Original Study

Analysis of Presentations and Outcomes of Care of Children with Disorders of Sexual Development in a Nigerian Hospital

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A B S T R A C T

Study Objective: To describe the presentation, diagnosis, management, and short-term outcome of children with disorders of sexual development (DSD) in the context of multidisciplinary team care.
Design: Prospective descriptive study.
Setting: University Teaching Hospital.
Participants: All children who presented with genital ambiguity.
Interventions and Main Outcome Measures: Records of all patients diagnosed and managed for DSD between January 2011 and December 2016 were reviewed. The care pathway included clinical, laboratory, internal genitalia evaluation, and panel (including parents) meeting.
Results: Fifteen children presented with DSD at a median age of 20 months. Only 5/15 (33.3%) presented in the neonatal period. Ten of fifteen patients (66.7%) presented with genital ambiguity. Ovotesticular DSD was the most common diagnosis (9/15; 60%). Seven of the patients were genetically female (46, XX), 1 was genetically male (46, XY) and 1 without genetic diagnosis. Six patients were assigned male gender and they underwent male genitoplasty. Five of them had excision of Müllerian structures with gonadectomy. Three of fifteen patients (20%) were diagnosed as 46, XX DSD, at a median age of 7 years. All of them were due to congenital adrenal hyperplasia and underwent female genitoplasty. Two patients were diagnosed as XY, DSD. They were both raised as female at presentation and were reassigned male sex. Both had urethroplasty done. Four patients had postoperative urethrocutaneous fistula and 1 had partial wound dehiscence. The median follow-up period was 21 months (interquartile range, 2-26 months).
Conclusion: The frequency of ovotesticular DSD is high in our setting. The decision of sex assignment was finally made at a median age of 7.5 months in most of our patients with satisfactory short-term surgical outcome.
Key Words: Ambiguous genitalia, Disorders of sexual development, Genital ambiguity, Intersex, Gonadal histology, Multidisciplinary team

Introduction

Disorders of sexual development (DSD) occur when an individual's chromosomal, gonadal, or anatomical sex develops atypically.[1] Children are suspected to have DSD when their genitalia are sufficiently ambiguous and immediate sex assignment is difficult. These children pose a variety of challenges for the treating physician as well as for the family. Prevalence data for Africa are not available. Hospital-based reports suggest that 1-9 new cases of DSD are seen every year in most tertiary referral centers.[2–5]

Most of the conditions require extensive diagnostic procedures, ongoing symptomatic therapy, and psychosocial support. Specific treatments are often difficult and studies to promote evidence-based treatment strategies are hampered by the heterogeneity of the etiology, clinical presentation, small number of individuals being treated in each center, and the lack of diagnostic tools in most centers.

A delay in making gender assignment or reassignment of the wrong gender is often fraught with emotional trauma and psychosocial issues. Children born with DSD represent a diverse group of underlying disorders that need complete diagnostic evaluation in the neonatal period at facilities where physicians and surgeons are well versed in the necessary laboratory tests and reconstructive surgical techniques.

The goals of DSD treatment are to accurately and appropriately assign sex through a multidisciplinary approach.[1,6] This study aimed to describe the presentation, diagnosis, management, and short-term outcome of children with DSD in the setting of multidisciplinary care.

Materials and Methods

The prospectively collected data and records of all patients diagnosed with DSD in a Nigerian tertiary institution

The authors indicate no conflicts of interest.

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between January 2011 and December 2016 were reviewed. The DSD were classified according to the 2006 consensus statement on management of DSD.[1] The care pathway (Fig. 1) included clinical, laboratory (serum electrolytes, polymerase chain reaction/karyotype, gonadal biopsy), and internal evaluation (imaging, laparoscopy, and cystourethroscopy). Gonadal biopsy was done as part of initial diagnostic laparoscopic workup.

Information obtained included age at initial presentation, clinical manifestations (presentations, phallic length, perineal opening, palpable gonads, and appearance of external genitalia),[7] age at definitive diagnosis, and surgery. Informed consent was obtained for the surgery and this study.

Sex Assignment

The multidisciplinary panel included a pediatric surgeon, pediatric endocrinologist, neonatologist, pathologists, nurses, and gynecologist. The team met the parents to discuss the results of all the investigations and adopt an open dialogue to ensure the sex of rearing decision is made by an informed family.

Gender assignment recommendations were on the basis of many factors including etiology of DSD, gonadal histology, sexually functioning genitalia, fertility potential, and surgical options. The consequence of agreed sex of rearing and surgical procedures were extensively discussed with the parents who were encouraged to make an informed decision on the basis of the information provided to them. The multidisciplinary team maintains an open communication with families to facilitate shared decision-making. The parents were also assured of the support of the management team irrespective of their decision on sex of rearing.

Surgical Procedures

For patients assigned male sex, the procedure of genitoplasty performed included urethroplasty, penis straightening, scrotoplasty, and orchidopexy. Urethroplasty was done using a lateral-based penile flap technique as described by Hadidi.[8]

Children assigned female sex and all patients with congenital adrenal hyperplasia (CAH) had feminizing genitoplasty. The most common anatomic findings in CAH were vagina and urethra opening jointly through a common urogenital sinus into the perineum (Fig. 2A) and enlarged clitoris (Fig. 2B). Repair involved clitoroplasty and an inverted-flap type vaginoplasty. In this procedure the single perineal opening is incised posteriorly and then an inverted U-shaped flap of skin is raised and sutured to the posterior vaginal wall (Fig. 2C). Partial/total urogenital mobilization is done for patients with long common channel greater than 3 cm. Clitoral recession is done to preserve the vascular and nerve bundles. Patients with discordant gonads had gonadectomy. The vaginal opening calibration was done using appropriately sized nasogastric tubes. All patients were followed-up in the pediatric surgery outpatient clinic.

The outcome measures were definitive diagnosis, gender assignment/reassignment, time to definitive diagnosis, and surgical outcomes (including postoperative complications). Postoperative complications were graded using Clavien-Dindo grading of surgical complications.[9]

Statistical Analyses

The collected data were analyzed using descriptive statistics and presented as median values and interquartile range (IQR). Analyses were done using SPSS, version 21.0 (IBM Corp). Differences were considered significant at P less than or equal to .05.

Results

Fifteen children presented with DSD at a median age of 20 months (IQR, 21 days to 7 years). Only 5/15 (33.3%) presented in the neonatal period and 7/15 (46.7%) patients were older than 2 years at presentation (Table 1).

Ten of 15 patients (66.7%) presented with genital ambiguity and hypospadias was present in 5/15 patients (33.3%).

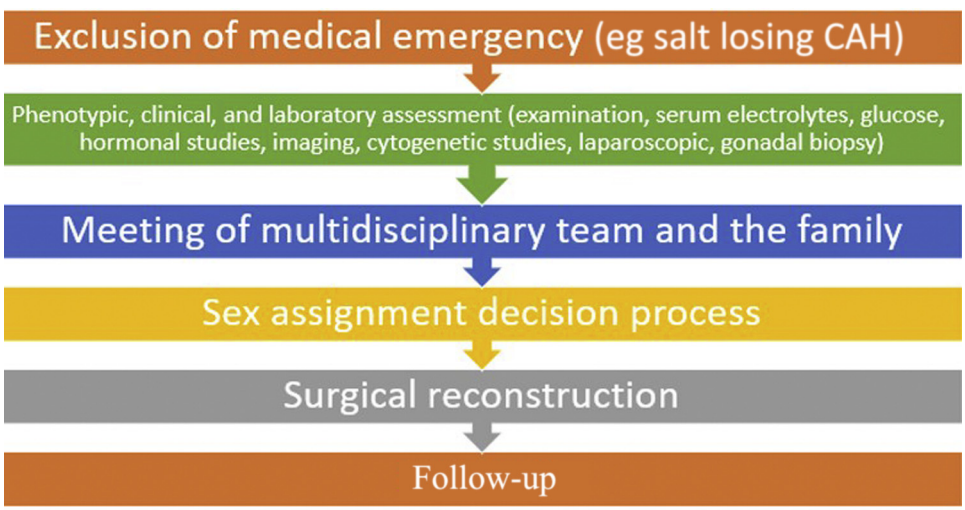

Fig. 1. Care pathway of patients with disorders of sexual development. CAH, congenital adrenal hyperplasia.

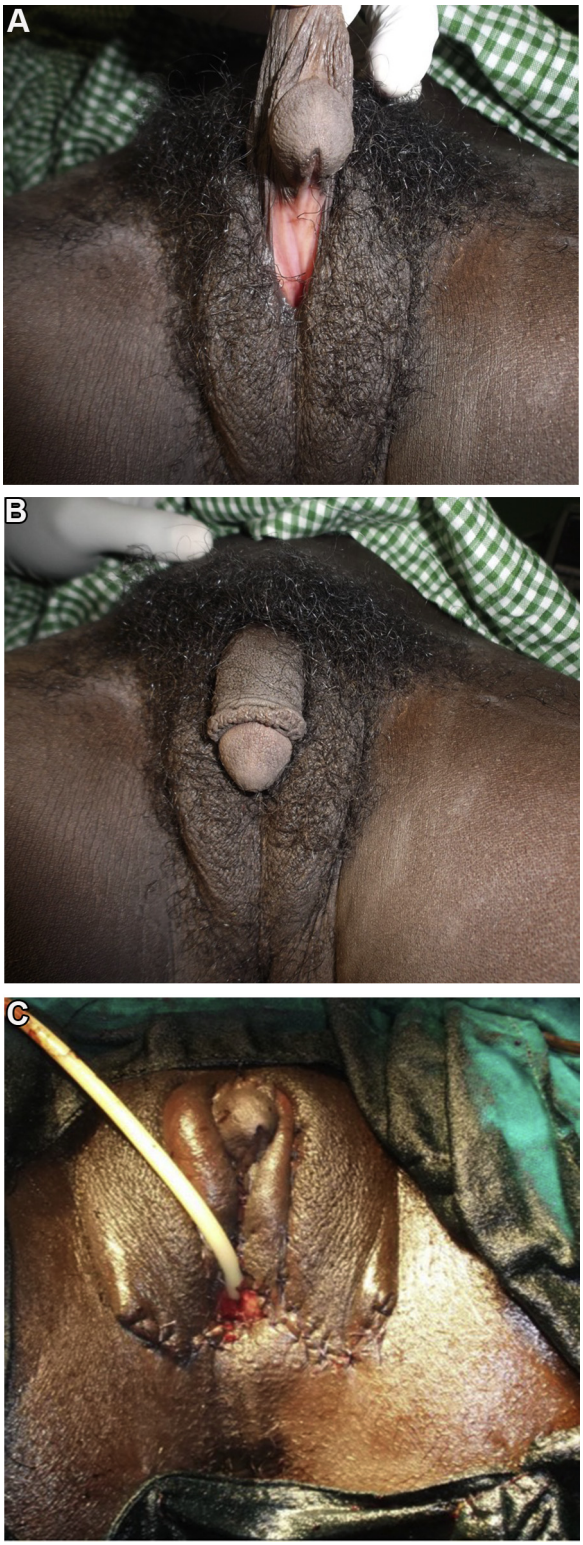

Fig. 2. An 8-year-old child with congenital adrenal hyperplasia showing (A) urogenital sinus, (B) clitoral enlargement, and (C) immediate picture after flap vaginoplasty genitoplasty and clitoral recession.

Seven of 15 patients (46.7%) had been raised as boys, 6/15 (40%) as girls, and 2/15 (13.3%) had uncertain gender identity at presentation. The demographic and clinical characteristics of the patients are shown in Table 2. The median length of the phallus at presentation was 3.5 cm (IQR, 3-5 cm).

Karyotype was 46, XX in 10 patients (66.7%), 46, XY in 3 patients (20%), and polymerase chain reaction analysis was inconclusive in 1 (6.7%). One patient did not have karyotype performed because of financial and logistical reasons. The histologic examination of gonads showed that there were 13 ovaries (9 left, 4 right), 10 testes (7 right and 3 left), and 5 ovotestes (ovotestes were seen unilaterally in 5 patients [3 right and 2 left]; Table 2).

Ovotesticular DSD (n = 9)

This was the most common diagnosis in this study, accounting for 60% (n = 9) of all cases seen. Seven of the patients were genetically female (46, XX), 1 was genetically male (46, XY), and 1 without genetic diagnosis. The age at diagnosis ranged from 2 days to 9 years (median, 4 months) and the median time to definitive diagnosis was 11 months. The median age at definitive surgery was 3.2 years (range, 1-10 years). Six patients were assigned male gender due because of presence of testis, well masculinized external genitalia, and social reasons. In 1 patient, who presented at 9 years, who was raised as male, a female gender was recommended because of the presence of an ovary and ovotestis; however, the parents declined. This patient underwent excision of Müllerian structures (uterus, bilateral gonadectomy), he had urethroplasty and testosterone injection treatment was started. Two patients were raised as girls. One of them is a 3-day-old child who presented with genital ambiguity and palpable gonad on the right (Fig. 3A). The karyotype was 46, XX; laparoscopy showed a normal uterus and ovary on the left with testis on the right (Fig. 3B). The child had flap vaginoplasty, clitoral recession, and excision of the testis. The other patient had a normal looking vagina and required a clitoral recession only. One patient is awaiting gender assignment. Seven of 9 patients had excision of 8 gonads (3 ovotestes, 3 ovaries, 1 testis, and 1 streak gonad) at a median age of 32 months (range, 13 months to 10 years; Table 2). Four patients had postoperative urethrocutaneous fistula and 1 had partial wound dehiscence. One patient raised as a girl had vaginal stenosis amenable to serial dilatation. These represent 5 Clavien-Dindo grade III and 1 grade II complication. Five patients had repair of fistula and 1 patient had repeat urethroplasty.

46, XX DSD (n = 3)

Three patients (20%) were diagnosed as 46, XX DSD, at a median age of 7 years (range, 20 months to 8 years). The 3 patients had adrenogenital syndrome due to CAH with elevated 17-α hydroxyprogesterone and 1 patient had

Table 1
Distribution of Age and Sex at Presentation

Age at Presentation	Sex of Rearing at Presentation			Total
	Male	Female	Uncertain	
Younger than 1 month	2	1	2	5
1-12 Months	1	1	0	2
13 Months to 5 years	2	2	0	4
Older than 5 years	2	2	0	4
Total	7	6	2	15

Table 2
Clinical Characteristics of Patients With DSD

Patient Number/Name	Age	Sex at Presentation	Karyotype/(PCR)	Müllerian Structure	Right Gonad	Left Gonad	Final Diagnosis	Assigned Sex	Excised Gonad(s)
Ovotesticular DSD (n = 9)									
1/OP	3 Days	Uncertain	XX	Normal	Testis	Ovary	Ovotesticular DSD	Female	Testis
2/MU	21 Days	Male	–	ND	Testis	Ovary	Ovotesticular DSD	Male	Ovary
3/EL	9 Years	Male	XX	ND	Ovotestis	Ovary	Ovotesticular DSD	Male	Ovary and ovotestis
4/OT	2 Days	Male	XX	Rudimentary	Ovary	Testis	Ovotesticular DSD	Male	Ovary
5/TK	4 Months	Male	XX	Normal	Ovotestis	Ovary	Ovotesticular DSD	Pending	Nil
6/IF	5 Years	Male	XY	Hemiuterus	Testis	Ovary	Ovotesticular DSD	Male	Pending
7/IB	3 Years	Male	XX	Absent	Testis	Ovotestis	Ovotesticular DSD	Male	Ovotestis
8/HS	8 Years	Male	XX	Absent	Streak	Ovotestis	Ovotesticular DSD	Male	Streak gonad
9/SF	4 Days	Uncertain	XX	Hemiuterus	Ovotestis	Ovary	Ovotesticular DSD	Female	Ovotestis
46, XX CAH (n = 3)									
10/KH	8 Years	Female	XX	Normal	Ovary	Ovary	46, XX DSD (CAH)	Female	Nil
11/AD	20 Months	Female	XX	Normal	Ovary	Ovary	46, XX DSD (CAH)	Female	Nil
12/AG	7 Years	Female	XX	Normal	Ovary	Ovary	46, XX DSD (CAH)	Female	Nil
46, XY DSD (n = 2)									
13/AM	30 Days	Female	XY	Absent	Testis	Testis	46, XY DSD	Male	Nil
14/HB	2 Years	Female	XY	Absent	Testis	Testis	46, XY DSD	Male	Nil
Mixed gonadal dysgenesis (n = 1)									
15/FV	2 Months	Female	Inconclusive	Rudimentary	Testis	Absent	Mixed gonadal dysgenesis	Male	Nil

CAH, congenital adrenal hyperplasia; DSD, disorders of sexual development; ND, not document; PCR, polymerase chain reaction.

hypertension probably due to 11β-hydroxylase deficiency; however, the exact enzyme deficiency and full hormonal assessment could not be done in our hospital. The genital ambiguity ranged from grade III to IV according to the Prader classification. The 3 patients required a flap vaginoplasty and clitoral recession at ages 14 months, 7 years, and 8 years, respectively. They were seen at follow-up with no complaint.

46, XY DSD (n = 2)

Two patients were diagnosed as XY, DSD. The 2 patients presented at 30 days and 2 years, respectively. They were both raised as female at presentation. Both had bilateral undescended testis and perineal hypospadias. Karyotype in each case was 46, XY. Both were reassigned male gender. One had urethroplasty at the age of 18 months and died on the third postoperative day of respiratory distress and the other child had 2-stage buccal mucosa urethroplasty at the age of 5 years. He developed partial wound dehiscence that required a repeat of urethroplasty.

Mixed Gonadal Dysgenesis (n = 1)

An 8-month-old child presented with genital ambiguity, polymerase chain reaction was inconclusive. Laparoscopy revealed a rudimentary Müllerian structure and intra-abdominal testis on the right and absent gonad on the left. The child is awaiting gender assignment.

Overall median time from presentation to definitive diagnosis was 7.50 months (IQR, 3.75-13 months). The median follow-up period was 21 months (IQR, 2-26 months).

Discussion

The assignment of gender to an infant at the time of birth is usually on the basis of an examination of the external genitalia. This process often brings considerable confusion on the part of the attending health care professionals and shame or guilt on the part of the parents when a child is born with ambiguous genitalia.[10]

It is generally agreed that the diagnosis of DSD should be promptly established after delivery and preferably before discharge so that an early sex of rearing can be assigned to an affected child and treatment can be planned.[11,12] However, early assessment is hampered by late presentation as seen in the current study where the median age at presentation was 20 months. More than half of affected children presented after 1 year of life and only 5 patients presented during the neonatal period. This finding contrasts with a report from Australia where 31 of 51 patients (60.7%) were seen during the neonatal period[12] but is somewhat similar to findings from India where Anil Kumar et al[13] reported median age at presentation of 9 years in a series of 14 patients with DSD seen over 6 years. Late presentation in low-income countries might be because of a lack of complete examination of newborn infants at birth by health care providers.

The median time to definitive diagnosis was more than 6 months in this study largely because of nonavailability of a device for cytogenetic study in our hospital necessitating collaboration with another health facility. Other reasons included delayed presentation and lack of funds to perform all of the investigations at once. Hormonal assays required for optimal care of DSD patients cannot be done in most public hospitals in Nigeria and are far more expensive in few private laboratories than our patients can afford. One of our patients with CAH had hypertension probably because of 11β-hydroxysteroid dehydrogenase deficiency. This patient did not have funds to do 17-hydroxyprogesterone and other hormonal assays to aid in establishing a definitive diagnosis.

In this study, ovotesticular DSD was the most common form of DSD, occurring in 60% of the study population. This finding is consistent with the reports from South Africa where 51% of DSD were ovotesticular.[2,14] This is in contrast to most large Western series of DSD in which CAH was documented as

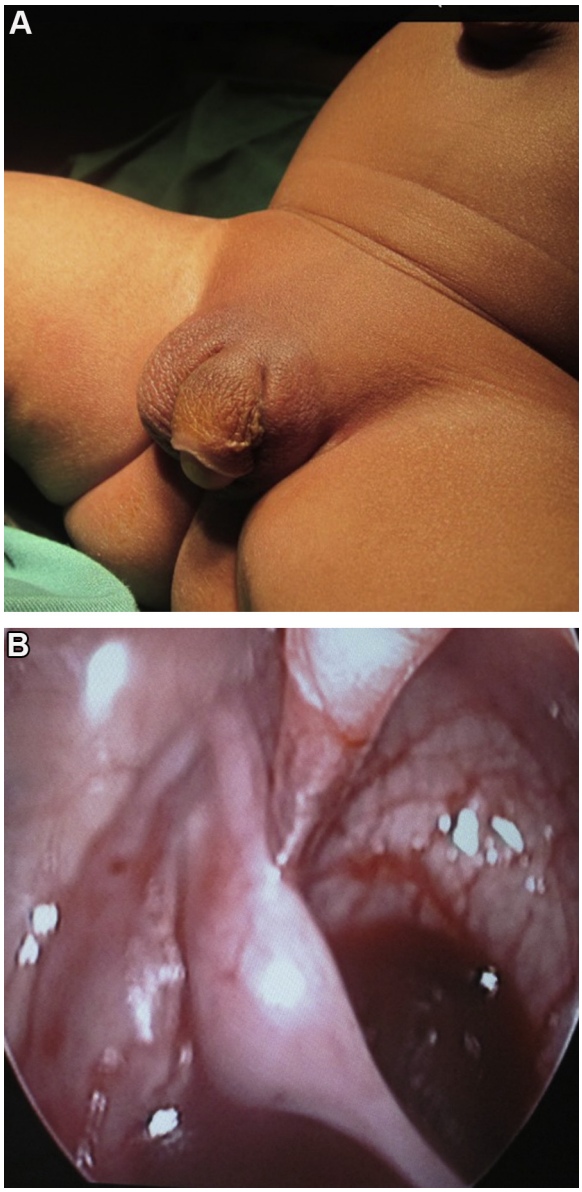

Fig. 3. Clinical picture of a 2-day-old child with ovotesticular disorder of sexual development with (A) palpable right gonads and (B) laparoscopic findings of uterus and ovary on the left, who presented with genital ambiguity.

the most common DSD[15,16] and also differs from previous studies in Nigeria.[3,4] In a review of DSD cases from 60 centers in 23 European countries, Pasterski et al[17] reported that Turner syndrome and CAH comprised 22.3% and 20.1%, respectively, of the total DSD cases. In Thailand, Turner syndrome and 21-OH deficiency CAH were also the 2 most common disorders of all DSD cases, occurring in 36.8% and 23.9% of cases, respectively.[18] Ovotesticular DSD are uncommon causes of DSD with an incidence of 7% in the literature.[18,19]

The reason for the high rate of ovotesticular DSD is not known despite considerable research regarding this condition.[14] In our experience, macroscopic inspection of a gonad cannot reliably identify the gonadal type and requires histological confirmation of the gonad. This view was supported by a report by Sowande et al in Ile Ife, who biopsied gonads of 2 of their patients at laparotomy and histology reports revealed ovotesticular tissue, which changed an initial diagnosis of CAH to ovotestis in 1 of these patients.[3] We recommend a thorough investigation of all patients with DSD by means of either exploratory laparoscopy/laparotomy to properly assess the exact nature of the internal genital system and biopsy of gonadal tissue for histological confirmation. In the present series of ovotesticular DSD, 7/9 patients (78%) were 46, XX. Five patients had to be assigned male sex, because of extreme masculinization of external genitalia, presence of testicle, and parental wish. In 1 patient, raised as male, a female gender was recommended because of the presence of an ovary and ovotestis; however, the parents refused. There was a low incidence of CAH in the study population because only 3 (20%) of our patients had CAH. This low incidence might reflect a geographic difference in the causes of DSD or might be mortality associated with missed cases of salt-wasting CAH. These variations might also be as a result of deficiencies of representative patient sampling or the effect of the new DSD classification system leading to an expanded clinical spectrum of the disease with a change in the distribution of etiological diagnoses of DSD.[13] Molecular diagnosis is made in approximately 20% of cases with DSD but limited in our setting because of cost and accessibility.[20] In our experience, laparoscopy has added value to our diagnostic armamentarium by aiding identification of internal genitalia and gonadal biopsy through a minimal access approach.

The decision-making of gender assignment is critical for optimal treatment of DSD. Ovotesticular DSD presents significant diagnostic and management challenges. Typically, Müllerian and Wolffian duct derivatives are seen in affected individuals. In this study, the decision for sex reassignment was on the basis of extensive discussion with the family, anchored on the potential for sexual function, and fertility, surgical options, and parental views all within the context of our cultural values.

We are also guided by 2 ethical considerations: one is to ensure strong alignment of various components of biological sex and also to prevent irreversible surgery, especially when the components of biological sex do not strongly align.[21] A final decision regarding surgical gonadal removal and reconstructive surgery were postponed in selected cases.

It is pertinent that the parents are counseled at the outset that the child could either be male or female. African preference of a boy might also affect the decision-making of sex assignment. The parent of a 9-year-old child who had an ovary and an ovotestis insisted that the child be assigned male gender because he was reared as phenotypic male since birth. As such, the advice and guidance of the multidisciplinary team to the family members are crucial.

We have used our multidisciplinary team approach to assign/reassign gender to 14 of 15 patients (93.3%) with no gender-related issues at a median follow-up period of 21 months. One of our patients who is still awaiting sex assignment is being followed in the outpatient clinic.

There is an ongoing debate on the ideal time for reconstructive surgery in children born with DSD. Most centers in Europe continue to offer early surgical intervention as part of a holistic treatment plan.[22–24] Some of the reasons for early surgery include the maternal estrogenic effect on

infant tissues, and reduced risk of urinary tract infections. Early surgery is also thought to be psychologically beneficial to the child because it allows for appropriate gender development and less stigma associated with DSD while also minimizing parental anxiety and allowing for better bonding. Centers in North America argue against early surgery because of poor surgical outcomes and such individuals had major reconstruction when the patient had no input in the decision-making.[22,25] Working in a largely conservative and poorly resourced African population implies that decisions on management need to reflect the importance of the family unit, the customs, and the lack of social services. Traditional values and beliefs are often strong in African cultures. African value systems typically honor and uphold the value of family autonomy over individual autonomy.[26] Equally, one needs to consider cost of care and poor long-term follow-up in our setting, because of transport and other socioeconomic factors. Because the upbringing in these communities is communal-based, an early decision on the gender of rearing is essential and assists early integration of the child into the society. Shared decision-making is an important concept to uphold in care of children with DSD. Open dialogue with parents must be adopted in the multidisciplinary group caring for DSD patients and base the need of every DSD child's management on many factors including etiology of DSD, genital anatomy, surgical options, potential for fertility (the presence of germ cells within the gonads), potential for sexual function, and cultural considerations.[27]

Open communication might help parents of young children make informed decisions that are in line with their personal and cultural values leading to greater confidence in decision-making with greater satisfaction and less regret.

The limitations of this study include a small sample size and short-term follow-up period. In conclusion, the frequency of children born with ovotesticular DSD is high in our setting and time to definitive diagnosis is delayed. The decision of sex assignment was finally made in most of our patients with satisfactory short-term outcomes.

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