Pediatric Surgery International (2019) 35:611–617
https://doi.org/10.1007/s00383-019-04457-6

ORIGINAL ARTICLE

Surgical management of hypospadias in cases with concomitant disorders of sex development

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Accepted: 8 February 2019 / Published online: 14 February 2019

Abstract

Introduction To review the surgical treatment of hypospadias (HP) associated with disorders of sex development (DSD).

Patients and methods HP cases were assessed for DSD by gross examination for atypical external genitalia, and assessment of hormone levels and karyotype. There were 58 HP cases with concomitant DSD treated between 1999 and 2017. DSD classification, type of HP, sex assignment, hormonal abnormality, surgical strategy, and post-urethroplasty complications (post-UPC) were reviewed.

Results DSD were sex chromosome abnormalities ($n=4$), 46,XY ($n=51$), 46,XX ($n=1$), and 47,XY + 21 ($n=2$). HP was perineal: ($n=26$), scrotal: (n = 16), penoscrotal: ($n=15$), and midshaft: ($n=1$); repair was primary ($n=6$) or staged ($n=52$). Mean age at final urethroplasty (UP) was 4.12 ± 0.21 years; all cases had soft tissue interposition at UP. At mean follow-up 5.16 ± 0.56 years after final UP, observed post-UPC ($n=8$; 13.8%) were urethral stenosis ($n=3$), urethral diverticulum ($n=2$), urethrocutaneous fistula ($n=2$), and curvature ($n=1$). Mean onset of post-UPC was 1.24 ± 0.77 years (range 0.1–6.3). The second half of our cases ($n=29$; treated 2015 ~) had significantly less post-UPC (0/29; 0%) than the first half (8/29; 27.6%) ($p=0.0075$).

Conclusions Although UP for HP + DSD was formidably challenging, we achieved a significant decrease in post-UPC through a combination of surgical techniques and experience.

Keywords Hypospadias · Disorders of sex development · Urethroplasty

Abbreviations

HP	Hypospadias
DSD	Disorders of sex development
UP	Urethroplasty
Post-UPC	Post-UP complications
UCF	Urethrocutaneous fistula
UDT	Undescended testis
SF-1	Steroidogenic factor-1

Introduction

Disorder of sex development (DSD) is diagnosed when chromosomal, gonadal, or anatomical sex are atypical [1]. It has the potential to cause social emergencies as sex assignment is involved and both families and health care professionals are often unprepared to deal with babies with such disturbing findings [2]. Therefore, a team approach designed to support the parents as thoroughly as possible, involving close liaising between a pediatric endocrinologist, pediatric psychiatrist or psychologist, and pediatric surgeon is best for the child.

Hypospadias (HP) is one of the most common congenital malformations of the male genitalia. When present in DSD cases, HP tends to be severe with more proximal urethral openings and a higher incidence of penile curvature [1, 3]. In addition, genital ambiguity such as micropenis, bifid scrotum, undescended testis (UDT), or a prostatic utricle further complicate HP repair, such that no standard surgical strategies exist and each case tends to be treated individually.

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Thus, there are few studies about technical aspects and postoperative complications [4, 5]. Here, we report our experience of treatment of HP in patients with DSD.

Patients and methods

We retrospectively reviewed 58 HP + DSD patients who underwent urethroplasty (UP) by a single surgeon between 1999 and 2017. We investigated the DSD classification, type of HP, sex assignment, hormonal abnormality, surgical strategy, and post-UP complications (post-UPC).

UP was performed after initial surgery (foreskin degloving with/without correction of chordee, dorsal plication, ventral penile shaft reinforcement with pedicled fat/connective tissue as soft tissue interposition especially if the urethral plate was thin [6], or a combination of these). Patients with micropenis had a trial of hormone therapy to stimulate growth of the penis preoperatively.

Statistical analyses were performed using GraphPad Prism software version 6.0 (GraphPad Software). The Fisher's exact test was used to assess significance between two groups. Data are presented as mean ± SD and differences at $p < 0.05$ were considered significant.

This study was approved by the Ethics Committee of Juntendo University School of Medicine and complies with the Helsinki Declaration of 1975 (revised 1983).

Results

The clinical details of the 58 subjects reviewed in this study are summarized in Table 1.

Sex chromosome DSD was identified in 4 (6.9%), 46,XY DSD in 51 (87.9%), 46,XX DSD in 1 (1.7%), and 47,XY + 21 in 2 (3.4%), all of whom were reared as males. Of 46,XY DSD patients, 5-α reductase deficiency was observed in 1/51 (2.0%), steroidogenic factor-1 (SF-1) mutations in 2/51 (3.9%), testosterone insufficiency in 1/51 (2.0%), and no definitive diagnosis in 47/51 (92.2%). All patients had genital ambiguity, of whom 50 (86.2%) had bifid scrotum, 47 (81.0%) had micropenis, and 17 (29.3%) had UDT. 2/58 cases (3.4%) were recognized in older children by karyotyping/gonadal histopathology with subsequent sex reassignment from female to male.

HP was perineal in 26, scrotal in 16, penoscrotal in 15, and midshaft in 1. Repair was primary ($n = 6$) or staged [7] ($n = 52$). Of the 52 staged repairs, 23 were primary UP and 29 were staged segmental UP [8].

Table 1 Case details

Number	Karyotype hormonal status	Type of hypospadias	Type of repair (age at last UP; years)	Period since last UP (years)	Post-UPC (onset after last UP; years)
Sex chromosome DSD ($n = 4$)					
1	45,X/46,XY	Perineal	S (3.2)	4.1	None
2	45,X/46,XY	Penoscrotal	S (4.0)	4.5	None
3	46,XX/46,XY	Scrotal	S (5.5)	5.6	None
4	46,X,+r1/46,X,+r2/45,X/46,X,+mar	Perineal	S (4.0)	3.0	None
46,XY DSD ($n = 51$)					
5	5-α reductase deficiency	Penoscrotal	S (4.9)	7.8	Fistula (0.1)
6	SF-1 mutations	Perineal	S (3.8)	10.5	Stenosis (6.3)
7	SF-1 mutations[a]	Perineal	S (8.4)	2.8	None
8	Testosterone insufficiency[a]	Perineal	S (12.1)	5.8	None
9–55	No definitive diagnosis ($n = 47$)	Perineal ($n = 19$) Scrotal ($n = 15$) Penoscrotal ($n = 12$) Midshaft ($n = 1$)	P (2.47 ± 0.26) ($n = 6$) S (4.02 ± 0.16) ($n = 41$)	5.27 ± 0.67	Stenosis (0.2) Diverticulum (0.7) Diverticulum (0.1) Fistula (0.1) Curvature (2.3)
46,XX DSD ($n = 1$)					
56	Testicular DSD	Perineal	S (4.1)	0.8	None
47,XY + 21 ($n = 2$)					
57	No definitive diagnosis	Perineal	S (3.9)	2.8	None
58	No definitive diagnosis	Penoscrotal	S (5.5)	4.2	Stenosis (0.1)

UP urethroplasty, *Post-UPC* post-UP complications, *DSD* disorders of sex development, *SF-1* steroidogenic factor-1, *P* primary, *S* staged

[a]Sex reassignment from female to male

Mean age at final UP was 4.12 ± 0.21 years (range 1.9–12.1); all cases had soft tissue interposition as a second-layer coverage of the neourethra [9, 10]. At mean follow-up 5.16 ± 0.56 years after final UP, observed post-UPC ($n = 8$; 13.8%) were urethral stenosis ($n = 3$), urethral diverticulum ($n = 2$), urethrocutaneous fistula (UCF) ($n = 2$), and curvature ($n = 1$). Mean onset of post-UPC was 1.24 ± 0.77 years (range 0.1–6.3).

In our series, when we compared the first half of our cases ($n = 29$; final UP performed between 1999 and 2014) with the second half ($n = 29$; final UP performed between 2015 and 2017), the second half had significantly less post-UPC (0/29; 0%) than the first half (8/29; 27.6%) ($p = 0.0075$).

Representative surgical techniques

Patient 6 in Table 1

This patient was diagnosed with 46,XY DSD with SF-1 mutations, and had perineal HP associated with severe curvature, bifid scrotum, and a prostatic utricle (Fig. 1a). Initial surgery was performed at 1.5 years of age. Because of the short length of the ventral penile shaft, skin flaps were designed using the skin around the original meatus on both sides (Fig. 1b). After excision of fibrous tissue to correct curvature (Fig. 1c), straightening of the shaft was confirmed by artificial erection and the skin closed (Fig. 1d). Secondary surgery was performed at 3.8 years of age. After carefully dissecting between the original meatus and the prostatic utricle using traction assistance (Fig. 1e), UP was performed using a tubularized incised plate technique [11, 12] (Fig. 1f), and the suture lines of the neourethra were covered by a dorsal dartos subcutaneous flap as soft tissue interposition [9, 13]. The penile shaft was then covered with foreskin (Fig. 1g). Urethral stenosis was identified 6.3 years after UP and responded well to urethral bougienage without requiring surgery.

Patient 8 in Table 1

This patient was being raised as female. During a left inguinal hernia repair at 5.7 years of age, the hernia sac contents looked like a testis, but histopathology was inconclusive with neither testicular nor ovarian tissue identified. This patient was diagnosed with 46,XY DSD with testosterone insufficiency. Close liaising between the parents and a medical team comprised of a pediatric endocrinologist, child psychiatrist, and pediatric surgeon concluded that the child be raised as male due to behavior and self identification that was more masculine than feminine and masculinizing genitoplasty was planned. On gross examination, a micropenis was present (Fig. 2a), and testosterone supplementation was commenced. At initial surgery, penile curvature was corrected by chordectomy (Fig. 2b) and at 6.5 years of age, a scrotum was created on the right side using excess skin. Surgery for the left UDT was performed at 7.4 years (Fig. 2c) and right UDT at 10.3 years. Staged segmental UP [8] was performed at 11.4 and 12.1 years, respectively. At the first UP, the neourethra from the perineum to the penoscrotal junction (Fig. 2d) was created and covered entirely by subcutaneous connective tissue flaps as soft tissue interposition [9], before the skin was closed (Fig. 2e). At the second UP, the neourethra from the penoscrotal junction to the glans (Fig. 2f) was created. No post-UPC have been observed after 5.8 years of follow-up after the final UP.

In both cases, prostatic utricles were not resected because they were asymptomatic.

Discussion

While surgical intervention for proximal HP has evolved [7, 14], there is still no consensus about the best approach. The authors have previously reported several techniques for preventing post-UPC especially UCF and urethral stenosis [6, 8–10, 12]. DSD further complicates HP repair because of a spectrum of ambiguous external genitalia including micropenis, severe curvature, UDT, and prostatic utricle, that must be addressed together with the identity and behavior of the child as well as issues related to future fertility. Thus, management of HP in DSD is not purely surgical; psychosocial care provided by health care workers with expertise in DSD is mandatory to promote positive adaptation [1]. Successful management thus relies on integrated communication between the medical team and the family especially when gender assignment or reassignment is problematic and requires a case-by-case approach to plan the timing of surgery, hormone supplementation programs for each patient [1, 2].

When researching the treatment of HP in DSD cases, there were only a few reports from Brazil [4], Israel [5] and India [15]; the current series of 58 cases treated by a single surgeon is the most comprehensive and involves modifications to existing surgical strategies that would seem to be reliably successful. In the present study, the incidence of post-UPC was 13.8%, which is much lower than the rates in the series mentioned earlier [4, 5, 15, 16]. Indeed, Sircili et al. [4] reported a 50% UCF rate, and a 22% urethral stenosis rate. Chertin et al. [5] and Gupta et al. [15] both reported reoperation rates above 40%. Nevertheless, these results were not considered remarkable given the spectrum of anatomic ambiguity associated with DSD. In contrast, instead of accepting high post-UPC rates as reasonable, every effort should be made to assess each DSD thoroughly to explain the appearance of the external genitalia and determine any

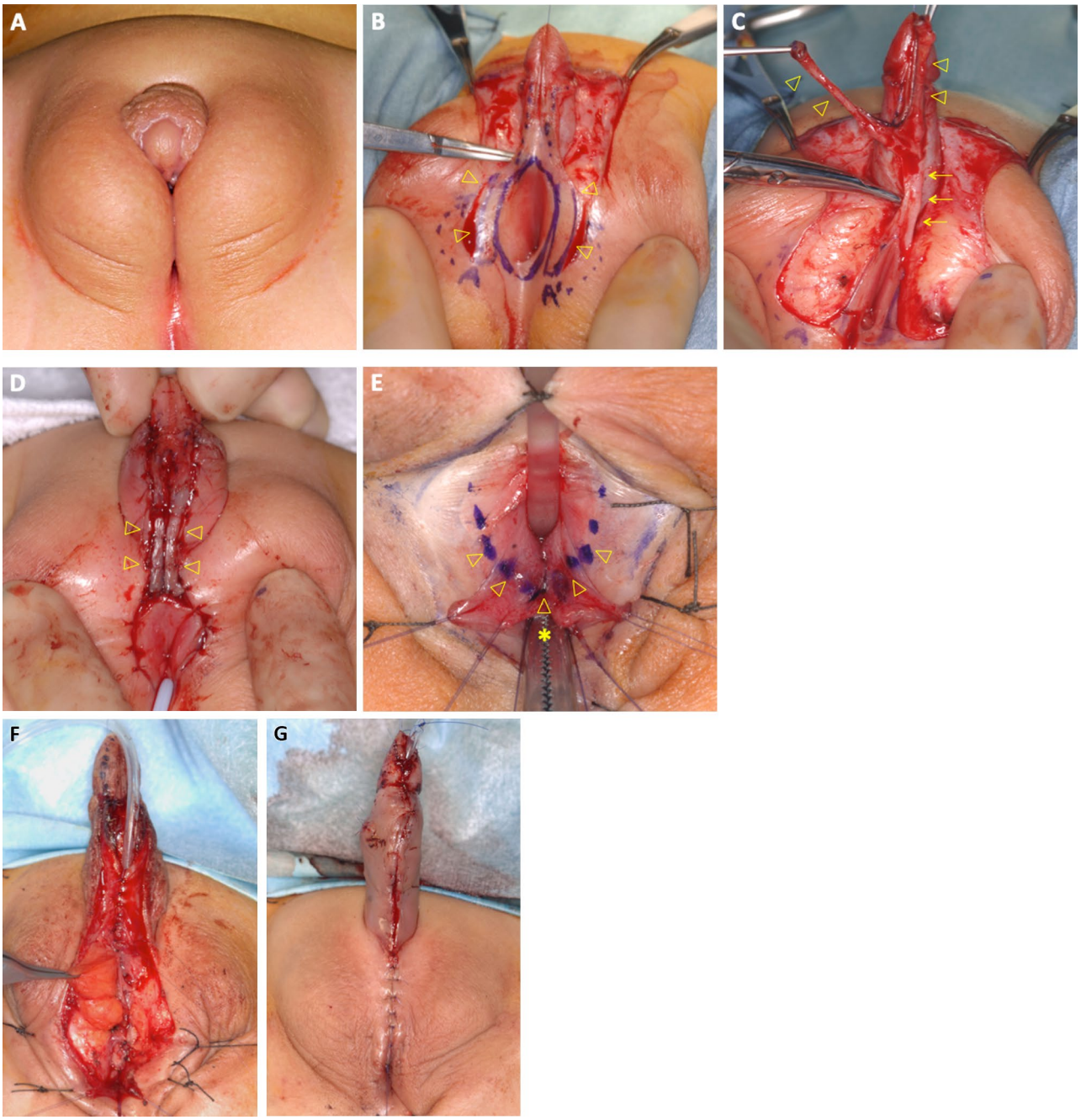

Fig. 1 Staged hypospadias repair for 46,XY DSD with SF-1 mutations. **a** Preoperative appearance. **b** Since the ventral penile shaft was short, skin flaps were created using skin from around the original meatus and the prostatic utricle (arrowheads), bilaterally. **c** Correction of curvature by excision of fibrotic tissue (arrows), skin flaps being mobilized (arrowheads). **d** Immediate postoperative appearance. The ventral penile shaft was covered by skin flaps (arrowheads). **e** Traction-assisted dissection between the original meatus (arrowheads) and the prostatic utricle (asterisks). **f** Primary urethroplasty being performed using a tubularized incised plate technique. **g** Immediate postoperative appearance

correctable causes before HP repair is commenced. DSD must be treated as a condition itself [16] and not as a collection of anatomic consequences.

For example, all patients with micropenis received hormone supplementation to increase the size of the penis prior to initial surgery in this series. Similarly, what should be done about prostatic utricles? In this series, asymptomatic cases were not resected. The natural history of prostatic utricles and the long-term outcome and complications of prostatic utricles that are left undrained are largely unknown,

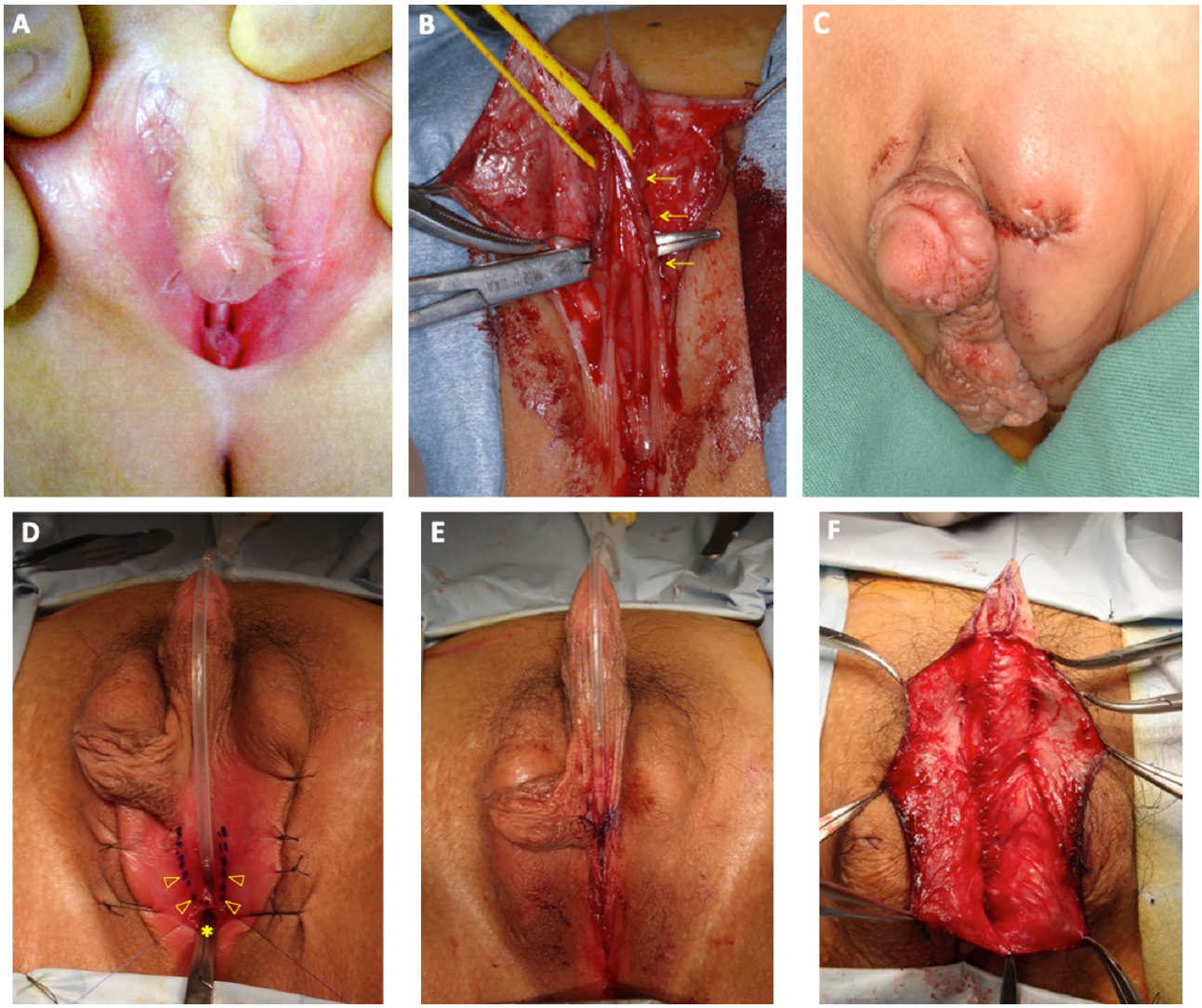

Fig. 2 Masculinizing genitoplasty for 46,XY DSD with testosterone insufficiency. **a** Initial inspection. **b** At initial surgery, penile curvature was corrected by chordectomy. Fibrotic tissue is shown (arrows). **c** Appearance after surgery for left undescended testis. **d** The neourethra being created from the perineum to the penoscrotal junction after dissection between the original meatus (arrowheads) and the prostatic utricle (asterisks) during the first UP. **e** Appearance after the first UP. **f** The neourethra being created from the penoscrotal junction to the tip of the glans during the second UP

but enlarged utricles can cause problems, but only on rare occasions [16]. Is cystoscopy warranted? Perhaps the only time when a prostatic utricle should be investigated and documented is in cases of perineal hypospadias with a prostatic utricle, because dissection must be meticulous and facilitated by traction assistance (Figs. 1e, 2d).

Because of the multifaceted nature of DSD and the need to repair HP, the surgical strategy for repair was often not finalized until the patient was anesthetized on the operating table. Choice of primary or staged HP repair including primary UP or staged segmental UP are all influenced ultimately by the tissue integrity and vascularity of the penis. UP was performed using a tubularized incised plate technique [11, 12] and the suture lines of the neourethra were covered by preputial inner dartos fascia, ventral dartos fascia, pedicled external spermatic fascia [10], pericordal/scrotal adipose tissue, or a combination of these, according to a technique for soft tissue interposition that the authors have described previously [9]. Ventral penile shaft reinforcement with pedicled fat/connective tissue to improve compromised vascular perfusion on both sides of the urethral plate was performed at the time of initial surgery [6], particularly if the urethral plate was poorly developed, or, the subcutaneous tissue of the ventral penile shaft was thin. We believe the crucial factor for preventing post-UPC is the thickness of the urethral plate.

All repairs were performed by a single surgeon over an 18-year period, and as such, there was a learning curve,

with improvement in surgical skills and strategic surgical planning over time because of increased experience of DSD resulting in significantly less incidence of post-UPC in the second half of our cases.

The timing of corrective surgery for HP in DSD cases is one of the important factors to promote positive adaptation, however, the timing of surgery remains controversial [16]. It is generally felt that surgery performed for cosmetic reasons in the first year of life relieves parental distress and improves attachment between the child and the parents, but evidence for this belief is lacking [1]. On the other hand, gender identity development is purported to begin before the age of 3 years of age [1], but the earliest age at which it can be reliably assessed remains unclear. Guidelines from the American Academy of Pediatrics recommended that an age of 6–18 months is ideal for HP repair [17]. In this series, the mean age at final UP was 4.12 ± 0.21 years which is relatively late compared with other reports. When age at final UP and post-UPC rates was compared, the mean age at final UP in cases who developed post-UPC ($n = 8$) was 4.10 ± 0.54 years (range 2.2–6.8) and in cases who did not develop post-UPC ($n = 50$) was 4.13 ± 0.23 years (range 1.9–12.1), which was not statistically significant. From experience, older age itself would not appear to influence the incidence of post-UPC; if anything, surgeons may feel more comfortable to perform HP repair in older cases. Age at the time of surgery is somewhat confusing with reports that morphological surgical results are not related to age at surgery [4], coexisting with reports that early surgery is associated with better long-term outcome [18, 19]. The deciding factor for timing should be the physical status of the patient and the psychosocial preparedness of the parents. Obviously, successful surgery for HP in DSD cases will impact on gender assignment/reassignment, so timing should aim to ensure the best possible result for each patient.

Conclusions

Surgical techniques for repairing HP in DSD cases were reviewed highlighting technical aspects and complications. There are of course functional and cosmetic issues that become more relevant as puberty approaches. Mid- to long-term follow-up will enable the actual incidence of complications to be assessed and provide insight into management problems that may need to be addressed at the time of initial surgery or at various times to achieve as normal looking and functioning external genitalia as possible despite HP and DSD.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest.

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