Surgery in disorders of sex development (DSD) with a gender issue: If (why), when, and how?

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Summary
Ten years after the consensus meeting on disorders of sex development (DSD), genital surgery continues to raise questions and criticisms concerning its indications, its technical aspects, timing and evaluation. This standpoint details each distinct situation and its possible management in 5 main groups of DSD patients with atypical genitalia: the 46,XX DSD group (congenital adrenal hyperplasia); the heterogeneous 46,XY DSD group (gonadal dysgenesis, disorders of steroidogenesis, target tissues impairments ...); gonosomic mosaicism (45.X/46,XY patients); ovo-testicular DSD; and "non-hormonal/non chromosomal" DSD. Questions are summarized for each DSD group with the support of literature and the feedback of several world experts.

Given the complexity and heterogeneity of presentation there is no consensus regarding the indications, the timing, the procedure nor the evaluation of outcome of DSD surgery. There are, however, some issues on which most experts would agree: 1) The need for identifying centres of expertise with a multidisciplinary approach; 2) A conservative management of the gonads in complete androgen insensitivity syndrome at least until puberty although some studies expressed concerns about the heightened tumour risk in this group; 3) To avoid vaginal dilatation in children after surgical reconstruction; 4) To keep asymptomatic mullerian remnants during childhood; 5) To remove confirmed streak gonads when Y material is present; 6) It is likely that 46,XY cloacal extrophy, aphaillia and severe micropenis would do best raised as male.
Introduction

Ten years after the Chicago consensus meeting [1], genital surgery continues to raise questions and criticisms concerning its indications, its timing, and its technical aspects [2,3]. Opinions are more common than facts as the volume of patients in each group of disorders of sex development (DSD) is small, management is extraordinarily heterogeneous across centers, and pre- and post-treatment evaluations are mostly subjective, examiner-dependent, and culturally influenced. Hence, the classical methodology of evidence-based medicine meets major hurdles, which are responsible for several unanswered questions that we attempt to list in this standpoint article.

The first major hurdle is the definition of the acronym DSD. Does it include all congenital developmental genito-sexual anomalies, and, if so, are undescended testicles, hypospadias, or even labial adhesions included? Or should the definition be limited to situations in which there is an inadequacy between genital anatomy (phenotype) and biological profile (biotype), which may raise questions about gender assignment? This restrictive definition of DSD does not identify genital anomalies with no detectable biological or chromosomal anomalies, which represent the vast majority of patients.

The second hurdle is semantic as the terms “gender,” “sex,” “sexual,” have discordant interpretations. “Gender” is a social concept, which is the way the society mirrors the “individual identity.” It does not take into account the “individual identity” (“inside identity”) and the future “gender role” (“behavioral identity”), which are invisible at birth and the modalities of which are mostly unknown, that is multifactorial [4]. The term “genital” has been avoided in the Chicago meeting, although atypical genito-sexual development should be the main focus of this discussion.

Hence, it is essential to correlate phenotype and biotype as atypical anatomy is the first clinical sign from which suspicion of a DSD is raised in the newborn and will lead to a chain of investigations to define to which group of DSD the patient belongs.

Who are we talking about? What difficulties are met in the management of each of the following DSD groups?

Using the Chicago canvas [5], five main groups of DSD patients may be identified, submitted to the gender assignment process, and may be considered for a surgical genital reconstruction.

(1) In the 46,XX DSD group, classical congenital adrenal hyperplasia (CAH) represents the most common diagnosis. There is usually no gender issue in this group, except in case of late diagnosis and severely masculinized 46,XX individuals. Genital phenotype of prenatally non-treated 46,XX CAH patients at birth includes an increased development of the genital tubercle (GT) along with an increased length of the urethra, the opening of which is usually located on the ventrum of the GT, although in the most severely masculinized cases it may constitute a normal-looking phallus [6]. These features are similar to those of a 46,XY hypospadiac GT with non-palpable testes.

(2) The 46,XY DSD group is more heterogeneous, mostly including: abnormal androgen steroidogenesis, particularly 17β-hydroxy steroid dehydrogenase (17β HSD) deficiency; and 5α reductase deficiency, which is more common in some areas in the world in which consanguinity is frequent (e.g. the Dominican Republic, New Guinea, and the Gaza strip). In these two first groups, the phenotype is often feminine at birth but will become virilized at puberty. The testicles are often palpable in the inguinal region. There are no mullerian structures as the AMH function remains intact. Internal genital organs are male.

These are two situations for which controversies exist regarding gender assignment, sex of rearing, and surgery [10]. One critical issue is the fate of the testicles: Should they be kept in place until the hypothetical age of self-gender determination? Or if female sex rearing is decided on, should they be removed early to avoid pubertal virilization? If conservative management is chosen, temporarily blocking pubertal virilization with a GnRH analog until gender-identity development is settled is an option.

The risk of gonadal tumor is small and probably equals the risk recorded with undescended testes.

Gonadal dysplasia or dysgenesis is characterized by failed production of androgens and AMH responsible for a poorly developed genital tubercle (usually severe...
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(3) There are multiple variants of sex-chromosome mosaicism. The most common situation for which gender assignment and surgery are discussed is mixed gonadal dysgenesis or 45,X/46,XY DSD [18]. Although many of these patients have a normal male phenotype, those seen by the surgeons commonly present with asymmetrical genitilia: On one side a scrotum containing a gonad (commonly on the right side for unexplained reasons), on the other side a labia majora with a gonad not palpable in the genital fold, poorly palpable in the groin, or often non-palpable at all. This gonad is usually undifferentiated or a streak gonad, that is composed of stromal tissue without tubules or follicles. The intrascrotal gonad is either a sub-normal testis or a gonad containing testicular tissue, the rule being that any gonad palpable in the genital folds is either a testis or a mixture of testicular and ovarian tissues. The genital tubercle is severely hypospadiac with a perineal division of the corpus spongiosum, that is with significant ventral curvature. There is a mullerian cavity located at the level of the veru montanum behind the proximal urethra and opened into it. This cavity is often tubular, narrow, and rigid, quite different from the vaginal cavity seen in CAH. This situation raises the question of gender assignment, timing of surgery, and the fate of the gonads, as dysplastic gonads bear a significant risk of tumor.

(4) Ovo-testicular DSD patients presents with both ovarian and testicular tissues and abnormally differentiated genital structures. Their great variability raises difficult questions regarding gender assignment and genital reconstruction.

(5) The "non-hormonal/non chromosomal DSD" are mainly represented by anomalies of the caudal extremity mostly found in cloacal extrophy patients or in aphallia, or in some severe micropenis. It is a failure of tubulization and cavitation of the caudal end of the body with a non-closure of the bladder, exposed abdominal organs in an unclosed pelvic ring [19]. Genitalia are considerably abnormal with a variable separation of the erectile structures. Internal organs, although often normal, may be duplicated. Gonads are usually normal but the genital tracts in the male are dysfunctional because of the abnormal anatomy of the posterior urethra and prostatic region. The genital tubercle is poorly developed and stretched by the separation of the two hemi-pelvises. Gender assignment and surgical reconstruction are difficult issues in this group.

What does DSD surgery entail?

Aims of surgery

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

The genital tubercle

The genital tubercle (clitoris and glans) can either be left intact or reduced in size in a female assigned patient or refashioned in a male assigned patient.

Clitoral reduction consists of reducing the length of the genital tubercle while striving to preserve the nerves and vessels leading to the clitoris. A more precise description of the anatomy of these nerves in the late 1990s allows a much finer dissection of the afferent fibers leading to the glans/clitoris [20,21]. The same nerve preservation applies for the reconstruction of the epispadiac penis [22]. Most techniques of clitoral reduction remove a variable segment of the corpora cavernosa. As this is an irreversible step of the procedure, some surgeons attempted to preserve the full length of each corpora and bury them around the vaginal opening with the idea that they could be reused in the future should the patient later choose the male gender [23]. However, such a reversion has not been reported to date.

Once the corpora cavernosa have been removed or displaced, the clitoris is reattached to the corporeal stumps near the lower edge of the pelvis. The skin shaft of the genital tubercle is split vertically to refashion the labia minora.

This is clearly delicate surgery. The potential damage to clitoral sensitivity and the irreversible character of this procedure are the two main criticisms made, although significant strides improving the surgery have been made. This is why clitoral reduction should be restricted to the significantly enlarged clitoris, knowing that in the CAH group, well conducted substitutive hormonal treatment permits a significant reduction in size. Attempts to avoid this surgery with prenatal hormonal substitution (dexamethasone) in the CAH group have been successfully reported as long as the treatment starts before week 6 of gestation, although potential side effects of steroids on the fetus and the mother during gestation are a source of discussion [24–26].

For reconstruction of the genital tubercle in the male, surgery is based on the principles of hypospadias surgery, which involves three main steps [27]:

(1) Degloving of the genital tubercle to assess the severity of the hypospadias based on the level of division of the corpus spongiosum, the degree of hypoplasia of the ventral tissues and the subsequent ventral curvature, the position of the urethral meatus, the length of urethra to be reconstructed, the size of the genital tubercle, the size and shape of the glans, and the availability of foreskin tissue.

(2) Refashioning of the missing urethra (urethroplasty) based on several different techniques, which can be divided into techniques solely using ventral tissues (Thiersch-Duplay, TIP, Mathieu), those combining ventral and dorsal tissues (Onlay, Duckett, Koyanagi-Hayashi) those using free grafts (i.e. buccal mucosa), those displacing the urethra (Beck-Koff), and two-stage procedures (Cloutier-Bracka) [28,29]. Ventral curvature of the genital tubercle is commonly assessed in proximal hypospadias and can either be corrected by dorsal plication of the corpora cavernosa or by ventral grafting [28,30].

(3) Refashioning the penile skin shaft.

This surgery is also difficult and complications are commonly reported, which can be divided into unsatisfactory cosmetic results, urethral healing failures (fistula, dehiscence), urine flow impairments (stenosis, urethroecele), persistent penile curvature, and ejaculation and erection disorders. Most patients will receive more than one procedure and long-term follow-up is mandatory [31].

Phalloplasty is an option primarily in the post-pubertal patient who chooses a male gender. Some would discuss this surgery earlier in life [32]. It is a highly specialized surgery with a significant morbidity, and should be confined to some centers specialized in trans-sexual surgery [32–34].

The vaginal cavity

It is important to understand what happens during embryogenesis and more specifically during the delimitation process which divides and separates the cloacal cavity into three compartments — urological, genital, and intestinal — which will be individually connected to the outside with a proper opening and sphincter. This cavitation and separation process fails in most DSD situations described before. The vagina which represents the mid compartment is said to come from two different embryonic structures: Mullerian ducts for its cephalad two-thirds and ectoderm for its caudal third [17]. In the CAH group, the upper two-thirds need to be connected to the pelvic floor and separated from the urological compartment, incorrectly called uro-genital sinus. In the 45.X/46.XY DSD group, the retro-urethral cavity is narrower and more rigid than in the CAH group. When the female gender is chosen, this cavity also needs to be connected to the pelvic floor and separated from the urological path. In all other DSD groups, there is either no genital cavity (17)HSD), that is no mullerian structures or a vaginal "cupule", which probably represents the lower third of the vagina. Complete absence of genital tract requires the creation of a new vagina using various techniques (intestine, peritoneum, buccal mucosa, etc.). The presence of a reasonable genital dimple can be subjected to progressive dilatations allowing the creation of a full length neo-vagina [35]. Current surgical techniques to
connect the vagina to the pelvic floor and to separate it from the urethra are based on two types of procedures, which can be combined: The “top-down” approach (total or partial uro-genital sinus mobilization: TUM or PUM [36]) consists of mobilizing downwards the urethral conduit up to the confluence with the vagina and connecting both independently on the perineal surface using the urethral tissue sitting distal to the confluence. The “down-top” approach [29] consists of creating a mucosal funnel (introitoplasty) between the perineal floor and the vaginal cavity using the urethral tissues sitting under the GT. When the vaginal cavity is high located, separation from the posterior wall of the urethra can be achieved either by laparoscopy [37] or with the anterior sagittal transrectal approach (ASTRA) [38].

Gonads

The gonads are an issue when the assigned gender is different from the gonadal sex mostly in the 46,XY DSD group, the 45,X/46,XY DSD group, and the ovo-testicular group, and when there is a risk of tumor related to the testicular tissue.

Gonad (testis) can either be partially or totally removed, or brought down (orchidopexy), or simply monitored with regular clinical examination, ultrasound scans, or biopsies.

Gonadal preservation in the prepubertal testis, although possible, has not yet been proven to assure future fertility.

Tumor risk is very low before puberty, although recent reports showed that gonadoblastomas have been identified early in life. This risk is particularly significant in dysplastic gonads and in any case in all undescended testes.

The role of testes after puberty in bone maturation and breast development in complete androgen insensitivity syndrome is well acknowledged, and the tumor risk may be low in this group, although probably equal to that of undescended testes.

The timing of gonadal removal is, therefore, a critical issue particularly in the DSD groups where pubertal virilization is expected [17].

Mullerian remnants

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 [17]. Cancers of the Mullerian remnants have been rarely reported [39].

The external genitalia

Although DSD surgery has been restrictively considered by some to be “cosmetic surgery,” the cosmetic aspect of genitalia and the related stigma risk are also important issues for many patients. 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.

Breasts

Breasts can either be removed (bilateral mastectomy), or enhanced (hormones, prosthesis) at or after puberty.

The context of decision

Before birth: When there is an index case in the family, especially CAH, targeting fetuses at risk has been considerably improved with early detection of fetal DNA (SRY) in maternal serum at 4–5 weeks of gestation, followed by chorionic villus sampling at 10 WG to possibly treat with dexamethasone affected 46,XX CAH fetuses. This option aims at diminishing fetal virilization [25,40].

In other cases, discrepancies between prenatal ultrasound findings and fetal karyotype may raise the question of a DSD. Ultrasound imaging of the genital tubercle is good enough to suspect a hypospadiac genital tubercle in some cases, especially when the fetal urethral stream is visualized. Medical interruption of gestation in isolated genital anomalies is not considered in most centers.

At birth: This is the most common situation. Legislation varies from one country to another but in many countries, it is allowed to delay any child’s gender registration until the medical situation is clarified. In some countries, the “no-gender” registration is allowed (decisions of various tribunals in Europe).

The indicators available in the neonatal period for gender assignment can be divided into four categories:

1. The biological and genetic profiles (“internal sex”) of the child.
2. The anatomy of the genitalia (“external sex”) which is of paramount importance in all births and will alert midwives, doctors and parents. It is essentially based on the size of the genital tubercle, the presence of palpable gonads and a vaginal opening.
3. The expected potential ability for sexual intercourse and reproduction as a male or a female (“functional sex”).
4. The cultural medium of education of the family (“social sex”).

This neonatal situation is paradoxical as a gender assignment is decided without consulting the individual himself or herself. The subtle identities of the newborn (individual sex identity and behavioral identity) are not visible in the early phases of life. The only identity that can be defined is the “social identity”, that is how the “society” mirrors the individual. This social visibility or gender assignment is recommended by most [6,41,42] to make the child socially visible. This attitude is, however, questioned by some. The central concern expressed by several is the irreversibility of the medical and surgical decisions [38–40,43,44].

During childhood and adolescence: The diagnosis of DSD is made in a child raised as a girl for whom testicles are found at the time of surgery for bilateral inguinal hernias; or in an adolescent with primary amenorrhea or absent development of breasts or virilization; or breast development in an adolescent raised as a boy. In these situations
seen in older patients, the patient’s participation in any decision is more obvious.

Where do we stand in 2015 with these very distinct situations?

To attempt to answer this question, a detailed questionnaire reviewing the most difficult clinical situations was sent to several world DSD experts.

The 46,XX DSD group (CAH)

Assignment decisions: Although most 46,XX CAH are declared and raised as females, some question this decision at birth in case of severely virilized genitalia [45]. Experience of 46,XX CAH raised as males is limited to situations in which the diagnosis was late, in countries in which DSD investigations are not well developed. Most 46,XX CAH raised as girls have no gender dysphoria [46–48]. In developed countries, choosing the male gender for a severely virilized 46,XX CAH as suggested by some, minimizes the place of fertility in the decision process. When the diagnosis is late, some suggest offering the option to raise the child as a boy, postpone surgery, and suppress puberty until a choice is made by the individual [45]. If necessary, cryopreservation of ovarian tissue should be discussed. Most 46,XX CAH raised male (usually with more marked degrees of genital masculinization) do not develop gender dysphoria. The cultural environment of the child is of utmost importance in the decision process.

Nature of treatment: If the female gender is chosen, several treatment options can be discussed: Vaginal connection to the perineum (whatever technique used) associated with clitoral reduction; clitoral reduction without vaginal surgery; no or delayed surgery knowing that an adjusted hormonal substitution may help to reduce the size of the clitoris after a few months of treatment. The first option has the merit to reconstruct in a one-stage procedure a nearly normal female anatomy making full usage of all genital and urological tissues. Experience shows that surgical revision of the vaginal introitus is common at puberty [49] with techniques used 20 or more years ago, which have since been abandoned. The second option is a limited procedure avoiding vaginal surgery, which is thought to be unnecessary by some during childhood, although clitoral reduction does discard urethral tissue, which is found useful to connect the vagina to the perineum and create a mucosal introitus. Most techniques used to reduce the length of the genital tubercle discard the joint segment of the corpora cavernosa down to their insertion on the pelvis. The Pippi Salle technique [23] preserves the corpora cavernosa and wraps them deep around the vaginal orifice arguing that this can be beneficial for the future sexual life and can give a theoretical possibility to refashion a penis if the individual chooses so, although long-term results are lacking. The first two options are at risk of damaging the clitoral nerves, that is sensitivity, although current techniques are likely to better preserve the multiple nerve fibers leading to the clitoris. Baskin demonstrated the nerve anatomy of the genital tubercle and therefore changed the surgical approach of the nerve dissection [20,21,50,51]. Series reported in literature are quite heterogeneous and not comparable. Some report very negative outcomes of the sexual life of CAH women [49,52–54] with techniques used 20 or more years ago, which have since entirely changed and were performed by surgeons with sporadic cases for feminizing genitoplasty. Keeping the genital tubercle intact is recommended if it is not too big (<2 cm) [26], although enhanced clitoris is a common cause of consultation in CAH girls with untouched clitoris. It may cause painful erections and may be visible in bathing suits. Another major criticism against these two options is the irreversibility of these procedures. Therefore, the third option (no or delayed surgery) is therefore favored by some because the patient herself is involved in the decision process, although there is not yet any published support for this option. Some stated that cosmetic results do not differ between early and late surgery [55], and girls who received flap vaginoplasties prepubertally experienced more complications than those who received these procedures postpubertally [40]. This raises further technical hurdles, however: Pubertal or post-pubertal surgery has a much greater risk of morbidity compared with surgery earlier in childhood. Blood loss and infection are more common in adult genital surgery. Very few surgeons have experience with late feminization. Onset of menstruation does limit the timing of surgery. There is no consensus regarding the technique used for feminization [3,26,56].

Timing of treatment: The choice is, therefore, between early or late surgery knowing that the onset of menstruation and future sexual life imply a vaginal connection to the perineum before puberty starts. Several cohorts of adult patients who underwent a feminization procedure at various ages have recently been interviewed in different French hospitals and all claimed that early surgery is highly preferable to late surgery [57,58]. Late surgery can have a better accompanying process, allowing the individual to participate in the decision process. It may also reduce the risk of a second procedure to enlarge the vaginal introitus as the patient complies with post-operative vaginal dilatations if necessary. When asked retrospectively when feminizing surgery should occur, more women with CAH responded that surgery should occur early compared with later in development [59,60]. Women with DSD because of CAH who received genitoplasty reported higher satisfaction with their care than those who did not receive early genital surgery [61]. Girls who received early genital surgery have a good or satisfactory cosmetic outcome, as assessed by healthcare providers, good quality of life, and a low incidence of gender dysphoria as reported by their parents [62,63]. It remains unclear how much harm non-corrected unusual genitalia may cause for an individual and the family. The psychological impact of late genital surgery is also likely to be more significant than in early life. There is no evidence showing which timing of surgery is better [24,52,60] [3,26,56,64].

46,XY DSD group

It is in the 46,XY DSD group that the most complex and controversial situations are found:
**DSD with initial female phenotype and subsequent pubertal virilization (17βHSD and 5α reductase deficits).** Assignment decision: For decades, most patients were feminized because of the female aspect of genitalia at birth and because it was and still is considered that creating a vaginal cavity is technically easier and more successful than creating a penis [65,66]. Gonads were removed early. Since molecular diagnosis became available and with a much better understanding of these situations, the current trend is to keep patients bearing Y material in the male gender with their gonads [67]. If the diagnosis is made late in a prepubertal child so far brought up as a female, the testes can either be removed or puberty blocked until the individual’s gender identity has consolidated.

Nature of treatment: If the individual is raised as a female, a vaginoplasty should be considered at or soon after puberty. Vaginal dilations of a vaginal dimple when it exists or vaginal substitution are the two options. Self-dilatations in a pubertal or post-pubertal individual are recommended after vaginoplasty before starting intercourse. The main issue in this group is the fate of the testes. If retained with no additional hormonal blockade, the individual will become virilized at puberty. The current trend is to keep these gonads in situ until the individual’s gender has consolidated. The risks of gonadal tumor in this group are likely equivalent to those of undescended testes, although some reported a higher risk [10,11]. However, tumor stage might be increased if the undescended testes are non-palpable and tumor growth unrecognized. When the male gender is chosen, hormonal stimulation (testosterone or dihydrotestosterone) should start early in life to make the genital tubercle grow. This treatment needs to be restricted in duration to avoid unwanted effects and its long-term results on the development of the genital tubercle are unpredictable [68].

Timing of treatment: Delayed surgery is recommended by most for the gonads and the vagina in girls with pubertal blockade as well as estrogen therapy until gender is confirmed. Androgen stimulation should start early after birth in boys [68].

Uncertainties: It remains unclear at what age and by which criteria gender identity in DSD patients can be considered firmly established. Here again, the magnitude, the morbidity, and psychological impact of late surgery is likely to be higher than early surgery.

**Partial androgen insensitivity syndrome (PAIS).** Assignment decision: Historically, many of these patients underwent feminizing reconstruction [67]. The current trend is to assign the male gender in patients bearing Y material except in case of complete androgen insensitivity or possibly in nearly complete AIS [16]. Depending on the molecular profile of PAIS, response to androgen treatment is variable. Dysphoria seems to be more common in individuals raised as girls (20%) compared with those raised as boys (7%) [47], but most PAIS develop a gender identity commensurate with gender assignment [69].

Nature and age of treatment: When the individual is raised as a male, hormonally and surgically the usual steps of severe hypospadias repair are followed [70]. The age of hypospadias surgery depends on the response to androgen stimulation. The testes should be brought down usually early in life for most and regularly examined considering the risks of tumor in undescended testes mostly at an adult age [11]. In all cases, clinical examination, ultrasound scans, and biological screenings (tumor markers) are recommended to follow-up the preserved gonads. When the female option is decided, some suggest a gonadectomy at the same time as feminization surgery considering the high risk of gonadal cancer (15%) [11,69,71].

Uncertainties: Unsatisfactory outcome in terms of genital reconstruction and quality of sexual life is common in this group [72].

**Complete androgen insensitivity syndrome (CAIS).** Gender assignment is not an issue [73]. Most individuals present with a normal female genital phenotype with no vagina or a vaginal dimple.

How should the gonads be managed? A common attitude is to keep the gonads in place until puberty as the androgens produced by the testes are converted into estrogens with the action of aromatase, although efficacy studies of female development are lacking [13,74,75]. Questions have been raised [11,13] regarding an increased tumor risk, which until recently was considered just similar to undescended testes. MRI has not proven efficient for monitoring the testes that remain undescended [74].

**The child with bilateral dysplastic gonads with a severe hypospadias, undescended testes and a Mullerian cavity.** The situation in terms of decisions and dilemmas is quite similar to PAIS individuals except that hormonal stimulation to make the genital tubercle grow is more efficient, because androgen receptors are normal. The presence of mullerian structures may cause symptoms especially at puberty. There is some consensus that persistent mullerian structures do not require early surgery and may be kept as long as no symptoms related to them (dysuria, infections, calculi) are noticed. Removing these structures has its own morbidity with a high risk of damaging the genital ducts in individuals who already have a very low fertility potential. Regular examination of the gonads is essential as the tumor risk is significant in this group (30%) [11].

**The mosaic DSD group**

Assignment decision: This is probably one of the most complex situations as no decision can be fully satisfactory. For decades, these individuals have undergone feminizing reconstruction with poor or at least highly variable results. The current trend [18] is to keep DSD individuals with Y material in the male gender despite the unlikelihood of fertility and uncertain surgical outcome. However, the combination of male and female structures, the potential short height at adulthood (45, X/46, XY), the most likely low fertility and the uncertainties about the future individual identity make the decision process extremely difficult for the multidisciplinary team and the parents [76]. If a feminine gender is considered, delaying irreversible surgery until individual sexual identity is established is recommended. Family dynamics and sensitivity play an essential role in the decision process. Assessment of family coping skills and support systems are essential.

Nature of treatment: For males, hypospadias surgery after androgen stimulation follows the usual steps of complex reconstruction of the genital tubercle. A unilateral...
intra-abdominal streak gonad should be removed considering the significant tumor risks and the lack of function [11,77]. Attitudes regarding gonadal biopsies are variable [78] and meet the same considerations as mentioned above [18]. The scrotal gonad (testis) needs a careful follow-up as it is dysplastic and presents with high tumor risks [11,71]. The female remnants (hemi-uterus), utricular cavity can be kept in situ until puberty as long as they remain asymptomatic. Individuals raised as female require feminizing surgery with the same options to be considered as in CAH girls. The Mullerian cavity is, however, quite different in this group (narrow and rigid) and the outcome of vaginal surgery may be unsatisfactory. Dilatations after vaginal connection are usual in the pubertal or post-pubertal individual.

Timing of treatment raises the same concerns as in other DSD groups [79].

Uncertainties: It is the typical situation for which whatever decision is taken, including no decision, the outcome is likely to be unsatisfactory. One of the main obstacles for the multidisciplinary team is to convey this information to the parents. All patients reared as males seem to have a strong male sexual identity, whereas those reared as females seem to be less adapted to their role [76]. Accompanying the patient and his family throughout childhood until adulthood is a delicate task for the multidisciplinary team. The aim is to make the patient and family accept his (her) situation ("coping").

Ovo-testicular group

Assignment decision is complex as both female and male structures live together. Age at diagnosis, anatomical evaluation of both external and internal genitalia, biological, genetic, and molecular profiles, and parents' perception of the situation should be carefully analyzed by a multidisciplinary team of experts. It seems, however, that males report greater satisfaction with their gender and sexual lives [80,81]. Retaining all of the child's potential for future choice may be the "least bad" option. However, the weight of consequences of delaying surgery or the "no decision" option are not measurable in advance. Infertility is likely with either sex of rearing, although pregnancy has been described in rare ovo-testicular DSD [82].

Non-hormonal/non-chromosomal DSD group

The "non-hormonal/non-chromosomal" DSD group is mainly represented by the 46,XY cloacal extrophy patients, aphallia, and severe micropenis.

Assignment decision: Here again, female assignment was the rule for many years [83,84]; however, disappointing outcome with significant dysphoria was reported, leading to a change of approach. Most patients are now assigned to the male gender [85].

Nature and timing of treatment: Reconstruction of the urinary tract and diversion of the colon with pelvic osteotomy usually occur soon after birth. Phalloplasty needs to be discussed usually at puberty or before for some, although most surgeons would recommend waiting until or after puberty [29,32,82,83,86,87].

Uncertainties: The outcome is often unsatisfactory and similar recommendations are made as in the previous groups. Male gender development is more likely to occur [86]. Even if female psychosexual development has been described in some cases of 46,XY cloacal extrophy [84], the male gender is most appropriate for recommendation [83] considering the significant rates of female to male transition in female-assigned children with this condition (33% dysphoria) [47].

Conclusions

It appears obvious that given the complexity and heterogeneity of presentation there is no consensus regarding the indications, the timing, the procedure, and the evaluation of outcome of DSD surgery. The levels of evidence of the answers given by the experts are low (B and C), most decisions being supported by team expertise. Literature mostly reports short clinical series, which cannot be compared considering the heterogeneity of pathologies and management between centers. There are, however, some issues on which most experts would agree: (1) The need for identifying centers of expertise with a multidisciplinary approach; 2) Conservative management of the gonads in complete androgen insensitivity syndrome at least until puberty, although some studies expressed concerns about the heightened tumor risk in this group; 3) Avoidance of vaginal dilatation in children after surgical reconstruction; 4) Retaining asymptomatic Mullerian remnants during childhood which can be removed later if necessary; 5) Removal of streak gonads (confirmed by biopsy when Y material is present); 6) It is likely that 46,XY cloacal extrophy, aphallia, and severe micropenis would do best raised as male, although this is based on limited outcome data, particularly to cloacal extrophy.

There is a general acknowledgement among experts that timing, the choice of the individual, and irreversibility of surgical procedures are sources of concerns. There is, however, little evidence provided regarding the impact of non-treated DSD during childhood for the individual development, the parents, the society, and the risk of stigmatization.

The low level of evidence in most DSD situations should lead multidisciplinary expert teams to design collaborative prospective studies involving all parties and using consensus protocols of evaluation.

Conflict of interest

None.

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None.

References


