Review

DOI: 10.5582/irdr.2023.01027

Urogenital sinus malformation: From development to management

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SUMMARY Urogenital sinus (UGS) malformation, also known as persistent urogenital sinus (PUGS), is a rare congenital malformation of the urogenital system. It arises when the urethra and vaginal opening fail to form properly in the vulva and fuse incorrectly. PUGS can occur as an isolated abnormality or as part of a complex syndrome, and is frequently associated with congenital adrenal hyperplasia (CAH). The management of PUGS is not well-established, and there are no standardized guidelines on when to perform surgery or how to follow up with patients over the long term. In this review, we discuss the embryonic development, clinical evaluation, diagnosis, and management of PUGS. We also review case reports and research findings to explore best practices for surgery and follow-up care, in hopes of increasing awareness of PUGS and improving patient outcomes.

Keywords UGS, PUGS, urogenital sinus malformation, embryology, management

1. Introduction

Urogenital sinus (UGS) malformation, also known as persistent urogenital sinus (PUGS), is a rare congenital pathological disease with an incidence of approximately 6/100,000 women (*1,2*). The urogenital sinus is a structure that typically develops during embryonic development. There is a confluence between the urethral and genital openings during the embryonic stage, and then the two structures separate and differentiate into the urinary and reproductive tracts. When the differentiation process is hindered or disrupted later, PUGS may occur. It can either be the sole malformation or a part of a complex syndrome. According to Campbell Walsh Wein Urology (*3*), PUGS occurs in four situations. It usually occurs in cases of unidentified external genitalia, and most frequently with congenital adrenal hyperplasia (CAH), which is an autosomal recessive disease with an incidence of 1/15,000-1/16,000 (*4,5*). Studies have reported that in atypical mild CAH, the incidence of PUGS can be as high as 1/500 (*6*). Additionally, it can occur with normal external genitalia, in cloacal malformations involving the rectum, as well as female exstrophy.

This review sought to summarize the relevant embryological development and pathogenesis, clinical assessment (manifestation and diagnosis), surgical and systematic management, case reports and research results, aiming to increase relevant medical personnel understanding of the PUGS.

2. Embryology and Etiology

Before the seventh week of pregnancy, the genitourinary system of male and female fetuses are in an identical undifferentiated precursor state. The differences in masculinization are mainly caused by the expression of the *Sry* gene and related downstream genes and their products, such as anti - Müllerian hormone and testosterone (*7*).

In normal female internal genitalia, without the presence of the *Sry* gene, the reproductive tract follows a feminization pathway (*8*). During embryonic development, the epithelium of the Müllerian ducts (pararenal ducts) fuse distally to form the ureterovaginal canal and migrate towards the caudal end of the urogenital sinus under the guidance of the Wolffian duct (mesonephric duct) (*9*), which contributes to the formation of the uterine cavity and most of the vagina. At approximately 10 weeks, the ureterovaginal tube attaches to the urogenital sinus, forming solid tissue coagulation commonly called sinus bulbs or sinus ridges. Previous studies have suggested that at weeks 10–20, the solid tissue portion of the sinus ridge extends caudally towards

the perineum to form the lower part of the vagina, while the upper part of the vagina is mostly derived from the ureterovaginal (*7*). However, as research progresses in humans, the intricacy of vaginal development may exceed prior assumptions. Robboy *et al*. (*10*) found that vaginal growth is not simply divided into upper and lower parts, but rather it dynamically proliferates by the pararenal epithelium and urogenital sinus epithelium during 10-21 weeks. Interestingly, vaginal development in mice is also dynamic. Kurita *et al.* reported that in embryonic and neonatal mice, the vagina consists of a fusion of the Müllerian duct epithelium and the urogenital sinus epithelium (*11*). However, as growth occurs into adulthood, the vaginal epithelium is derived only from the Müllerian duct (pararenal duct) epithelium (*11*). This was also confirmed by a recent study conducted by Harada M *et al.* (*12*). They found that postnatal descending growth of the Müllerian duct epithelium is attributed to rapid cell proliferation in the Müllerian duct epithelium and its surrounding mesenchymal tissue, as well as the apoptosis of urogenital sinus epithelial cells (*12*).

In the development of external genitalia, the cloaca subdivides to form the urogenital sinus, and the cloacal membrane ruptures to form the urogenital plate on the surface of the perineum. In front of the urogenital plate, interstitial condensation forms the genital tubercle. In females, the genital tubercle develops into the clitoris, the urogenital folds form the labial folds (labia major and minora), and the urogenital plate remains open, creating vaginal introversion (*13*). A study of female fetal external genitalia development in the second trimester found that the solid urethral plate opens through cell proliferation and extends laterally to form the vestibular groove in a zipper-like manner (*14*). However, unlike in males, where the double zippers close to form the tubular penis urethra, there is no evidence of zipper activity in females, and the vestibular sulcus remains open to form the vestibule and inner chamber (*14*). Between the 12th and 16th weeks of gestation, the junction between the developing lower vagina and urogenital sinus is displaced caudally until it stops at the urogenital sinus posterior wall, separating from the urethra in the vestibule to obtain a separate vaginal opening (*8*).

Although some studies have suggested that renal duct hypoplasia or insufficient growth of the tail urogenital wedge may cause some cases of PUGS (*15,16*), most are caused by the high androgen levels stimulated by CAH. CAH is an enzyme deficiency, commonly involving 21-hydroxylase deficiency (*17*). This deficiency leads to a blockade in hormone synthesis pathways, resulting in the accumulation of steroid precursors that ultimately convert to circulating testosterone *via* 4-androstenedione. Excessive circulating testosterone leads to variable degrees of virilization of the developing external genitalia in female fetuses (*18,19*). The formation of the urethral groove, which plays a role in both male and female, is independent of androgen stimulation, while the closure of the urethral groove to form the tubular male urethra by the closed zipper mechanism is an androgen-dependent process (*7*). In male fetuses, the formation of a tabular urethra occurs *via* a closed zipper mechanism, where the urethral plate fuses from the bottom to the tip which is an androgen dependent process (*20*). Disruptions in the process of tubulization are associated with disturbances in the androgen signaling pathway. Genetic variations in the androgen signaling pathway can affect the development of the urethra, such as the formation of hypospadias (*21*). Unlike males, in female fetuses, the urethral sulcus remains open to form the vestibule due to the low levels of testosterone. When this normal structure undergoes tubalization, which is stimulated by elevated androgen levels and involves a zipper-like closure mechanism, a urethral-vaginal fusion can occur, resulting in PUGS.

Although some individuals may appear male, those with a 46,XX karyotype have female internal sex organs, including the ovaries and vagina. However, the vaginal opening may be connected to the urethra instead of the vulva, with the junction of the vagina and urethra varying from the proximal confluence near the bladder neck to the distal confluence near the perineum, depending on the androgen dependent closure of the zipper mechanism. The urethral groove may be partially or completely closed, forming a tubular male urethra of variable length (*18*). Meanwhile, the location of the vaginal confluence depends on the descending position of the sinus ridge, which is related to androgen levels. Androgens inhibit the descending movement of the sinus ridge (*22,23*) and can prevent the formation of the vaginal opening in the vulva. Prenatal exposure to androgens in female mice has been found to inhibit the decline of the sinus ridge and prevent the formation of the vaginal opening in the vulva (*24*). The specific time and duration of androgen exposure determined the location of the confluence of the vagina and urethra (*24*). Mesenchymal cells adjacent to the urothelium are likely the primary target of androgen signaling for urogenital sinus ridge morphogenesis (*24*). Recent studies also showed that the position of the sinus ridge is influenced by the amount of androgen exposure, such that higher doses of androgen result in a proximal shift of the region where the vagina and urethra meet (*i.e.*, towards the bladder neck) (*25-27*).

3. Clinical manifestation and diagnosis

The clinical manifestations of PUGS are quite variable and mainly depend on the location of the confluence entrance and the size of the sinus ostium. Children with a lower confluence location and larger sinuses are more likely to be asymptomatic or prone to urinary tract infections, while those with smaller sinuses are more susceptible to urinary tract infections. If the confluence location is high, urinary incontinence or menstrual

hematuria may occur. In addition, when the sinus opening is small, it can lead to a congenital absence of the vagina, which can cause dyspareunia. In addition, PUGS can present as a pelvic mass (associated with bladder distention due to dilation of the vagina and uterus resulting from obstruction), hydrometrocolpos (atresia of the hymen or urogenital sinus stenosis), and hydronephrosis (dilation of the upper urinary tract due to obstruction). As most patients of PUGS are secondary to CAH, there is also genital ambiguity and possible hypertension (*3*).

Early diagnosis and timely decompression of PUGS is crucial due to the potential compression of the urinary and reproductive systems. Prenatal diagnosis is commonly performed using ultrasonography during the 20th to 24th weeks of gestation (*28*), the observation of a pelvic cystic mass containing fluid-filled debris situated posterior to the bladder may be representative of hydrometrocolpos (*1*), and the septum visible across the cystic structure is likely to be the urogenital septum (*29*), these may suggest the diagnosis of PUGS. Postpartum diagnosis should be considered for girls presenting with urinary incontinence, urinary tract infection at birth, vaginal swelling or fluid accumulation, and for adults with cyclical periods and vaginal atresia (*30*). Most patients are identified due to ambiguous genitalia, and diagnosis requires a combination of medical history, clinical examination, laboratory tests, and imaging tools. The medical history should include details about the mother's physical condition during pregnancy, the use of androgen-containing drugs during the first trimester, a family history of similar deformities, and the presence of monthly regular urine with blood during puberty or adulthood. The physical examination should include a thorough examination of the internal and external genitalia, such as groin examination, anus and abdominal examination to see if the uterus is palpable. The laboratory examination should include peripheral blood karyotyping to identify female or male pseudohermaphroditism, androgen levels and peripheral blood 17α-hydroxyprogesterone (17α-OHP). For patients with increased 17α-OHP levels, a further dexamethasone suppression test should be performed to determine the presence of CAH. The primary imaging modality used is ultrasound (*1,31*), while other imaging methods, including voiding cystourethrography (*3,32*), magnetic resonance imaging (MRI) (*3,33,34*), computed tomography (CT) (*35*), cystoscopy (*36-38*), and contrast-enhanced genital angiography (*39*) (Figure 1), are commonly utilized to provide assistance (*1*). The roles, advantages and disadvantages of these methods are summarized in Table 1.

4. Classification

The classification of PUGS is essential for the treatment team to reach a consensus in discussion and describing the condition, which in turn allows for a better design of subsequent surgical plans. The examinations used for classification include evaluating the shape and size of the penis or clitoris, the labia-scrotal fold, the position of the vagina and urethra, the length of the urethra and common channel. However, there is currently no internationally recognized standard. Typically, clinicians use two classification methods, Powell (*40*) and Prader (*41*), based on the confluence location of the vaginal urethra and the degree of virilization of the vulva (as shown in Table 2). However, some studies suggest that these two methods have limitations (*29*). In normal women, the urethra begins from the internal urethral orifice, passes through the urogenital diaphragm (UGD), and extends down some distance to the perineal opening. Therefore, the bladder neck and proximal urethra in normal women are located above the UGD. When the bladder neck is appropriately supported by the UGD , the urethral pressure remains higher than the bladder pressure. Any stressful event that increases intra-abdominal and intravesical pressure closes the urethra, preventing leakage and maintaining continence (*42*). Although the length of the common channel was previously believed to affect continence, some researchers have shown that the length of the urethra also plays an important role (*43*). Moreover, the relationship between the location of confluence and bladder neck is a crucial factor in surgical intervention, as opposed to the length of the common channel, for the management of urogenital sinus malformation (*3*). The goals of treatment include achieving voiding control and normal sexual function.

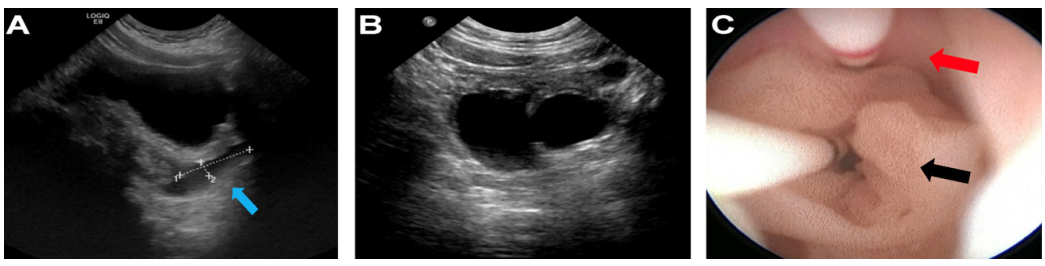

Figure 1. Imaging morphology of persistent urogenital sinus. Ultrasound scan shows two different imaging morphology: **(A)** vaginal effusion (indicated by blue arrows) and **(B)** double uterus and double vaginal malformation; cystoscopy shows **(C)** common channel of urethra (red arrow) and vagina (black arrow).

Table 1. Diagnostic imaging methods for persistent urogenital sinus

Image method (*Ref.*)	Application selection	Role	Advantages	Disadvantage
Ultrasound (*1,31*)	Prenatal diagnosis; Postpartum diagnosis.	Identify the location of the urinary and reproductive organs and whether the hydrops is expanding.	First-line diagnostic method; Simple and convenient; Prenatal diagnosis; No radiation.	Anatomy is unclear; Need to combine other imaging methods.
Voiding Cystourethrography (*3,32*)	Urethral malformation or dysfunction children at higher risk.	Identify the relationship between the urogenital sinus, vagina, urethra, bladder, and uterine contours.	No need for anesthesia; Urogenital permissible system anatomical assessment.	Can only be assessed during the excretion period; The effect depends on the operator's experience.
CT (*35*)	Children with complex malformations or rectal cloacal malformations.	With 3D reconstruction, a description of the cloacal malformation can be obtained.	Clearly, delineate regional anatomically relevant structures.	Radiation exposure; Not recommended in the absence of complex deformities.
MRI (*3,33,34*)	Children with pure PUGS or other sexual developmental abnormalities and cloacal malformations.	Accurate description of internal organs and evaluation of their relationship to the rectum.	No contrast agent required; No need to limit urination period.	Limited value in CAH diagnosis; Need anesthesia.
Cystoscopy (*36-38*)	Before or during surgical reconstruction.	Determining the anatomical relationship of the genitourinary tract.	Compared with other methods, the accuracy rate is very high; Can clearly determine the length of the urethra and vagina and opening position.	Need anesthesia; Invasive operation.
Enhance reproductive tract radiography (*39*)	Preoperative planning of surgical plan.	Determine the length of the urethra, genital tract, and the length of the confluence.	The uterus can be directly displayed at the same time.	Contrast agent required; Generally, not recommended.

Table 2. Preoperative classification of persistent urogenital sinus

Type name (*Ref.*)	Typing method	Specific type	Disadvantage
Powell (*40*)	Where the vaginal urethra joins	Type I is characterized by lip infusion; Type II is characterized by distal inflow; Type III is defined as proximal or high influx and long common tract; Type IV is characterized by vaginal absence.	Virilization assessment in individuals without external genitalia; No common channel and urethral length.
Prader (*41*)	The degree of virilization of the external genitalia and whether there is convergence of urethra and vagina	Type I: The clitoris is slightly larger, and the vagina and urethra are normal; Type II: The clitoris is larger and the vaginal opening is funnel-shaped, but the vagina and urethral opening are still separated; Type III: The clitoris is significantly enlarged, only one opening is visible in the vulva; Type IV: The clitoris is significantly enlarged like a penis, one opening at the base of the clitoris, similar to hypospadias; Type V: The clitoris resembles a male penis, the urethral opening is at the head of the clitoris, and complete fusion of labia majoris.	There is no exact correlation between the degree of virilization of the external genitalia and the location of the vaginal-urethral fusion; No common channel and urethral length.

5. General management

5.1. Surgical treatment

The current treatment for PUGS involves reconstructive surgery of the female genitalia, which comprises clitoroplasty, labioplasty and vaginoplasty. Vaginoplasty is the most critical step, and there are currently five surgical techniques in clinical practice: urogenital sinus incision, perineal flap vaginoplasty (Fortunoff flap, Ω-shaped flap), "pull-through" vaginoplasty (recumbent position, incision for lithotripsy position, and anterior sagittal transrectal approach, ASTRA), genitourinary mobilization (total urogenital mobilization or TUM, and partial urogenital mobilization or PUM) and total vaginal replacement. Urogenital sinus incision was the earliest technique used in vaginoplasty (*44*) and is only suitable for children with Prader grades I and II (*45*). Due to the lower Prader grade, the vulva shape is closer to that of a typical female, resulting in a better postoperative appearance. However, this technique does not address the narrow vaginal opening, leading to a relatively narrow vaginal opening in adulthood. The flap vaginoplasty technique widens the vaginal entrance using the posterior

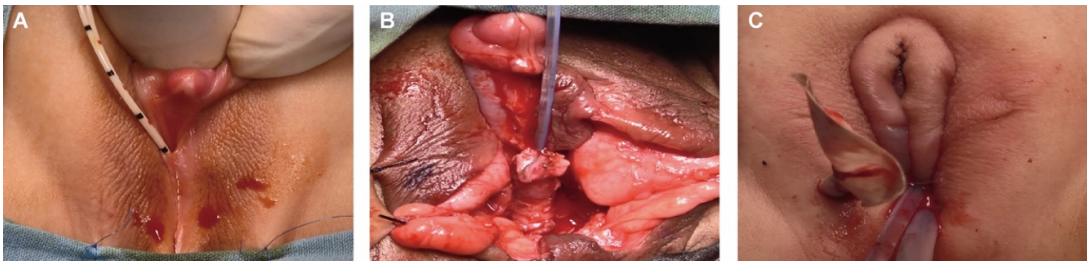

Figure 2. Total urogenital mobilization vaginoplasty method. (A) Initial perineal opening in a patient with PUGS; **(B)** Annular separation to release urogenital sinus; **(C)** Final appearance after surgery.

perineal flap. The insertion of the perineal U-shaped flap, also known as the Fortunoff flap, is a standard surgical approach for repairing low confluence genitourinary sinus abnormalities (*46*). In 2001, Jenak *et al.* modified this approach into a perineal omega-shaped flap (*36*). This procedure only opens the vaginal opening and urogenital sinus without changing the location of the vaginal confluence, making it generally unsuitable for high vaginal confluence due to the risk of complications such as vaginal urination, infection, and incontinence. This procedure is usually used alone for urogenital sinus plasty in patients below Prader III and more often in combination with other vaginoplasty procedures, such as urogenital mobilization (*36*). The "pull-through" vaginoplasty was first proposed by Hendren and Crawford in 1969, involves separating the vagina from the urogenital sinus and using the genital sinus to form the urethra. The free vagina is then pulled to the perineum, but most cases require surrounding flaps to form the vaginal opening (*47*). Among them, the separation of the anterior vaginal wall from the urethra and bladder neck is critical, as this area is difficult to fully expose and it is also the complex nerve supply area for the vagina and urethra (*48*). Complications such as vaginal urethral fistula, urinary continence disorder, vaginal stenosis, and poor appearance are prone to occur. Based on this, Salle *et al*. developed the ASTRA procedure to increase the exposure field of the surgical area and improve the free vagina, but it requires to change the patient's surgical position and involves the rectum (*49*). Therefore, this procedure is generally only used when the vaginal confluence location is high and urogenital mobilization cannot pull the vagina to the perineum without tension. Braga *et al*. (*50*) recommended it only when the common channel length exceeds 3 cm. TUM was first used as a vaginoplasty method when Pena completed cloacaplasty in 1997 (*51*). During the operation, the entire urogenital sinus was annularly separated and moved outward to the perineum (as shown in Figure 2). This method significantly shortens the operation time, improves the appearance of the vulva after surgery, and reduces the risk of complications such as urethrovaginal fistula and vaginal stenosis. Furthermore, in 2005, Rink *et al*. (*52*) proposed the use of PUM as an alternative to TUM due to the potential risk of nerve and sphincter between the urogenital sinus and the pubis during annular separation of the proximal urogenital sinus, which can result in complications such as urinary incontinence and sexual dysfunction. The difference is that in PUM, the circular anatomy of the urogenital sinus is performed but terminates at the level of the pubourethral ligament, which avoids damaging the nerve and sphincter between the urogenital sinus and the pubic bone (*52*). Acoording to Rink *et al*., the choice of these two surgical methods can be determined based on the location of the vaginal confluence. TUM is utilized when vaginal confluence is positioned high, and more urogenital sinuses need to be freed to make the vagina reach the perineal area without tension. PUM is recommended in cases where this is not necessary. Genitourinary mobilization is suitable for most patients, except in rare cases of poor vaginal development or extremely high vaginal confluence location. Total vaginal replacement, which is only used for hypoplastic or missing vaginas (*53*), is rarely performed.

However, the literature on PUGS surgical data is very limited. Most of the research data are retrospective and based on a small number of cases, with a focus only on short-term outcomes such as the appearance of the vulva and complications after surgery. These studies do not provide strong evidence on the long-term efficacy of these procedures, particularly with regards to sexual function. We summarized the available literature on PUGS surgical data in recent years (*36, 54-64*) (Table 3).

5.2. Surgical timing and selection

The optimal age for female genital reconstruction has been debated. At the IVth World Congress of the International Society of Hypospadias and Disorders of the Sex Development (ISHID), 78% of global delegates voted in favor of surgery before the age of 2, and most recommended one-stage plasty that includes clitoroplasty, labiaplasty, and vaginal surgery (*65,66*). This approach is designed to impart an early appearance consistent with the female parenting gender and cause less psychological harm than delayed surgery (*67*). However, there is a growing belief that surgical interventions in childhood, especially irreversible surgery, should be limited or postponed until the child

Table 3. Literature summary of persistent urogenital sinus surgical data

References (Year) (*Ref.*)	Type of study	Length of common channel	Surgical method	Complication	Key conclusion
Jenak R, *et al.* (2001) (*36*)	Case-report	> 3 cm	TUM	No lower urinary tract symptoms; No urinary incontinence.	TUM does not affect urination or urinary incontinence.
Kryger JV, *et al*. (2004) (*54*)	Review case study	2.1 cm (average)	TUM	2 cases lower urinary tract symptoms; 1 case urgent urination.	Patients with urinary control before surgery have immediate control ability after TUM; TUM does not appear to interfere with the normal development of urinary control in children undergoing surgery before the age of urinary control.
Kitta T, *et al.* (2004) (*55*)	Case-report	Not mentioned	Flap vaginoplasty	No lower urinary tract symptoms; No urinary incontinence.	Appropriate urinary care is crucial for preventing urinary complications in patients with simple PUGS.
Gosalbez R, *et al*. (2005) (*56*)	Review case study	Not mentioned	TUM + Fortunoff	No lower urinary tract symptoms; No urinary incontinence.	TUM does not affect urination or urinary incontinence.
Braga LH, *et al*. (2006) (*57*)	Prospective case study	3 cases < 2 cm 21 cases > 2 cm	PUM	No lower urinary tract symptoms; No urinary incontinence.	PUM enables urination control and good appearance, and fully exposes vaginal and urethral openings.
Palmer BW, *et al*. (2012) (*58*)	Review case study	13cases < 3cm 12cases > 3cm	18 cases TUM 7 cases PUM	5 cases after TUM with nocturnal enuresis for more than 1 year.	There was no significant difference between TUM and PUM in postoperative urinary incontinence, with a postoperative urinary control rate of 96%.
Ludwikowski BM, *et al*. (2013) (*59*)	Review	Not mentioned	TUM	No lower urinary tract symptoms; No urinary incontinence.	TUM does not affect urination or urinary incontinence.
Bailez MM, *et al*. (2014) (*60*)	Review case study	3.75 cm (19 cases, average) 6.34 cm (33 cases, average) 11.5 cm (3 cases, average)	PUM (low position) TUM (median position) TUM + ASTRA (high position)	No lower urinary tract symptoms; No urinary incontinence; Three cases were reported to have a normal sexual life.	TUM/PUM does not affect urination or urinary incontinence.
Jesus VM, *et al.* (2018) (*61*)	Review case study	Not mentioned	TUM/PUM	No lower urinary tract symptoms; No urinary incontinence.	TUM/PUM does not affect urination or urinary incontinence.
Fares AE, *et al*. (2019) (*62*)	Review case study	< 1.5 cm	Laparoscopic assistance "pull-through" vaginoplasty	No lower urinary tract symptoms; No urinary incontinence.	Laparoscopic assisted pull-through vaginoplasty provides good exposure, helps to separate the vagina from the urethra, and avoids damage to the urethral structure.
Ulusoy O, *et al.* (2021) (*63*)	Review case study	4.6 cm (average)	Posterior prone approach "pull-through" vaginoplasty	No lower urinary tract symptoms; No urinary incontinence.	Posterior prone approach "pull-through" vaginoplasty does not affect urination or urinary incontinence.
Yang J, *et al.* (2023) (*64*)	Case-report	Not mentioned	Robotic UGS mobilization	No lower urinary tract symptoms; No urinary incontinence.	Very high confluence PUGS can use robotic UGS mobilization.

becomes an adolescent, allowing them to be more involved in the surgical decision. Some researchers also suggest that the timing of surgery should depend on the location of the vaginal confluence point. Early one-stage plasty has become the standard for patients with a low vaginal confluence, but there is still much controversy for patients with a high vaginal confluence. Most believe that vaginoplasty should be performed at the same time as clitoroplasty and labiaplasty so that the excess clitoral foreskin can be used for reconstruction. However, some scholars suggest that these patients can participate in the choice of surgical methods during puberty, when their estrogen levels facilitate tissue healing, vaginal growth, and dilation. Therefore, delayed vaginoplasty is recommended for patients with short vaginas (< 3 cm) and high confluence points (*45*).

Accurate choosing of the surgical approach and implementing skilled surgical technique are key factors in ensuring a favorable postoperative appearance. Urogenital sinus incision may be used for patients with Prader class I, while perineal flap vaginoplasty may be employed for patients with Prader class I and II. For patients with Prader grade II or above, the surgical approach must be determined based on the location of the vaginal confluence point, the length of the common channel and the length of the urethra. First, the degree of external masculinization is not completely related to internal anatomy, and the depth of the vaginal confluence point is an indicator of the range of motion required for perineal approach surgery. PUM is suitable for low confluence and median confluence (the vaginal confluence point is at the level of the external urethral sphincter), and TUM can be used for high confluence. The "pull-through" method is suitable for very high confluence. Studies have shown that in 90% of cases (1–3 years old), this depth is < 20 mm, so PUM may be appropriate in most cases (*68*). Second, regarding the length of the common channel, Tugtepe *et al*. (*69*) recommended using PUM for patients with less than 2 cm and TUM for patients with a length of 2.5 to 3.5 cm. When it exceeds 4 cm, the "pull-through" method is recommended (*69*). Braga *et al*. (*57*) considered that PUM can still be used when the length exceeds 3 cm. Third, The bladder neck and proximal urethra of normal women are located above the urogenital diaphragm. When the bladder neck is well supported by the urogenital diaphragm, the urethral pressure is always higher than the bladder pressure. Stressful events that increase stress close the urethra, preventing leakage and maintaining continence (*42*). The previous view was that this depends on the length of the public channel, but some research teams believe that the length of the urethra also plays a key role (*43*). A sufficiently long urethra ensures that the bladder neck is placed over the urogenital diaphragm when reconstruction is complete, minimizing the risk of future incontinence. Researchers have reviewed voiding cystourethrography in 91 healthy women aged 6 to 36 months and measured urethral length of at least 1.5 cm in most normal control patients (*70*), whereas urethral length in children with PUGS was usually normal (*71*). According to the experience of Gonzalez R *et al*. (*72*) , the length of the urethra is always sufficient in PUGS with a high confluence position when performing PUM/TUM. Therefore, most of the patients above Prader II are suitable for PUM/TUM.

5.3. Hormone replacement

Since most PUGS are secondary to CAH, the main follow-up treatment after surgical female genital reconstruction is long-term glucocorticoid therapy, which aims to suppress excess hormones, replace deficient hormones, and avoid potential Cushing-like side effects (*17*). Generally, high doses of glucocorticoids are required to fully suppress the massive secretion of adrenocorticotropic hormone (ACTH) and reduce androgen production, as insufficient cortisol supplementation is not enough. In pediatric patients with non-classical forms congenital adrenal hyperplasia, low-dose glucocorticoid therapy is generally employed as a hormone treatment strategy when necessary (*73*). All children with CAH who receive glucocorticoid therapy are at risk of growth retardation and short stature, as the effects of glucocorticoids on growth are dose-dependent (*74*). Therefore, it is necessary to cooperate with endocrinologists to use low effective doses of glucocorticoids (medium- and short-acting preparations) as much as possible and adjust dosage based on 17α-OHP, testosterone levels, and clinical manifestations of cortisol deficiency or excess. Estrogen replacement therapy with progesterone (women) should be initiated around physiological puberty to induce periodic bleeding (menstruation) and gradually transition to an adult regimen (*75*).

5.4. Following

A survey of 62 pediatric urologists conducted by the American Association of Urology (AUA) indicates that establishing appropriate long-term follow-up is crucial for a successful transition to adulthood in pediatric patients with complex genitourinary conditions (*76*). According to the 2006 "Chicago Consensus Statement", in addition to evaluating appearance and lower urinary tract symptoms follwing surgical reconstruction of the female genitalia, attention should be given to future sexual function (*77*). This is because complications such as sexual dysfunction may take decades to develop, and pubertal development may significantly affect the final outcome (*78,79*). However, current literature data are limited, and the results of a few studies differ. For example, Ellerkamp V *et al*. reported (*80*) that perineal flaps with partial urogenital mobilization provided normal anatomical results with normal sexual function

in patients following female genital repair. In contrast, several other studies reported unsatisfactory follow-up outcomes after female genital reconstruction. A meta-analysis reported impaired clitoral sensitivity, vaginal stenosis, and pain and discomfort during intercourse (*81*). Two other studies with long-term follow-up showed that postoperative outcomes in children with CAH in terms of sexual function and clitoral sensitivity were unsatisfactory (*82,83*). Therefore, more research is needed to evaluate long-term genital sensitivity and sexual function in children after surgery. Close collaboration between the pediatric urologist and the adult urologist and provision of long-term monitoring is considered a better long-term follow-up modality, ensuring continuity and eliminating the anxiety about being transferred to another team (*84*). Another option is to transition from a pediatric urologist to an adolescent or adult specialist with an interest in the field, usually at the age of 16–20 (*85*). The transition specialist must have an understanding of pediatric diagnosis and treatment and training in urology (*86*).

6. Conclusion

PUGS is a very rare congenital malformation of the genitourinary system, and in this manuscript, we found that the management of PUGS remains a very thorny challenge throughout childhood, adolescence and adulthood, lacking of consensus, especially the timing of surgery and long-term follow-up of sexual function. Multidisciplinary engagement is required to overcome the rarity of this PUGS and a combined team of specialists in psychology, endocrinology, pediatric urology, and adult urology should be established to conduct long-term collaborative management. In addition to CAH, which causes PUGS as a result of abnormally high androgen levels, the pathogenesis of other causes of PUGS remains unclear. Further research on etiology and genetic factors will enhance our understanding of this rare disease.

Funding: This work was supported by grants from the National Natural Science Foundation of China (81970572, 82270702).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received March 29, 2023; Revised May 5, 2023; Accepted May 15, 2023.

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Released online in J-STAGE as advance publication May 18, 2023.