REVIEW ARTICLE

DISORDERS OF SEXUAL DEVELOPMENT: UNDERSTANDING THE BASICS

Abdulkadir A.

Urology Unit, Department of Surgery, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria.

Correspondence and reprint request to: **Dr Abubakar Abdulkadir**
Department of Surgery Bayero University/Aminu Kano Teaching Hospital, Kano, PMB 3011, Kano State, Nigeria.
eMail:- aabdulkadir21@gmail.com **Phone number:-** +2348036781418

ABSTRACT

Background: The enthusiasms on 'intersex' have been with humanity since antique. Inadequacies in the management of the condition backwash in Psychosocial and medical morbidities with occasional mortality. The upsurge in the knowledge of its pathophysiology over generations has incredibly improved the management outcome. This study aims to present the fundamentals of the Pathophysiology and Management of DSD. The information provided is intended to guide in the basic evaluation and care of individuals with the disorder.

Material and Method: Search from PubMed, EMBASE and AJOL for Literature on Disorders of Sexual development was reviewed. The search words were; intersex, the disorder of sexual differentiation (DSD), Pseudohermaphroditism, Hermaphroditism and Ambiguous genitalia. The literature on the Pathophysiology and the management was appraised and summarized.

Conclusion: Genetic inquest and advances in molecular biology had provided cognizance on the pathophysiology of DSD. Patient's advocacy groups and denovo medical ethics necessitated the transformations in the approach to the management.

Keywords: Pathophysiology, management, intersex, disorder of sexual differentiation, hermaphroditism, pseudohermaphroditism, ambiguous genitalia, XX male, XY female

INTRODUCTION

Disorders of Sexual differentiation (DSD), heretofore referred to as "intersex disorders", are congenital anomalies in which the development of chromosomal, gonadal or phenotypic sex is atypical, the earliest presentations are frequently in scenarios in which the gender of the neonates is bewildering based on the appearance of the external genitalia1.[1,2]

The DSD has been of interest since ages.[3] Claudius Galenus of Pergamum (129-200 AD) presumed that fertilization of the ovum by a sperm of the left testis results in female gender and of the right result in male gender; but if the left and right blend the repercussion is Hermaphroditism. Genetic inquest and the breakthrough in molecular biology continue to give intuition on the pathophysiology of DSD; these with patient's advocacy societies and further advances in medical ethics guided to the changes in the approach of management of DSDs.[2] The changes so far included subsumption of patient-centred interventions by a multidisciplinary approach, with the purging of beguiling and often demeaning terms. The DSD persons are now globally protected from prejudice; have access to erudition and justice; and can have endorsed gender identity of their preference either 'male,' female,' 'X' or 'indeterminate'.[4,5]

In survey, the incidence of DSD in neonates was 1:5 000 births and the Predominant was CAH followed by Androgen insensitivity syndrome and mixed gonadal dysgenesis.[6] The overall incidence of

ambiguous genitalia depends on the societal defining realms notwithstanding, it is about 2/10,000 live births per year in Germany.[7]

This review aims to provide the requisites in the comprehension of the basic Pathophysiology and Management of DSD. The information provided will guide the Health caregiver in the evaluation and care of individuals with the disorder.

MATERIALS AND METHOD

Search from Pub Med, EMBASE, Google Scholar and AJOL for Articles on DSDs were studied. The latter search was on 27th February 2016. The keywords were intersex, the disorder of sexual differentiation, Pseudohermaphroditism, hermaphroditism, and ambiguous genitalia. Some of the references were reviewed to extend the search. Information from the experts on DSDs including avant-garde scripts serves as additional materials. Exclusively English language studies were incorporated and articles on the pathophysiology and management primarily selected. No restraints on the year of publication of the included pieces. Applying these criteria, seventy-seven relevant studies that provided basic comprehension of the subject were appraised and summarized.

Normal Development

The typical sexual development hinged on normal chromosomal complements and configuration. At fertilization, 46XY ordinarily developed into male and 46XX into a female. The appropriate migration of germ cells to the urogenital ridge from the yolk sac and proper hormone synthesis by the gonads in addition to apt response at the end organs (target organs) are wholly critical preconditions to normal sexual development. The deviation from any of these timely well-ordered proceedings of sexual differentiation and determination results into DSD.

At up to the 6th weeks of the embryonic life; sexual differential is in the indifferent form. From around the 7th weeks, the testicular determinants in the Y chromosome pilots the evolution of the testicular cord containing primordial seminiferous tubules and the sertoli's cell and afterward the Leydig cells development.[8,9,10] This emanates in the production of Mullerian inhibitory substance and Dihydrotestosterone respectively.[4] Hence, the development of Wolffian structures with testicular descent;[4] phallic growth and the regression of Mullerian structures seen in normal virilisation customarily completed at 12th to 16th of intrauterine life.[11,12,13] At about 7 to 8 weeks, ovarian development commences and most probably as the sequel to the effects oestrogen and other determinant leads to regression of Wolffian duct and development of Mullerian structures that established the normal feminization.[2,3,5]

NOMENCLATURE AND CLASSIFICATION

In 2006, the Lawson Wilkins Paediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) announced a proposed switch from the previously used intersex.[14,15] The switch presented the standard nomenclature displaying the genetic settings of the disorders. This fits the spectrum of phenotypic variations seen within the equivalent genetic complex; furthermore, it renders better diagnostic identification with greater precision.[3,16] The new nomenclature additionally aids correlations in research findings and oust confusions to the subject, the family and among health experts inherent to use of Intersex which is conceivably 'demeaning' to victims that can uniquely function as either man or woman.[5] Based on the switch in the nomenclature, male pseudohermaphrodite is 46XY DSD; female pseudohermaphrodite 46XX DSD, true hermaphrodites is ovotestis DSD; XX male is 46XX testicular DSD or 46XY complete gonadal dysgenesis and then the miscellaneous group as shown in Table 1.

TABLE 1: SHOWING CURRENT NOMENCLATURE GROUPS WITH AETIOLOGY[15,16]

Sex chromosome DSD	**46,XY DSD** **Disorders of testicular development**	**46,XX DSD** **Disorder of Ovarian development**
45, X Turner and variants 47, XXY Klinefelter and its variants 45, X/46XY MGD Chromosomal ovotesticular DSD	Complete or partial Gonadal dysgenesis Gonadal regression Ovotesticular DSD **Disorder of androgen synthesis/Action** Androgen synthesis defect LH receptor defect Androgen insensitivity 5α Reductase deficiency Endocrine disrupters	Ovotesticular DSD Testicular DSD Gonadal dysgenesis **CAH** 21-OH Deficiency 11-OH Deficiency Fetal androgen Excess **NON CAH** Aromatase deficiency Maternal luteoma Iatrogenic POR gene **UNCLASSIFIED/ MISCELLANEOUS GROUP** Mayer-Rokitansky-Küster-Hauser syndrome (congenital absence of uterus and vagina), Vagina atresia, Cloaca Extropy, Penile agenesis

MGD = mixed gonadal dysgenesis . POR =P450 (cytochrome) oxidoreductase

GENETICS OF DSD

The tally of genes involved in the normal sexual evolutions and in DSDs [8,9,10,17] are long and are best to survey in the medical genetics texts. Ingemination of SOX9 gene is an entrenched cause of XX sex reversal and its Haplodeficiency produces the Sex reversal in XY persons. The healthy gene is, however, mandatory for Sertoli cell differentiation which produces the Mullerian Inhibitory Substance (MIS) after the 7th week of the intrauterine life. The SFI gene has a big role in steroidogenesis, male sexual differentiation, and fertility; its mutation effects in XY sex reversal, undescended testis, and micropenis. The WT1 genes are linked to the kidney and gonad development; its deletion amidst that of PAX-6 gene is observed in WAGR syndrome, its pair splice isoforms protein have altered ratio in Frasier syndrome[18]. The WT1 mutation is similarly seen in Deny Drash syndrome.[19] The normal DAX-1 gene on the X-chromosome when duplicated silences the SRY gene leading to phenotypic female XY. [20]

THE MANAGEMENT

The neonate with DSD may present as a social[20] and medical[21] emergency necessitating an expedient but cautious approach to management. The Physician must avoid the use of gender explicit terms such as she/he; your boy/your girl; or his/her in reference to the patient at the presentation and advice the parents against gender clear-cut naming before an ample assessment for sex assignment. The indefinite gender reference such as 'your child' or 'your baby' could be used instead. The initial goal must be expeditious diagnosis and early gender assignment following adequate resuscitation where needed (as CAH – salt-losing type).

The global management of DSD often requires a multidisciplinary with input base on the need from neonatologist, clinical biochemist, Clinical geneticist, Urologist, Endocrinologist, Radiologist, clinical Psychologist, Gynaecologist, medical ethicist, Nurses, support group and importantly the patient's family.[9,16,22]

Presentation and evaluation

The findings in a child that suggests DSD are diverse and so is the time of presentation.[23] Unlike intersex in which verdict is often limited to the abnormality of external genitalia and hence often clinically apparent at birth, the spectrum of DSDs presentations stretches to the grown-ups. The hallmark of DSDs in early life includes a termed apparently male child with nonpalpable testes, severe hypospadias linked with bifid scrotum, undescended testis/testes with hypospadias and severe micropenis. In an assumed female clitoral hypertrophy and palpable gonads plus a Vulva with a lone opening suggests DSD. Other states are when genitalia appear ambiguous, Cloacal exstrophy, severe exstrophy complex, penile agenesis, scrotal transposition and conflict between genital appearance and prenatal karyotype. In grown-ups infertility, abnormal statue, amenorrhea as in Mayer-Rokitansky-Küster-Hauser syndrome and absent of pubertal development could be an initial presentation. In situations such as Turner syndrome and 46, XX ovarian dysgenesis the female external genitalia appear normal but the anomaly is chromosomal alongside gonadal and gonadal sexual development respectively. Most disorders emerging from impaired gonad hormone synthesis or inappropriate response at the end organs (target organs) are linked with genital ambiguity and are the principle classes in the old intersex definitions.[20]
The clinical appraisal should incorporate neonatal, maternal and family history. The parent commonly presents a newborn with ambiguous external genitalia or any of the aforementioned traits of DSD. Vomiting in the neonate approximately day two to four of life is discerned in classical CAH (salt-losing type). The positive history of failure to thrive, inappropriate or slowed development, breast development and cyclical low abdominal pain with or without haematuria in a presumed male may prevail. Parental consanguinity is not unusual among the DSD, chiefly in the developing countries. The family history of DSD, genital anomalies, previous neonatal mortality from severe dehydration plus primary amenorrhea or infertility in other family members should be inquired. The disclosure of maternal exposure to androgenic medications as in assisted reproductive techniques or history signifying endogenous production from tumors may be positive. History evocative of other congenital problems should be inquired as well.

The psychosexual developmental appraisal which is influenced by nature[24] and nurture[25, 26] is crucial to the overall agreeable outcome. The sexual identity is forecasted at around 3yrs,[27] gender role is expected at 6yrs[28] and in adulthood, sexual orientation should be evident.[24]

Examination

The clinical examinations must be detailed. These should incorporate the hydration status and the blood pressure that may be deranged in CAH.[29] The presence of Dysmorphic facie as found in Turners Syndrome which is the most frequent sex chromosome anomalies amid the DSDs with an incidence of 1: 2500 in live-born females.[30] Another trait that may be seen in these patients includes Campomelic dysplasia and the presence of a midline defect. In an adult body habitus, voice and body hair distribution should be noted. The Pigmentation of the external genital and the areolar area; a presence of labioscrotal fusion; the dimension and contour of the phallus, urethral plate, and meatal opening are all indispensable and should be noted. The majority of DSDs have associated hypospadias, urogenital sinus, and palpable and / or asymmetrical gonads.[31]

Assigning the designated Prader stage or score using External masculinization scoring and search for other congenital anomalies is basic in the management.

PARAMETERS FOR PRADER CLASSIFICATION[32]

Prader 1) Female external genitalia amidst clitoromegaly;
Prader 2) Clitoromegaly with incomplete labial fusion forming a funnel-shaped urogenital sinus;
Prader 3) Increased phallic size with whole labioscrotal fusion forming a urogenital sinus with a single opening;
Prader 4) complete scrotal fusion with the opening of the urogenital sinus at the base of the phallus;
Prader 5) Normal male external genitalia.

TABLE 2: EXTERNAL MASCULINIZATION SCORE [33]

	YES	**NO**	**NORMAL**	**TESTICULAR DESCENTS**		
3.0						
2.0			**GLAN**			
				SCROTAL	**SCROTAL**	**1.5**
1.0			**PENILE**	**INGUINAL**	**INGUINAL**	**1.0**
				ABDOMINAL	**ABDOMINAL**	**0.5**
0	**NO**	**YES**	**PERINEAL**	**ABSENT**	**ABSENT**	**0**
	SCROTAL FUSION	**MICRO PENIS**	**URETHRAL MEATUS**	**RIGHT GONAD**	**LEFT GONAD**	

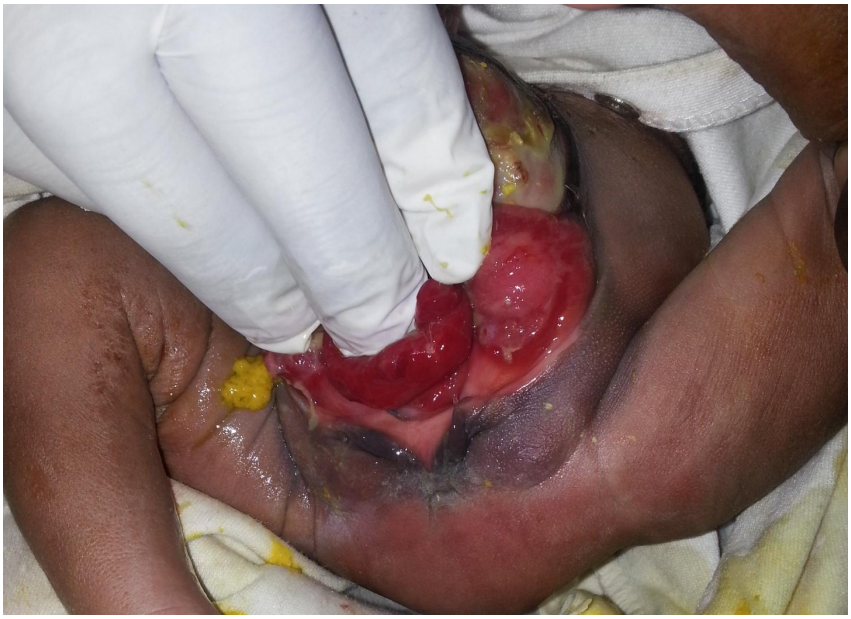

Figure 1: AMBIGUOUS EXTERNAL GENITALIA IN A NEONATE WITH THE CLOACA EXTROPY

Laboratory and imaging assessments:

The scope of laboratory assays should be dictated by the clinical findings. This customarily encompasses serum chemistry; the electrolytes, random blood glucose, Follicle stimulating hormone, Luteinizing hormone, 17-hydroxyprogesterone, Cortisol, ACTH plus anti mullerian hormone levels. Urine assay for adrenal steroid; serum testosterone to dihydrotestosterone ratio, buccal smear for the presence of bars bodies; Karyotyping with X & Y-specific probe detection may be vital. The Abdominopelvic Ultrasound is

requisite to assess for female pelvic organs. Other occasional requisites are the Genitogram and Genitoscopy, hCG stimulation test, androgen-binding analysis and Fluorescent Insitu Hybridization. Appraisal of the sensitivity to androgen sometimes guides to the require sex of rearing.[34] Identification of the androgen-receptor gene in serum DNA by PCR is effective in separating amid complete and partial androgen-receptor resistance.[35]

Examination under general anesthesia and PAN endoscopy with or without laparoscopy may be required for the definitive diagnosis and outlining the treatment. Medical photography is suitable for correlating results and as a possible medico-legal reference, however, should rather be taken during procedures whilst the patient is under general anaesthesia.

Parental and patient counselling

The appositeness of parental and patient (children and adolescent) counselling cannot be over stressed. This could be via step by step manner of increase refinement that rhythm with varying psychological and mental development.[36] The counselling should provide pandect of sexual differentiation as it pertains the patient; the diagnosis and the intended operative /no operative therapies alongside the restraints of such interventions. The patient should be convinced of his or her potentials; that he or she can be a functional part of a community and should not be embarrassed. The paucity of reliable results in the field especially as it may affect the psychosexual development may be addressed.[37] The genetic counselling could also focus on recurrence frequency especially in familial DSD, likely carrier detection, prenatal analysis and prenatal interventions for the future pregnancy. Peer support; ''someone that has been there'' leads to the perception of normalcy and promote the quality of life[1] of DSD patients.

GENDER ASSIGNMENT

The gender assignment must be as expeditious as through investigations permits to avert later gender dysphoria[24,27,28,38] popular amongst treated DSD subjects if the gender chosen is incorrect. The gender assignment banks on the verdicts of the evaluation, patient's age at presentation, the fertility prospects, and the manifestation of a functional vagina, the hormonal actions, and the malignancy chances.[39] Additional determinants are the antecedent in utero testosterone vulnerability, the overall genital features, psychosocial health and the subject's stable gender status. The forethought on the necessity for permanent replacement medications and surgical alternatives, the circumstances related to the customs and traditions are all central in the gender assignment. It is paramount that subject's and family's misgivings are respected and addressed with stringent assurance.

SURGICAL TREATMENT

The surgical treatment is individuated as prescribe by the subject's need. The triumph at reconstruction will depend on an accurate preoperative grasp of the anatomical defect; the comprehension of the pathophysiology and allegiance to the principles of reconstruction. Genital surgery for DSDS is debated in several settings.[40] The Surgical reconstruction is indicated where an inveterate outcome is affirmative with the priority at the attainment of the best possible useful outcome seconded by the cosmesis. Surgical interventions could be early at infancy or shelved to the adolescent age.

The basis for the early surgery includes the invaluable effects of oestrogen only on female infants on ousting unnecessary androgen from the testis. Early surgery averts intricacies from anatomical anomalies such as the communication of urinary tract with the peritoneal cavity. The proclivity to early surgery is to lessen family worries, mitigates the risks of stigmatization and the dilemma of gender identity. Some studies suggested early interventions are better-adjusted psychologically[41, 42] and further reconstruction refined at the time of puberty if need be.[43] The early surgery may be conducted in patients with high confluent urogenital tracts, females (46 XX with CAH) with severely masculinized genitalia and males with under virilized external genitals. Early surgery, however, does not guarantee optimal long-term anatomical, cosmetic and functional outcome later in life.[44,45]

The merit of the delayed surgery embodies patient

can give an informed consent. Following the delay Sexual identity and role become better spell out and hence limited sexual dysphoria in adult life. Furthermore, surgeries that modify appearance are often not urgent. The inimical outcomes of unnecessary surgery at an early age are also avoided. It's urged that vaginoplasty should be deferred until puberty in DSDs with mild forms of masculization.[46, 47]

FEMINIZING GENITOPLASTY

As for the feminizing genitoplasty; clitoroplasty may be sole indicated. Historically this was by clitoridectomy[48] and clitoral recession [49]but the pair are linked with high prevalence of psychosexual morbidity. The more recent subtotal resection of the shaft with reservation of the Glans and neurovascular bundle in the form of Ventral reduction clitoroplasty minimized the psychosexual dysfunction and the abnormal sensation in the clitoris. The snag of subtotal resection includes occasional clitoral atrophy with unusual prominent glans clitoris.[50]

with respect to vaginoplasty, indications comprises MRKH syndrome, vaginal agenesis (CAIS) or severe vaginal hypoplasia. The upshot of these procedure influences the quality of life of the subjects. It is of preeminent concern the anatomical location of the vaginal opening in the urogenital sinus either high or low in its relationship to the pelvic floor and external sphincter. The preeminent goal is the creation of an acceptable neovagina in the perineum with healthy looking wet introitus fully isolated from the urethral orifice. The neovagina should possess an adequate caliber that will enable penovaginal intercourse and be pleasing cosmetically. There is no model of vaginoplasty that gives a flawless substitute to the natural vagina. Frank's procedure entails sequential dilation of a vagina remnant or perineal dimple although hardly practice now notwithstanding the published successes.[51,52] The vaginoplasty may, however, necessitate total urogenital sinus mobilization and reconstruction; or use of tissue replacement by Flap, graft or both. The procedures described include the old Williams vulvovaginoplasty now out-dated;[53] open or Laparoscopic Vecchietti[54,55] and Davydov.[56] Others modes are Abbe–McIndoe–Reed technique that employs the Split skin graft,[57] the modified Mcindoe which utilizes Scalp,[58] human amnion,[59] buccal mucosa and Silicone membrane with the inclusion of recombinant fibroblast growth factor to promote epithelisation.[60] Intestinal models of replacement comprising the use of jejunum,[61] Ileum or Colon were reported although sigmoid[62,63] is promoted among the intestinal segments. The application of flaps from Perineal Pedicles, e.g. pudendal thigh flap,[64] gracilis,[65] and labia minora flap[66] were all depicted other flaps are the Singapore[67] and Malaga[68] flaps. All of these procedures have their snag that may necessitate extra interventions.

MASCULINIZATION GENITOPLASTY

For the individual masculinization genitoplasty, the foremost objective is the attainment of sufficient painless erection that facilitates competent penetration during sexual intercourse in the subject through orthoplasty, urethroplasty, and glanuloplasty of a perineal hypospadias. The abscission of unsuitable Mullerian structures and remodeling of the scrotum in scrotal transposition may be mandatory. In dysgenetic gonads, the peril of malignant transformation is substantial hence gonadectomy is justified especially when the genetic analysis revealed very high risk.[69] Judicious usage of testosterone supplementation will be required as the corrective therapy in severe primary hypogonadism.[70,71,72]Subcutaneous mastectomy will be indicated in subjects with associated gynaecomastia.

Phallic creation through the use of free innervated radial forearm flaps,[73] Rectus abdominis myocutaneous flaps or tubed abdominal flap[74] with the incorporation of the prosthesis may be required in very severe micropenis and penile agenesis. The whole reconstruction should be in line with the sexual identity and orientation to lessened rates of sexual dysphoria. With the headway in tissue engineering and technology, better suited phallic reconstruction will soon be within range.

PRENATAL AND NEONATAL INTERVENTIONS OF CAH

CAH is the most prevalent in 46, XX DSD group, and is the most common cause of ambiguous genitalia amongst the DSDs. Its global incidence is 1:14 000 live births and it's an aftermath of mutation

of a Steroidogenic enzyme gene resulting in faulty cortisol synthesis that can run in families. The most common CAH is the 21-hydroxylase deficiency (98%)[75]. Prenatal diagnosis and intervention after screening at risk are not widely adopted. For the very high-risk pregnancy; although still avant-garde because of the obscure long-term risks; the mother receives Dexamethasone on confirmation of the pregnancy.[76] At 16th weeks, Karyotyping plus mutational analysis for CYP21A2 are done to confirm the presence of CAH and the necessity for maintaining Dexamethasone remedy.

The neonate with CAH is started on Glucocorticoid replacement to suppress ACTH and modify the metabolic abnormalities. Hydrocortisone with a mineralocorticoid (in the salt-losing form) such as 9α-fludrocortisone including salt is given. Hormonal induction for pubertal maturation with psychosocial support may be needed for further psychosexual maturity.

Additional challenges that may require intervention are sexual dysfunctions, infertility, accompanying lesions such as renal and other congenital problems if present. Transsexualism is more common in DSD managed not in concordance with their natural sexuality. Follow up in DSD patients may be for life.

SOCIO-CULTURAL PECULIARITIES OF MANAGEMENT OF DSD IN NIGERIA

In Nigeria, there is no public data on the national prevalence nor on other epidemiological indices regarding DSDs; and the research on the pathophysiology and management of the disorder remain scanty. There is no grounded neonatal screening programme as is the case in some of the advanced world and hence, the presentation is oftentimes delayed especially for chromosomal and gonadal sexual disorders. There are notably very few designated centers with resources, diagnostic facilities, and combined super specialist team for the management of the disorder. The socio-cultural prejudice for the masculine gender, the myths encompassing DSDs and the societal reproach occasionally undermines appropriates gender assignment following delayed presentation when the outcome of the evaluation is feminine. The effects of Poverty, illiteracy and ineptitudes in insurance coverage among the populace alongside limited access to the few centers with the facilities. Female infertility may preclude marriage, may also affect employment prospects and hence creates economic dependency. Religious and philosophical viewpoints can determine how parents respond to the birth of a newborn with this condition. Guilt perceptions amidst DSDs parent may have an impact while poverty and ignorance all negatively affect access to care. Hence, the quality of life of DSDs subjects is often impaired as obtained in most of the other developing countries.[77]

CONCLUSION

While no particular management strategy is absolute for every DSD subjects. The physicians and health caregivers require the basic understanding of pathophysiology and the multiple interventions to ensure pleasant clinicopsychosexual outcome; with guaranteed patient and parental satisfaction. Identifying and improving on prevailing concepts and techniques will move us closer to an ideal intervention.

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