Review Article

Disorders of Sex Development: Can You Be Sure This Baby Is A Boy or Girl? We Must See Beyond The Diagnosis

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Throughout the pregnancy, the parents have anticipated whether their child will be a boy or a girl. No part of a newborn baby's anatomy arouses as much interest initially as the external genitalia. Most newborn children have the typical features of a boy or girl, but in some cases the baby's sex can't be clearly identified. Infants born with ambiguous or abnormal genitalia may have indeterminate phenotypic sex.[1] Disorders of sex development (DSDs), formerly termed intersex conditions, are congenital conditions in which development of the chromosomal, gonadal, or anatomic sex is atypical and may affect up to 1:1000 individuals in the population.[2]

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These situations are a serious concern for the family, the first physician examining the child, and may confound difficulties later for the affected person themselves.We must see beyond the diagnosis, the anatomic variations, and see the individual. Indeed, DSD is unique among the conditions that we treat as pediatric urologists – the inferences of our care are rational.[3]

The purpose of these reviews is to assist health care professionals in the provision of diagnosis, treatment, education, and support to children born with disorders of sex development (DSDs) and to their families.

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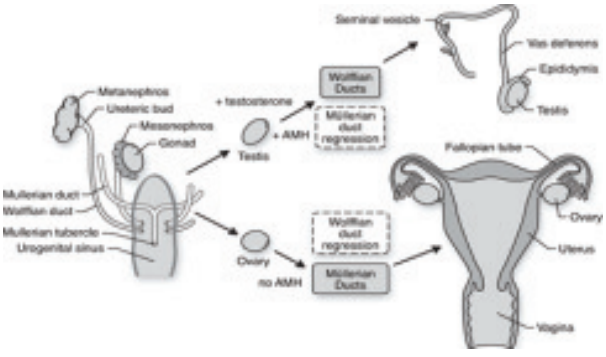
Embryology of sexual differentiation:

Expression of a gene on the Y chromosome initiates a genetic cascade that causes the undifferentiated gonad to develop as a testis.[4] In turn, hormones secreted by the testis cause the Wolffian ducts to differentiate as seminal vesicles, vas deferens, and epididymis and cause the Mullerian ducts to regress.[5] In the absence of a Y chromosome and expression of this gene, a testis does not develop , the Wolffian ducts regress, and the Mullerian ducts develop as fallopian tubes, uterus, and upper third of the vagina.[6]



The new classification has arisen because of advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management and ethical issues.[7]Controversial and disapproving terminology, e.g. 'pseudohermaphroditism' and 'hermaphroditism', have been renamed according to

the new pathophysiological insights. Furthermore, some conditions presenting with severe male genital malformation, such as penile agenesis, cloacalexstrophy, which could not be categorized, have also been included. Classification based on gonadal status:a) Over-androgenized female (ovary + ovary), b) Under-androgenized male (testis + testis), c)True hermaphrodite (ovary + testis), d) Mixed gonadal dysgenesis (testis + streak), e)Pure gonadal dysgenesis (streak + streak).[8]The term 'disorders of sex development' (DSD) is currently classified into four main groups[9]:

1) The46,XX DSD(over-virilized genetic female)

Most common form of intersex, Karyotype = 46 XX, TDF gene not present, Ovarian tissue only, Normal female internal genitalia.External genitalia isvirilized, and presenting with an overdeveloped genital tubercle (clitoris), no vaginal connection to the perineum and enlarged and merged genital folds.

It is depends on potency of androgen, time of exposure, duration of exposure.

Congenital adrenal hyperplasia:

Congenital adrenal hyperplasia (also known as CAH) - comprises majority of cases. A condition that causes excessive androgen production, which causes excessive virilization. It is most problematic in genetic females, where severe virilization can result in her having vaginal agenesis (absence of vagina) and a functional penis which is capable of penetrative intercourse. Females with this condition are usually fertile, with the ability to become pregnant and give birth. The salt-wasting variety of this condition is fatal in infants if left untreated.

Most common inheritance pattern in CAH is autosomal recessive. Enzymatic deficiency results in reduced production of glucocorticoids. Lack of feedback inhibition on hypothalamus and pituitary, which causes increase ACTH production, increase adrenal androgen release. The following things may occur:

A) Androgen excess Fetal (e.g. 21 hydroxylase deficiency, 11 hydroxylase deficiency, and glucocorticoid receptor mutations). 21-hydroxylase deficiency most common, 50% of patients "salt losers" death at 7-10 days post-natally (adrenal crisis).Fetoplacental (aromatase deficiency, oxidoreductase deficiency-POR) Maternal (luteoma, Androgenic drugs, etc.)

B) Disorders of ovarian development 1. Testicular DSD (e.g. SRYs,, dup SOX9, RSP01) 2.Ovotesticular DSD Gonadal dysgenesis.

C) Other (e.g. cloacalextrophy, vaginal atresia, MURCS, labial adhesions, other syndromes)

Müllerian agenesis (also known as MRKH or Vaginal Agenesis) –

A condition that causes the uterus and other reproductive organs in a 46,XX female to be small or absent, as well as the vaginal canal itself. It affects 1 out of 4,500 to 5,000 females and can also come with skeletal or endocrine system issues at conception.

2)The 46,XY DSD (under-virilized genetic male)

Patients are genetically male (Karyotype = 46 XY), Testicular tissue onlyand constitute a more heterogeneous group representing a spectrum from normal appearing females to males with hypospadias and infertility.

These patients may have underdevelopment of the genital tubercle (hypospadias and/or micropenis) with or without undescended gonads, with or without feminine remnants (mullerian structures). Within this group are patients with dysfunctional gonads (gonadal dysgenesis), impaired steroidogenesis (17 beta hydroxysteroid dehydrogenase deficit…), dysfunctional central hormonal control, and dysfunctional target tissues (androgen insensitivity; 5 alpha reductase deficiency).

Testicular feminization (complete AI)**,** it is phenotypically normal female with a short vagina**.**Presentationmay beprimary amenorrhea**,** testes found in inguinal hernias in female**.**

The following things could occur:

A) Disorders of testicular development 1. Complete or partial gonadal dysgenesis (e.g. SRY, SOX9, SFI, WT1, DHH, etc.) 2. Testis regression Ovotesticular DSD.

B) Disorders in androgen synthesis/action Androgen biosynthesis defect (e.g. 17-hydoxysteroid dehydrogenase deficiency, 5a reductase deficiency, StAR mutations)**,** Defect in androgen action (e.g. CAIS, PAIS, drugs)**,** LH receptor defects (e.g. Leydig cell Aplasia, hypoplasia)**,** Disorders of AMH and receptor (Persistent Mullerian Duct Syndrome)**.** InIncomplete insensitivity**,** phenotype can run the gamuttheymight develoed clitoromegaly, partial fusion of labio-scrotal folds, short blind ending vagina**.**

C) Other (e.g. cloacal exstrophy, severe hypospadias)

The **chromosomal abnormalities** or mosaicisms are mostly represented by the 46XY/45XO mosaic individuals (mixed gonadal dysgenesis).

3) **Mixed Gonadal Dysgenesis** is second most common cause of intersex. Unilateral testis with dysgenetic (streak) gonad contralaterally.Testis has Sertoli and Leydig cells but no germinal elements. there is risk of risk of

gonadoblastoma. Internal genitalia variable due to ±MIS. External genitalia could be hypospadias, partial labioscrotal fusion, and undescended testes.

4) **Ovo-testicular DSD** (True Hermaphroditism) is the rarest group (10% of intersex). The karyotype might 60-70% 46XX and remainder 46XY or a mosaic that is characterized by presence of ovarian and testicular tissue.

These two last groups (3 and 4) of patients bear both female and male genetic and anatomic elements. They typically have asymmetric genitalia with one side more masculine and the other side more feminine. The gonads can be testis, ovary or both, or dysgenetic gonads with a high risk for gonadal tumour development later in life.

Other Genetic Abnormalities:

Pure Gonadal Dysgenesis:

(Also known as Swyer Syndrome or XY gonadal dysgenesis) is a type of hypogonadism in a person whose karyotype is 46XY. They have bilateral dysgenetic (streak) gonads, present as females with sexual infantilism where left untreated, will not experience puberty. Immature Müllerian structures are present due to low levels of fetal MIS. Such gonads are typically surgically removed (as they have a significant risk of developing tumors) and a typical medical treatment would include hormone replacement therapy with female hormones.

Klinefelter's syndrome:

(Also known as 47, XXY and XXY syndrome) - A condition that describes a male born with at least one extra female chromosome. Though the most common variation is 47, XXY, a man may also be 48, XXXY or 49, XXXXY. It is a common occurrence, affecting 1 in 500 to 1,000 men. While some men may have no issues related to the syndrome, some may experience impaired sexual maturation, gynecomastia, and azoospermia, micropenis, cognitive difficulties, hypogonadism, reduced fertility/infertility, and/or little or no facial hair. Testosterone therapy may be pursued by men who desire a more masculine appearance and those with gynecomastia may opt to undergo a reduction mammoplasty. Men who wish to father children may be able to do so with the help of IVF.

XX Sex reversal: Rare phenotypic males with 46XX karyotypeoften have hypospadias and gynecomastia**.** Usually fragments of Y chromosome short arm found in distal short arm of X chromosome.

Turner's syndrome:

Characteristic phenotype 45 XO.

Also known as Ullrich-Turner syndrome and gonadal dysgenesis - A condition that describes a female born without a female chromosome or with an abnormal female chromosome, making her karotype 45, XO. It occurs in 1 in 2,000 to 5,000 females. Turner syndrome causes numerous health and development problems, including but not limited to short stature, lymphedema, infertility, webbed neck, coarctation of the aorta, ADHD, amenorrhoea, and obesity.

What are the possible consequences of these situations?

Atypically developed genitalia can affect not only physical appearance and body image, but also function of the urinary tract, kidneys, gonads, and the psychological and psychosexual development of the individual. Therapeutic management of these patients is, therefore, not limited to "cosmetic" surgery as stated in some reports but has a direct impact on:

1. Assignment of gender in rare and complex conditions.
2. Poor penile development and its consequences on sexuality in the adult male.
3. Connection of the genital cavities to the perineum which may lead to fluid retention early in life and dysmenorrhoea and sexual dysfunction later.
4. Enlargement of the clitoris which can alter body image and be associated with painful erections in the female.
5. Fertility in both males and females.
6. The risk of gonadal cancers early and later in life.
7. The risk of urological symptoms such as incontinence and the development of urinary tract infection.
8. Development of an individual's gender identity and gender role, a multifactorial process in which anatomical appearance likely plays a role.

Practical decisions in management

If the baby's genitalia are abnormal, such that the gender is in doubt, it is a crisis. Three aspects are important in the management of infants with a DSD causing ambiguous genitalia are: 1) The specific diagnosis, 2) The sex of rearing, 3) The explanation and counseling given to the parents. Referral to a regional centre with expertise in managing DSD is essential to ensure optimal anatomical and functional outcomes.

Diagnostic evaluation

The first step is to recognise the possibility of DSD (Table 1) and to refer the newborn baby immediately to atertiary pediatriccentre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. At the paediatriccentre, the situation should be explained to the parents fully and kindly. Registering and namingthe newborn should be delayed as long as necessary.

Table 1

Findings in a newborn suggesting the possibility of DSD

Apparent male
Severe hypospadias associated with bifid scrotum
Undescended testis/testes with hypospadias
Bilateral non-palpable testes in a full-term apparently male infant
Apparent female
Clitoral hypertrophy of any degree, non-palpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

Family history and clinical examination:

A careful family history must be taken followed by a thorough clinical examination (Table II).

Table-II

History and Physical examination of neonates with DSD

History (family, maternal, neonatal)
Parental consanguinity
Previous DSD or genital anomalies
Previous neonatal deaths
Primary amenorrhoea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhoea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure

Clinical examination

A thorough clinical examination in a neonate presenting with DSD is important. As well as a accurate description of the DSD, some detailed information should be given on palpability andlocalisation of the gonads. Information gathered by the various examinations described below should help theteam to come to a final diagnosis.If it is possible to feel a gonad that is Palpable gonad, it is almost certainly a testis; this clinical finding thereforevirtually excludes 46XXDSD.[10]

Medical photography can be useful but requires sensitivity and consent.

The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of thestretched phallus allows for a good measurement of phallic length.The opening of the urogenital sinus must be well evaluated. Is there only one openingvisible? Can a hymenal ring be seen? What does the fusion of the labioscrotal folds look like; do the folds showrugae or some discolouration?

Investigations:

Ultrasound can help to describe the palpated gonads or to detect non-palpable gonads. However, the sensitivity and specificity is not high. On ultrasound the Mullerian structure can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utriculur structure visible? [11]

Table-III

Investigations for DSD

Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH
Urine: adrenal steroids
Karyotype
Ultrasound
Genitogram
hCG stimulation test
Androgen-binding studies
Endoscopy
Laparoscopy

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; hCG = human chorionicgonadotrophin; LH = luteinising hormone; TST = testosterone.

Genitography can provide some more information on the urogenital sinus. How low or how high is the confluence? Is there any duplication of the vagina? How does the urethra relate to the vagina?

On **cystoscopy**, the urogenital sinus can be evaluated and the level of confluence between the bladder neck and the bladder. Cystoscopy can also be used to evaluate the vagina or utriculus, e.g. the presence of a cervix at

the top of the vagina can be important information.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Mullerian structure. If indicated, Laparoscopic gonadal biopsy, gonadopexy, and gonadectomy can be performed successfully, even in patients with germ cell tumors.[12]

Gender assignment (Sex of rearing):

This is a very complicated task. It should take place after a definitive diagnosis has been made. The idea thatan individual is sex-neutral at birth and that rearing determines

gender development is no longer the standardapproach. Instead, gender assignment decisions should be based upon:age at presentation, fertility potential, size of penis, presence of a functional vagina, endocrine function, malignancy potential, antenatal testosterone exposure, general appearance, psychosocial well-being and a stable gender identity, sociocultural aspect, parental opinions etc.[13]Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits. Minimal time needed is 48 hrs. During this period any referral to gender should be avoided, better to address the patient as "the child", "your child".

Role of the pediatric urologist

The role of the pediatric urologist can be divided into a diagnostic role and a therapeutic role (Table 4). Each of these roles will be discussed briefly.

Table-IV

Role of the pediatric urologist

Diagnostic role
Clinical examination
Ultrasound
Genitography
Cystoscopy
Diagnostic laparoscopy
Therapeutic role
Masculinizing surgery
Feminizing surgery
Gonadectomy.

Disease management:

It is clear that the timing of surgery is much more controversial than it used to be.Timing of surgery will be dependent on the severity of the condition and on the assigned sex.The rationale for early surgery contains that in severe anomalies in girls early surgical treatment is indicated. In less severe cases, in consultation with the parents, a more conservative approach might be followed. In boys the surgical correction will mainly consist of hypospadias repair and orchiopexy, so the timing will follow the recommendations for hypospadias repair and orchiopexy (from 6 months onwards and before 2 years of age).[14.15]

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Early surgery should be reserved for those patients with high confluent urogenital tracts, girls with severely masculinised genitalia and boys with undervirilised genitals. Vaginoplasty should be delayed until puberty and milder forms of

masculinisation should not be treated surgically. Recently ESPU and SPU have taken a position in the debate on surgery for DSD.[16]

Feminising surgery

Clitororeduction. Reduction of an enlarged clitoris should be done with preservation of the neurovascular bundle. Clitoral surgery has been reported to have an adverse outcome on sexual function and should therefore

be limited to severely enlarged clitorises. Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown.

Separation of the vagina and the urethra is preserved for high confluence anomalies. Many techniques for urogenital sinus repair have been described, but their outcome has not been evaluated prospectively.[17]

Vaginoplasty should be performed during the teenage years.[18] Every technique (self-dilatation, skin or bowel substitution) has its specific advantages and disadvantages [686]. All carry a potential for scarring that would require further surgery before sexual function was possible.

The goals of genital surgery are to augment anatomy to allow sexual function and romantic partnering. Aesthetics improvements are important in this perspective. The reconstruction of minor labiae from an enlarged clitoral hood is an example of aesthetic refinement.

Masculinising surgery

Hormone therapy early in life is advocated by many doctors. The level of evidence is low for restoration of normal penile size.Hypospadias surgery. Excision of Mullerian structures excised. There is no evidence on whether utricular cysts need to be excised.

Orchiopexy: Laparoscopic gonadal biopsy, gonadectomy, and Orchidopexy can be performed successfully.

Phalloplasty. The increasing experience of phalloplasty in the treatment of female to male transsexual patients has led to reports about the reliability and feasibility of this technique. It has therefore become available to treatsevere penile inadequacy in DSD patients.

Discussion:

Disorders of sex development (DSDs) may arise from genetic defects in testis or ovary determination.[19]Proper gender assignment to a neonate born with DSD is a social emergency of the newborn period.It is seen that 'gender

panic', social and religious concepts affect the decision-making process in gender assignment, especially in delayed cases.[20]Current observes will provide a baseline overview, answering the questions, "where are we now, and what do we have to work with?"

What does DSD surgery entail?

Aims of surgery

1. Reduce urological hazards related to abnormal genito-urinary anatomy, that is urinary tract infections, with potential upper urinary tract consequences and urinary incontinence,
2. Restore functional genital anatomy to allow future penetrative intercourse (as a male or a female),
3. Facilitate future reproduction (as a male or a female) when possible,
4. Avoid fluid or blood retention in vaginal or uterine cavities,
5. Avoid late virilization at puberty in individuals raised as girls or breast development in individuals raised as boys,
6. Reduce the risk of gonadal cancers, Foster development of "individual" and "social identities,"
7. Avoid stigmatization related to atypical anatomy,
8. To respond to the parents' desire to bring up a child in the best possible conditions.

Perineoplasty and reconstruction of the genital tubercle are parts of the techniques mentioned above and play an important role in the patient's satisfaction or dissatisfaction after DSD surgery.Pippi Salle et al (2007) describe a new technique, corporeal sparing dismembered clitoroplasty in 8 patients with clitoral enlargement. Five girls had congenital adrenal hyperplasia (Prader IV and V in 4 and 1, respectively), 1 had ovotesticular disorder of sexual differentiation and 2 had partial androgen insensitivity syndrome. The initial cosmetic result was good in all girls. The hemicorpora were easily palpated inside their labia majora pouches, which retained the desired cosmetic appearance following feminizing genitoplasty. All glans clitoris were preserved. The teenaged patient does not report painful erections. She has maintained clitoral sensation and is satisfied with the cosmetic result.[21]

Complete absence of genital tract requires the creation of a new vagina using various techniques (intestine, peritoneum, buccal mucosa, etc.).[22, 23]Nowier A et al (2012) assess the use of sigmoid colon in vaginal reconstruction of 31 patients with disorders of sex development, which included mullerian aplasia (16 cases), androgen insensitivity syndrome (12 cases) and previous failed vaginoplasty (3 cases). Associated surgical procedures were gonadectomy in 5 cases and gonadectomy combined with clitoroplasty and vulvoplasty in 7 cases. No intra-operative or early postoperative complications occurred. A cosmetic neovagina with adequate size was achieved in all cases. Long term follow up showed introital stenosis in 4 cases (12.9 %). Two of them responded to vaginal dilatation. The third one needed y-v plasty while the fourth one presented by acute abdomen secondary to ruptured vagina and was submitted to urgent laparotomy. Mucosal prolapse occurred in 1 case (3.2%). Reoperation rate was 9.6%. Sexual satisfaction was achieved among 9 sexually active cases. The subjective satisfaction score of the surgical outcome was 8.03.[24]

Atta I et al (2014) described A total of 187 patients met the criteria of XY DSD. Age ranged from 1 month to 15 years, 55 (29.4%) presented in infancy, 104 (55.6%) between 1 and 10 years and 28 (15%) older than 10 years. Twenty five (13.4%) were raised as female and 162 as (86.6%) male. The main complaints were ambiguous genitalia, unilateral cryptorchidism, bilateral cryptorchidism, micropenis, delayed puberty, hypospadias, female like genitalia with gonads, inguinal mass. The karyotype was 46 XY in 183 (97.9%), 46 XX in 2 (1.1%), 47 XXY in 1 (0.5%), 45 X/46 XY in 1 (0.5%) patient. HCG stimulation test showed low testosterone response in 43 (23 %), high testosterone response in 62 (33.2%), partial testosterone response in 32 (17.1%) and normal testosterone response in 50 (26.7%). Genitogram was carried out in 86 (45.98%) patients.[25]

The Mullerian remnants are an issue in the male assigned patients with symptoms, that is dysuria, urinary tract infections, cyclic pain, stone formation, etc. In these cases removing the Mullerian pouch can be performed either laparoscopically or with open surgery. In most cases, Mullerian remnants are asymptomatic. Cancers of the Mullerian remnants have been rarely reported.[26] When the vaginal cavity is high located, separation from the posterior wall of the urethra can be achieved either by laparoscopy or with the anterior sagittal transrectal approach (ASTRA).[27]

Christine Burgmeier et al (2016) reported 12 patients undergoing 14 laparoscopic procedures. In seven children, laparoscopic gonadectomy was necessary. Histopathologic examination revealed germ cell tumors in four children. In two patients, a gonadoblastoma was identified; in two patients, a dysgerminoma was found. Inguinal exploration was performed in four patients and led to removal of gonadal remnants in one case and gonadopexy in three cases. In two patients presenting

with repeated urinary tract infections, laparoscopic removal of anutriculus was performed.[28]

Wang LC et al (2017) has performed a literature search on PubMed of publications addressing CAH and genital reconstruction published in the English language from 1990 to the present. In accordance with their institutional review board, they performed a retrospective analysis of clitoroplasty and/or vaginoplasty procedures performed by a single surgeon at their institution from 1996 to 2015. They found that genital reconstruction in 46, XX CAH patients is associated with few immediate post-operative, infectious, and urinary complications. Vaginal stenosis is a common complication of vaginal reconstruction. Clitoral pain or decreased sensation can be associated with clitoral recession and clitorectomy. Outcomes in sexual satisfaction and gender identity can also be impacted by surgical technique and success.[29]

Conclusion:

Disorders of sex development are a challenging and complicated situation, but when understood can often be dealt with effectively. Evaluation and management of this patients group must be organized as quickly as possible. The immediate interventions should be done timely and in an accurate manner. The gender assignment is decided according to the definitive diagnosis, fertility potential, genital appearance, surgical options, and the parents' opinion.In babies with 'hypospadias' and undescended testes and/or

bifid scrotum, full investigation for DSD is required. There are many thinkable medical, social, and psychological ramifications. Therefore, disorders of sex development (DSDs) require a careful evaluation and management should be performed in a center with a multidisciplinary team,[30] comprised of pediatric specialists in surgery, typically in pediatric urology, endocrinology, neonatology, nursing, psychology, genetics, and medical ethics.Better long-term outcome studies are needed to evaluate the effectiveness of distinctive methods of treatment.[31]

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