as the parents were surprised and in despair, knowing that their daughter was genetically male. Another challenge was to legally assign the patient into gender, congruent to patient's psychology. After thorough evaluation and psychiatrist opinion, the patient undertook a legal affidavit to be recognized as a female. Hence, this patient underwent vaginoplasty.

46,XX DSD

The 46,XX DSD are classified as follows [10,11].

1. Disorders of gonadal differentiation (testicular /ovo-testicular /primary ovarian insufficiency). These occur due to the abnormality of the genes involved in gonadal development.
2. Disorders with excessive amounts of androgens. These can occur due to fetal, placental or maternal causes:
   a. fetal cause – congenital adrenal hyperplasia – 21-hydroxylase deficiency, 11-beta-hydroxylase deficiency, 3-beta-hydroxyl-steroid dehydrogenase deficiency, virilizing ovarian tumors, virilizing adrenal tumors, glucocorticoid receptor gene mutation;
   b. placental cause – aromatase deficiency;
   c. maternal cause – luteoma, exogenous androgen excess.

Tab. 1. The ESHRE/ESGE classification system – female genital tract system.

	UTERINE ANOMALY			CERVICAL/VAGINAL ANOMALY
	MAIN CLASS	SUB CLASS		
U 0	Normal uterus		C0	normal cervix
			C1	septate cervix
			C2	double "normal" cervix
U 1	Dysmorphic uterus	a. T-shaped	C3	unilateral cervical aplasia
		b. infantile	C4	cervical aplasia
		c. others		
U 2	Septate uterus	a. partial		
		b. complete	V0	normal vagina
			V1	longitudinal non-obstructing vaginal septum
U 3	Bicorporeal uterus	a. partial	V2	longitudinal obstructing vaginal septum
		b. complete	V3	transverse vaginal septum and/or imperforate hymen
		c. bicorporeal septae	V4	vaginal aplasia
U 4	Hemi-uterus	a. with rudimentary cavity		
		b. without rudimentary cavity		
U 5	Aplastic uterus	a. with rudimentary cavity		
		b. without rudimentary cavity		
U 6	Unclassified malformation			

3. Other
   a. MRKH syndrome—type I& II;
   b. complex syndromic disorders;
   c. non-syndromic disorders – cloacal exstrophy, Müllerian duct agenesis, vaginal atresia, labial fusion.

Testicular DSD

It is characterized by the presence of testes in 46,XX patients (but with azoospermia and subsequent testosterone deficiency), absent Müllerian derivatives, and normal, or sometimes ambiguous, external genitalia (15% of cases) [12,13]. These patients will need testosterone replacement therapy. Infertility is often the reason why these patients are evaluated in adulthood. In children, testicular hypoplasia and short stature can be observed at puberty.

Ovo-testicular DSD

These disorders are defined by testicular as well as ovarian tissue in both gonads or one testis and one ovary on each side in the same individual. In another situation, the patient will have one ovo-testis on one side and an ovary or a testis on the other side.

46,XX primary ovarian failure

In these patients, there is a primary ovarian defect, either because of a developmental abnormality or due to the resistance to gonadotropin stimulation, which leads to premature ovarian failure. Elaborate discussion on these cases is not done in this article as none of our cases belonged to this category.

Syndromic DSD

MRKH syndrome

It is also referred to as Müllerian aplasia or congenital absence of the uterus and the vagina. It is a congenital disorder characterized by agenesis or aplasia of the uterus and the upper part of the vagina in females with a normal female karyotype (46,XX). MRKH syndrome is classified as type I (isolated utero-vaginal aplasia) or type II (associated with extra-genital manifestations). In these patients, external genitalia appear normal, and the patients typically have a normal reproductive endocrine function. They attain puberty showing normal signs of thelarche and pubarche. MRKH syndrome has been reported in ~ 16% of patients with primary amenorrhea. It is considered the second most common cause of primary amenorrhea after ovarian failure [14].

The treatment of patients with MRKH syndrome is complex and requires a patient-centered multidisciplinary approach. It requires careful dialogue with the patient addressing all-together gynecological, sexual, psychological and infertility issues. Correction of vaginal agenesis in MRKH syndrome with creation of a functional neovagina has been a hallmark in the treatment [15]. Various surgical procedures described include McIndoe vaginoplasty (split-skin graft covering a mold placed in the dissected

pouch between the rectum and the bladder), Baldwin vaginoplasty (bowel graft), Davydov vaginoplasty (peritoneal graft), and William's vulva-vaginoplasty (labia majora flaps) [16–19].

Two of our patients had typical presentation of type I. Both patients had normal female phenotype and karyotype. The patients did not have any signs of virilization. The only complaint was primary amenorrhea. One of the patients had wide urethral opening. When thoroughly questioned, she had tried to dilate urethral opening using dilators, thinking that it was vaginal opening. Both patients had normal looking external genitalia except the vaginal opening. On radiological evaluation the internal genital organs were absent. Then the patient and the parents counseled and as per request the neovagina was created using the Mc Indoe's technique. These patients were explained the pros and cons of different methods of vaginoplasty. They were unwilling for any intra-abdominal surgical manipulation. Hence, Mc Indoe's technique was preferred.

The other patient was a case of MRKH type 1 only. After the marriage, the patient started her sexual activity. She was sexually active for almost 2 years without any complaint. However, she developed a recto-vaginal fistula due to repeated insult on the ill-developed vaginal wall. After some time, the patient visited the hospital because of the complaints of fecal smell after sexual intercourse. The clinical diagnosis of recto-vaginal fistula was simple but the patient had underlying MRKH which needed a battery of investigations. The first clue was given by abdominal USG, which was confirmed by MRI and karyotyping. Although the diagnosis was challenging, the treatment was simple as the patient had well developed fistulous tract which could be used for vaginal recanalization.

Persistent urogenital sinus

Persistent urogenital sinus (PUGS) is a congenital pathological condition characterized by an abnormal communication between the urethra and the vagina and by the fail to form and fuse properly. The incidence is estimated 0.6/10,000 female births [20]. According to Powell et al., four different types of PUGS can be identified depending on the vaginal location [21]:

- type I – characterized by labial fusion;
- type II – characterized by the distal confluence;
- type III – defined by proximal or high confluence and long common tract;
- type IV – defined by absence of the vagina.

PUGS commonly presents as a pelvic mass, related to a distended bladder, hydrometrocolpos, which is caused by dilation of the vagina and obstruction of the uterus (i.e., imperforate hymen, transverse vaginal septum or atresia or both) [22,23]. Hydronephrosis, caused by distention of the upper urinary tract and developing into renal dysplasia, can also be associated. Our patient was unaware of the deformity. She had well developed secondary sexual characters and menarche. The patient had regular menstrual cycles as well. Accidentally, when a surgeon noticed that she had no vaginal opening, she was informed. Then the patient visited a gynecologist, who referred the patient to us.

As per literature, radiological assessment is useful for clinicians. Imaging studies like ultrasonography, voiding cystourethrography (VCUG), and MRI define the exact anatomical deformity [24]. The surgical approach depends on the anatomical definition of the point of confluence between the urethra and the vagina. In the low confluence of PUGS, the treatment consists of flap vaginoplasty. The flap vaginoplasty should not be a viable surgical option for correction of a high confluence of PUGS. In this case, the treatment is the pull through vaginoplasty. In very severe or high-grade cases, Wang et al. described the need of urethral reconstruction as well as artificial vaginoplasty [25]. In very severe or complex cases, robotic intestinal mobilization for vaginoplasty has been described. In our patient, VCUG clinched the diagnosis and defined it as PUGS with low confluence of urethra and vagina. Although we had planned pull-through vaginoplasty, perioperatively, flap vaginoplasty was enough to restore the anatomy [26,27].

Conclusion

DSDs are a spectrum of manifestation caused by various causative factors. The complex embryological process gives a scope for various deformities. The diagnosis involves thorough clinical and biochemical evaluation. Radiological and other imaging investigations (USG, MRI, MCU) define the anatomical deformities of internal genital organs. Karyotyping of the patient is a must for definitive diagnosis. The diagnosis of these disorders is challenging as it involves genetic, phenotypical and biochemical evaluation. Once the diagnosis is made, the treatment needs a multidisciplinary approach. McIndoe's vaginoplasty is a safe and simple surgical option for those who need vaginal reconstruction only. The treatment of these disorders is challenging as the patient needs to be psychologically congruent with his/her sex and the treatment should also be in legal limits.

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Limitation of the study: The study population is low.

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dards. Since the study had any new intervention, approval from the institutional ethics committee was not necessary.

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