Consensus statement on management of intersex disorders

Ieuan A Hughes, Chris Houk, S Faisal Ahmed and Peter A Lee

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CONSENSUS STATEMENT ON MANAGEMENT OF INTERSEX DISORDERS

IA Hughes, C Houk, SF Ahmed, PA Lee and LWPES[1]/ESPE[2] Consensus Group

[1] Lawson Wilkins Pediatric Endocrine Society

[2] European Society for Paediatric Endocrinology

Consensus Group: The following participants contributed to the production of the Consensus document:

John Achermann (London, UK), Faisal Ahmed (Glasgow, UK), Laurence Baskin (San Francisco, USA), Sheri Berenbaum (University Park, USA), Sylvano Bertelloni (Pisa, Italy), John Brock (Nashville, USA), Polly Carmichael (London, UK), Cheryl Chase (Rohnert Park, USA), Peggy Cohen-Kettenis (Amsterdam, Netherlands), Felix Conte (San Francisco, USA), Patricia Donohoue (Iowa City, USA), Chris Driver (Aberdeen, UK), Stenvert Drop (Rotterdam, Netherlands), Erica Eugster (Indianapolis, USA), Kenji Fujieda (Asahikawa, Japan), Jay Giedd (Bethesda, USA), Richard Green (London, UK), Melvin Grumbach (San Francisco, USA), Vincent Harley (Victoria, Australia), Melissa Hines (London, UK), Olaf Hiort (Lübeck, Germany), Ieuan Hughes (Cambridge, UK), Peter Lee (Hershey, USA), Leendert Looijenga (Rotterdam, Netherlands), Berenice Mendonça (Sao Paulo, Brazil), Heino Meyer-Bahlburg (New York, USA), Claude Migeon (Baltimore, USA), Yves Morel (Lyon, France), Pierre Mouriquand (Lyon, France), Anna Nordenström (Stockholm, Sweden), Phillip Ransley (London, UK), Robert Rapaport (New York, USA), William Reiner (Oklahoma City, USA), Hertha Richter-Appelt (Hamburg, Germany), Richard Rink (Indianapolis, USA), Emilie Rissman (Charlottesville, USA), Paul Saenger (New York, USA), David Sandberg (Buffalo, USA), Justine Schober (Erie, USA), Norman Spack (Boston, USA), Barbara Thomas (Rottenburg am Neckar, Germany), Ute Thyen (Lübeck, Germany), Eric Vilain (Los Angeles, USA), Garry Warne (Melbourne, Australia), Amy Wisniewski (Des Moines, USA), Jean Wilson (Dallas, USA), Christopher Woodhouse (London, UK), Kenneth Zucker (Toronto, Canada).

Address for correspondence: Professor Ieuan A Hughes
Department of Paediatrics
University of Cambridge
Addenbrooke's Hospital
Box 116, Level 8, Hills Road
Cambridge CB2 2QQ, UK

Email: iah1000@cam.ac.uk
Tel: 44 (0) 1223 336885
Fax: 44 (0) 1223 336996

INTRODUCTION

The birth of an intersex child prompts a long-term management strategy that involves a myriad of professionals working with the family. It is estimated that genital anomalies occur in 1 in 4500 births. There has been progress in diagnosis, surgical techniques, understanding psychosocial issues and in recognising and accepting the place of patient advocacy. The Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) considered it timely to review the management of intersex disorders from a broad perspective, to review data on longer term outcome and to formulate proposals for future studies. The methodology comprised establishing a number of working groups whose membership was drawn from 50 international experts in the field. The groups prepared prior written responses to a defined set of questions resulting from an evidence based review of the literature. At a subsequent gathering of participants, a framework for a consensus document was agreed. This paper constitutes its final form.

NOMENCLATURE AND DEFINITIONS

Advances in identification of molecular genetic causes of abnormal sex with heightened awareness of ethical issues and patient advocacy concerns necessitate a re-examination of nomenclature[1]. Terms such as intersex, pseudohermaphroditism, hermaphroditism, sex reversal, and gender-based diagnostic labels are particularly controversial. These terms are perceived as potentially pejorative by patients[2], and can be confusing to practitioners and parents alike. The term Disorders of Sex Development (DSD) is proposed, as defined by congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical.

The proposed changes in terminology are summarised in Table 1. A modern lexicon is needed to integrate progress in molecular genetic aspects of sex development. Since outcome data in individuals with DSD is limited, it is essential to employ precision when applying definitions and diagnostic labels[3,4]. It is also appropriate to use terminology that is sensitive to the concerns of patients. The ideal nomenclature should be sufficiently flexible to incorporate new information yet robust enough to maintain a consistent framework. Terms should be descriptive and reflect genetic aetiology when available, and accommodate the spectrum of phenotypic variation. Clinicians and scientists must value its use and it must be understandable to patients and their families. An example of how the proposed nomenclature could be applied in a classification of DSD is shown in Table 2.

Psychosexual development is traditionally conceptualized as three components. Gender identity refers to a person's self-representation as male or female (with the caveat that some individuals may not identify exclusively with either). Gender role (sex-typical behaviours) describes the psychological characteristics that are sexually dimorphic within the general population, such as toy preferences and physical aggression. Sexual orientation refers to the direction(s) of erotic interest (heterosexual, bisexual, homosexual) and includes behaviour, fantasies, and attractions. Psychosexual development is influenced by multiple factors such as exposure to androgens, sex chromosome genes, and brain structure, as well as social circumstance and family dynamics.

Gender dissatisfaction denotes unhappiness with assigned sex. Causes of gender dissatisfaction are poorly understood, even among individuals without DSD. Gender dissatisfaction occurs more frequently in individuals with DSD than in the general population, but is difficult to predict from karyotype, prenatal androgen exposure, degree of genital virilization, or assigned gender[5-7]. Prenatal androgen exposure is clearly associated with other aspects of psychosexual development[8,9]. There are dose-related effects on childhood play behaviour in girls with congenital adrenal hyperplasia (CAH), whereby those with the more severe mutations and marked genital virilization play more with boys' toys[10]. Prenatal androgen exposure is also associated with other psychological characteristics such as maternal interest and sexual orientation. It is important to emphasize the separability of sex-typical behaviour, sexual orientation, and gender identity. Thus, homosexual orientation (relative to sex of rearing) or strong cross-sex interest in an individual with DSD is *not* an indication of incorrect gender assignment. Understanding variations in psychosexual development in individuals with DSD requires reference to studies in non-human species that show marked but complex effects of androgens on sex differentiation of the brain and on behaviour. Outcomes can be influenced by timing, dose and type of androgen exposure, receptor availability and modification by the social environment[11-14].

Data from rodent studies suggest that sex chromosome genes may also influence brain structure and behaviour directly[15,16]. However, studies in individuals with complete androgen insensitivity syndrome (CAIS) do not indicate a behavioural role for Y-chromosome genes, although data are limited[17]. Sex differences in brain structures have been identified across species, some of which coincide with pubertal onset,

perhaps suggesting hormonal responsivity[18-20]. The limbic system and hypothalamus, both playing a role in reproduction, show sex differences in specific nuclei but it is not clear when these differences emerge. Interpretation of sex differences is complicated by the effect of cell death and synaptic pruning on normal maturation and by effects of experience on the brain. Structure of the brain is not currently useful for gender assignment.

INVESTIGATION AND MANAGEMENT OF DSD

General Concepts of Care

Optimal clinical management of individuals with DSD[21] should comprise the following: 1) gender assignment must be avoided prior to expert evaluation in newborns; 2) evaluation and long-term management must be performed at a centre with an experienced multidisciplinary team; 3) all individuals should receive a gender assignment; 4) open communication with patients and families is essential and participation in decision-making is encouraged; 5) patient and family concerns should be respected and addressed in strict confidence.

The initial contact with the parents of a child with a DSD is important as first impressions from these encounters often persist. A key point to emphasise is that the DSD child has the potential to become a well-adjusted, functional member of society. While privacy needs to be respected, DSD is not shameful. It should be explained to the parents that the best course of action may not initially be clear, but the health care team will work with the family to reach the best possible set of decisions in the circumstances. The health care team should discuss with the parents what information to share in the early stages with family members and friends. Parents

need to be informed about sexual development and web-based information may be helpful, provided the content and focus of the information is balanced and sound (http://www.sickkids.ca/childphysiology/cpwp/genital/genitalintro.html).

Ample time and opportunity should be made for continued discussion with review of information previously provided[1].

The Multidisciplinary Team

Optimal care for children with DSD requires an experienced multidisciplinary team that is generally found in tertiary care centres. Ideally, the team includes paediatric subspecialists in endocrinology, surgery and/or urology, psychology/psychiatry, gynaecology, genetics, neonatology and, if available, social work, nursing and medical ethics[22]. Core composition will vary according to DSD type, local resources, developmental context and location. Ongoing communication with the family primary care physician is essential[23].

The team has a responsibility to educate other health care staff in the appropriate initial management of affected newborns and their families. For new DSD patients, the team should develop a plan for clinical management with respect to diagnosis, gender assignment and treatment options before making any recommendations. Ideally, discussions with the family are conducted by one professional with appropriate communication skills[24]. Transitional care should be organized with the multidisciplinary team operating in an environment comprising specialists with experience in both paediatric and adult practice. Support groups have an important role in the delivery of care to DSD patients and their families[25] (see Appendix I).

Clinical Evaluation

A family and prenatal history, a general physical examination with attention to any associated dysmorphic features and an assessment of the genital anatomy in comparison to published norms needs to be recorded (Table 3). Criteria that suggest DSD include: 1) overt genital ambiguity (eg cloacal exstrophy); 2) apparent female genitalia with an enlarged clitoris, posterior labial fusion, or an inguinal/labial mass; 3) apparent male genitalia with bilateral undescended testes, micropenis, isolated perineal hypospadias or mild hypospadias with undescended testis; 4) a family history of DSD such as complete androgen insensitivity syndrome (CAIS); 5) a discordance between genital appearance and a prenatal karyotype. Most causes of DSD are recognized in the neonatal period; later presentations in older children and young adults include: 1) previously unrecognized genital ambiguity; 2) inguinal hernia in a female; 3) delayed or incomplete puberty; 4) virilization in a female; 5) primary amenorrhea; 6) breast development in a male; 7) gross and occasionally cyclic hematuria in a male.

Diagnostic Evaluation

Considerable progress has been made with understanding the genetic basis of human sexual development[35], yet a specific molecular diagnosis is identified in only about 20% of cases of DSD. The majority of virilized 46, XX infants will have CAH. In contrast, only 50% of 46 XY children with DSD will receive a definitive diagnosis[36,37]. Diagnostic algorithms do exist, but with the spectrum of findings and diagnoses, no single evaluation protocol can be recommended in all circumstances. Some tests, such as imaging by ultrasound, are operator dependent. Hormone measurements need to be interpreted in relation to the specific assay characteristics,

and to normal values for gestational and chronological age. In some cases serial measurements may be needed.

First-line testing in newborns includes: karyotyping with X and Y-specific probe detection (even when prenatal karyotype is available), imaging (abdomino-pelvic ultrasound), measurement of 17-hydroxyprogesterone, testosterone, gonadotropins, anti-Müllerian Hormone, serum electrolytes and urinanalysis. The results of these investigations are generally available within 48 hours and will be sufficient for making a working diagnosis. Decision-making algorithms are available to guide further investigation[38]. These include hCG and ACTH stimulation tests to assess testicular and adrenal steroid biosynthesis, urinary steroid analysis by GC mass spectroscopy, imaging studies and biopsies of gonadal material. Some gene analyses are performed in clinical service laboratories. However, current molecular diagnosis is limited by cost, accessibility and quality control[39]. Research laboratories provide genetic testing, including functional analysis, but may face restrictions on communicating results[40].

Gender Assignment in Newborns

Initial gender uncertainty is unsettling and stressful for families. Expediting a thorough assessment and decision is required. Factors that influence gender assignment include the diagnosis, genital appearance, surgical options, need for life-long replacement therapy, the potential for fertility, views of the family and sometimes, circumstances relating to cultural practices. More than 90% of 46,XX CAH patients[41] and all 46,XY CAIS assigned female in infancy[42] identify as females. Evidence supports the current recommendation to raise markedly virilized 46,XX infants with CAH as female[43]. Approximately 60% of 5α-reductase (5αRD2)

deficient patients assigned female in infancy and virilizing at puberty (and all assigned male) live as males[5]. In 5αRD2 and possibly 17β-hydroxysteroid dehydrogenase (17βHSD3) deficiencies, where the diagnosis is made in infancy, the combination of a male gender identity in the majority and the potential for fertility (documented in 5αRD2, but unknown in 17βHSD3) should be discussed when providing evidence for gender assignment[5,44,45]. Among patients with PAIS, androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with the sex of rearing in about 25% of individuals whether raised male or female[46]. Available data supports male rearing in all patients with micropenis, taking into account equal satisfaction with assigned gender in those raised male or female, but no need for surgery, and the potential for fertility in patients reared male[42]. The decision on sex of rearing in ovotesticular DSD should consider the potential for fertility based on gonadal differentiation and genital development, and assuming the genitalia are, or can be made, consistent with the chosen sex. In the case of mixed gonadal dysgenesis (MGD), factors to consider include prenatal androgen exposure, testicular function at and after puberty, phallic development and gonadal location. Individuals with cloacal exstrophy reared female show variability in gender identity outcome, but more than 65% appear to live as female[6].

Surgical Management

The surgeon has a responsibility to outline the surgical sequence and subsequent consequences from infancy to adulthood. Only surgeons with expertise in the care of children and specific training in the surgery of DSD should perform these procedures. Parents now appear to be less inclined to choose surgery for less severe clitoromegaly[47]. Surgery should only be considered in cases of severe virilization

(Prader III, IV and V) and be performed in conjunction, when appropriate, with repair of the common urogenital sinus. As orgasmic function and erectile sensation may be disturbed by clitoral surgery, the surgical procedure should be anatomically based to preserve erectile function and the innervation of the clitoris. Emphasis is on functional outcome, rather than a strictly cosmetic appearance. It is generally felt that surgery that is performed for cosmetic reasons in the first year of life relieves parental distress and improves attachment between the child and the parents[48-51]. The systematic evidence for this belief is lacking.

There is inadequate evidence currently in relation to establishment of functional anatomy, to abandon the practice of early separation of the vagina and urethra[52]. The rationale for early reconstruction is based on guidelines on the timing of genital surgery from the American Academy of Pediatrics (AAP)[53], the beneficial effects of estrogen on tissue in early infancy and the avoidance of potential complications from the connection between the urinary tract and peritoneum via the Fallopian tubes. It is anticipated that surgical reconstruction in infancy will need to be refined at the time of puberty[54-56]. Vaginal dilatation should not be undertaken before puberty. The surgeon must be familiar with a number of operative techniques in order to reconstruct the spectrum of urogenital sinus disorders. An absent or inadequate vagina (with rare exceptions) requires a vaginoplasty performed in adolescence when the patient is psychologically motivated and a full partner in the procedure. No one technique has been universally successful; self -dilatation, skin substitution and bowel vaginoplasty each have specific advantages and disadvantages.

In the case of a DSD associated with hypospadias[57], standard techniques for surgical repair such as chordee correction, urethral reconstruction and the judicious use of testosterone supplementation apply. The magnitude and complexity of phalloplasty in adulthood should be taken into account during the initial counselling period if successful gender assignment is dependent on this procedure[58]. At times this may affect the balance of gender assignment. Patients must not be given unrealistic expectations about penile reconstruction, including the use of tissue engineering. There is no evidence that prophylactic removal of asymptomatic discordant structures, such as a utriculus or Müllerian remnants, is required although symptoms in future may indicate surgical removal. For the male who has a successful neophalloplasty in adulthood, an erectile prosthesis may be inserted but has a high morbidity.

The testes in patients with CAIS[35] and those with PAIS, raised female, should be removed to prevent malignancy in adulthood. The availability of estrogen replacement therapy allows for the option of early removal at the time of diagnosis which also takes care of the associated hernia, psychological problems with the presence of testes and the malignancy risk. Parental choice allows deferment until adolescence, recognizing that the earliest reported malignancy in CAIS is at 14 years of age[59]. The streak gonad in a patient with MGD raised male should be removed laparoscopically (or by laparotomy) in early childhood[35]. Bilateral gonadectomy is performed in early childhood in females (bilateral streak gonads) with gonadal dysgenesis and Y chromosome material. In patients with androgen biosynthetic defects raised female, gonadectomy should be performed before puberty. A scrotal testis in patients with gonadal dysgenesis is at risk for malignancy. Current recommendations are testicular biopsy at puberty seeking signs of the pre-malignant

lesion termed carcinoma-in-situ or undifferentiated intratubular germ cell neoplasia. If positive, the option is sperm banking before treatment with local low dose radiotherapy which is curative[60].

Surgical management in DSD should also consider options that will facilitate the chances of fertility. In patients with a symptomatic utriculus, removal is best performed laparoscopically to increase the chance of preserving continuity of the vasa deferentia. Patients with bilateral ovotestes are potentially fertile from functional ovarian tissue[35,61]. Separation of ovarian and testicular tissue can be technically difficult and should be undertaken, if possible, in early life.

Sex Steroid Replacement

Hypogonadism is common in patients with dysgenetic gonads, defects in sex steroid biosynthesis and resistance to androgens. The timing of initiation of puberty may vary but this is an occasion that provides an opportunity to discuss the condition and set a foundation for long-term adherence to therapy. Hormonal induction of puberty should attempt to replicate normal pubertal maturation to induce secondary sexual characteristics, a pubertal growth spurt, and optimal bone mineral accumulation, together with psychosocial support for psychosexual maturation[62]. Intramuscular depot injections of testosterone esters are commonly used in males; other options include oral testosterone undecanoate and transdermal preparations are also available[63-65]. Patients with PAIS may require supraphysiologic doses of testosterone for optimal effect[66]. Females with hypogonadism require estrogen supplementation to induce pubertal changes and menses. A progestin is usually added after breakthrough

bleeding develops or within 1-2 years of continuous estrogen. There is no evidence that the addition of cyclic progesterone is beneficial in women without a uterus.

Psychosocial Management

Psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management in order to promote positive adaptation. This expertise can facilitate team decisions about gender assignment/reassignment, timing of surgery and sex hormone replacement. Psychosocial screening tools that identify families at risk for maladaptive coping with a child's medical condition are available[67]. Once the child is sufficiently developed for a psychological assessment of gender identity, such an evaluation must be included in discussions about gender reassignment. Gender identity development begins before the age of 3 years[68], but the earliest age at which it can be reliably assessed remains unclear. The generalization that the age of 18 months is the upper limit of imposed gender reassignment should be treated with caution and viewed conservatively. Atypical gender role behaviour is more common in children with DSD than in the general population, but should not be taken as an indicator for gender reassignment. In affected children and adolescents who report significant gender dysphoria, a comprehensive psychological evaluation[69] and an opportunity to explore feelings about gender with a qualified clinician is required over a period of time. If the desire to change gender persists, the patient's wish should be supported, and may require the input of a specialist skilled in the management of gender change.

The process of disclosure concerning facts about karyotype, gonadal status and prospects for future fertility is a collaborative ongoing action which requires a flexible

individual-based approach. It should be planned with the parents from the time of diagnosis[70]. Studies in other chronic medical disorders and of adoptees indicate that disclosure is associated with enhanced psychosocial adaptation[71]. Medical education and counselling for children is a recurrent gradual process of increasing sophistication which is commensurate with changing cognitive and psychological development[72].

Quality of life encompasses falling in love, dating, attraction, ability to develop intimate relationships, sexual functioning, the opportunity to marry, and to raise children, regardless of biological indicators of sex. The most frequent problems encountered in DSD patients are sexual aversion and lack of arousability, which are often misinterpreted as low libido[73]. Health care staff should offer adolescent patients opportunities to talk confidentially without their parents and encourage the participation in condition-specific support groups which enhance the ability of the patient to comfortably discuss their concerns. Some patients avoid intimate relationships and it is important to address fears of rejection and advise on the process of building a relationship with a partner. The focus should be on interpersonal relationships and not solely on sexual function and activity. Referral for sex therapy may be needed. Repeated examination of the genitalia, including medical photography, may be experienced as deeply shaming[74]. Medical photography has its place for record keeping and education, but should be undertaken whenever possible if the patient is under anaesthesia for a procedure and with appropriate consent. Medical interventions and negative sexual experiences may have fostered symptoms of post-traumatic stress disorder and referral to a qualified mental health professional may be indicated[75].

OUTCOME IN DSD

As a general statement, information across a range of assessments is insufficient in DSD. The following is based on those disorders where some evidence base is available. They include CAH, CAIS and PAIS, disorders of androgen biosynthesis, gonadal dysgenesis syndromes (complete and partial) and micropenis. Long term outcome in DSD should include the following: external and internal genital phenotype, physical health including fertility, sexual function, social and psychosexual adjustment, mental health, quality of life and social participation. There are additional health problems in individuals with DSD. These include the consequences of associated problems such as other malformations, developmental delay and intellectual impairment, delayed growth and development, and unwanted effects of hormones on libido and body image[76].

Surgical outcome

Some studies suggest satisfactory outcomes from early surgery[43,46,47,77]. Nevertheless, outcomes from clitoroplasty identify problems related to decreased sexual sensitivity, loss of clitoral tissue and cosmetic issues[78]. Techniques for vaginoplasty carry the potential for scarring at the introitus necessitating repeated modification before sexual function can be reliable. Surgery to construct a neo-vagina carries a risk of neoplasia[79]. The risks from vaginoplasty are different for high and low confluence of the urethra and vagina. Analysis of long-term outcomes is complicated by a mixture of surgical techniques and diagnostic categories[80]. Few women with CAIS need surgery to lengthen the vagina[81].

The outcome in undermasculinised males with a phallus is dependent on the degree of hypospadias and the amount of erectile tissue. Feminizing genitoplasty as opposed to masculinizing genitoplasty requires less surgery to achieve an acceptable outcome and results in fewer urological difficulties[46]. Long-term data regarding sexual function and quality of life among both those assigned female as well as male show great variability. There are no controlled clinical trials of the efficacy of early (less than 12 months of age) versus late (in adolescence and adulthood) surgery or of the efficacy of different techniques.

Risk of gonadal tumours

Interpretation of the literature is hampered by unclear terminology and effects of normal cell maturation delay[82-84]. The highest tumour risk is found in TSPY (testis-specific protein Y encoded) positive gonadal dysgenesis and PAIS with intra-abdominal gonads, while the lowest risk (<5%) is found in ovotestis[85] and CAIS[83,86]. Table 4 provides a summary of the risk of tumour development according to diagnosis and recommendations for management.

Cultural and social factors

DSD may carry a stigma. Social and cultural factors, as well as hormonal effects, appear to influence gender role in 5α-reductase deficiency. Gender role change occurs at different rates in different societies suggesting that social factors may also be important modifiers of gender role change.

In some societies, female infertility precludes marriage, which also affects employment prospects and creates economic dependence. Religious and philosophical views may influence how parents respond to the birth of an infant with

a medical condition. Fatalism and guilt feelings in relation to congenital malformations or genetic conditions have an influence, while poverty and illiteracy negatively affect access to health care[87].

FUTURE STUDIES

Establishing a precise diagnosis in DSD is just as important as in other chronic medical conditions with life-long consequences. Considerable progress has been achieved with molecular studies as illustrated in Table 5 which summarises the genes known to be involved in DSD. Use of tissue-specific animal knock out models, comparative genomic hybridization and microarray screens of the mouse urogenital ridge will provide benefits in identifying new genes causing DSD[89]. It is essential that the momentum for an international collaborative approach to this task is maintained.

Much remains to be clarified about the determinants of gender identity in DSD. Future studies require representative sampling to carefully conceptualise and measure gender identity, recognizing that there are multiple determinants to consider and gender identity may change into adulthood. In terms of psychological management, studies are needed to evaluate the effectiveness of information management with regard to timing and content. The pattern of surgical practice in DSD is changing with respect to the timing of surgery and the techniques employed. It is essential to evaluate the effects of early versus later surgery in an holistic manner, recognizing the difficulties posed by an ever evolving clinical practice.

The consensus has clearly identified a major shortfall in information about long-term outcome. Future studies should use appropriate instruments that assess outcomes in a standard manner[68,69] and take cognizance of guidelines relevant to all chronic conditions (http://www.who.int/classifications/icf/en/). These should preferably be prospective in nature and designed to avoid selection bias. A number of countries already have registers of DSD cases but there could be added benefit from pooling such resources to enable prospective, multicentre studies to be undertaken on a larger number of cases that are clearly defined. Allied to this should be an educational programme to ensure that multi-professionals tasked with providing care to DSD families are suitably trained to discharge their responsibilities.

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APPENDIX I

Role of Support Groups

The value of peer and parent support for many chronic medical conditions is widely accepted, and DSDs, being lifelong conditions which affect developmental tasks at many stages of life, are no exception.

Those affected by DSDs and parent members value the following:

- Peer support ends isolation and stigma, providing a context in which conditions are put into perspective, and where intimate issues of concern can be discussed safely with someone who has "been there".
- Children who form relationships with peers and affected adults early in their lives benefit from a feeling of normalcy early on, with support in place well before adolescence. Adolescents often resist attempts to introduce them to peer support.
- Support groups can help families and consumers find the best quality care.

While clinical practice may focus on gender and genital appearance as key outcomes, stigma and experiences associated with having a DSD (both within and outside the medical environment) are more salient issues for many affected people.

Support groups complement the work of the health care team and, together, can help improve services. Initiatives by support groups have led to improvements in management of DSD and research directed towards clinically relevant issues.

Dialogue between health care professionals and support groups, and collaboration as partners is to be encouraged.

APPENDIX II

Legal issues

Basic principles of medical law will remain, even as research and clinical experience evolve in aetiology, diagnosis, and treatment. This Appendix draws on practice in three countries on standards of medical negligence and patient informed consent. In the United States, the medical profession sets standards of care based on prevailing medical custom[90]. However, a treatment may also be that used by a respected minority of practitioners.

Informed consent in the US was founded on the principle of battery whereby it is an offence to violate another person's bodily integrity without consent. Nowadays, most states are concerned with negligent non-disclosure to the patient. The standard of adequate disclosure may be physician-based, requiring conduct of a reasonable practitioner. Or, it may be patient-based, asking what a reasonable patient would find material. Physician-based disclosure must include information about risks, alternatives, outcomes and prognosis, with or without treatment.

US courts assume that parents know what is best for their child when parental authority applies to consent for the child (substituted judgement). Parental decisions are deferred to except in situations where potentially life-saving treatment is withheld. Consent to treatment by a child is dependent on an understanding of its nature and consequences.

Medical negligence in the United Kingdom defines treatment that falls below the standard expected of a reasonably competent practitioner. The standard of proof in

court is whether negligence is demonstrated on the balance of probabilities. It is incumbent on the practitioner to demonstrate that treatment was consistent with a rationally defensible body of medical opinion. A shift in parental prerogative to consent to treatment was reflected in the Children Act 1989 in which parental rights were replaced by parental responsibilities[91]. UK courts can intervene with orders made requiring or preventing a specific action related to the child. Age is not a barrier to informed consent, providing that a minor demonstrates an understanding of the issues sufficient to have the capacity to consent.

Colombian law is noted for a reasoned set of guidelines advanced by the highest court in cases of DSD[92]. A protocol was formulated for parental and physician intervention. The process of consent requires "qualified and persistent informed consent" over an extended period of time. Authorization is given in stages to allow time for the parents to come to terms with their child's condition. The court aimed to strike a balance between parental autonomy for those who did, and those who did not want early surgery for their child, until there was clear evidence of harm in deferring surgery until the child was competent to decide. Parents cannot consent for children over five years of age, as by then, children are deemed to have identified with a gender and so are considered to be autonomous.

Table 1 Proposed Revised Nomenclature

PREVIOUS	PROPOSED
Intersex	**Disorders of Sex Development (DSD)**
Male pseudohermaphrodite Undervirilisation of an XY male Undermasculinisation of an XY male	46,XY DSD
Female pseudohermaphrodite Overvirilisation of an XX female Masculinisation of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

Table 2 An example of a DSD classification

Sex Chromosome DSD	46,XY DSD	46,XX DSD
A: 45,X (Turner Syndrome and variants) **B: 47,XXY (Klinefelter Syndrome and variants)** **C: 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)** **D: 46,XX/46,XY (chimeric, ovotesticular DSD)**	**A: Disorders of gonadal (testicular) development** 1. Complete gonadal dysgenesis (Swyer syndrome) 2. Partial gonadal dysgenesis 3. Gonadal regression 4. Ovotesticular DSD	**A: Disorders of gonadal (ovarian) development** 1. Ovotesticular DSD 2. Testicular DSD (eg SRY+, dup SOX9) 3. Gonadal dysgenesis
	B: Disorders in androgen synthesis or action 1. Androgen biosynthesis defect (eg 17 Hydoxysteroid dehydrogenase deficiency, 5α reductase deficiency, StAR mutations 2. Defect in androgen action (eg CAIS, PAIS) 3. LH receptor defects (eg Leydig cell hypoplasia, aplasia) 4. Disorders of AMH and AMH receptor (Persistent Mullerian Duct Syndrome)	**B: Androgen excess** 1. Fetal (eg 21 hydroxylase deficiency, 11 hydroxylase deficiency) 2. Fetoplacental (aromatase deficiency, POR) 3. Maternal (luteoma, exogenous, etc)
	C: Other (eg severe hypospadias, cloacal extrophy)	**C: Other** (eg cloacal extrophy, vaginal atresia, MURCS, other syndromes)

Footnote: Whilst consideration of karyotype is useful for classification, unnecessary reference to karyotype should be avoided; ideally, a system based on descriptive terms (eg androgen insensitivity syndrome) should be used wherever possible

Table 3 Anthropometric measurements of the external genitalia

Sex	Population	Age	Stretched penile length (PL) Mean (cm) ± SD	Penile width Mean (cm) ± SD	Mean testicular volume (cc)	Ref
M	USA	30 wks GA	2.5 ± 0.4			26
M	USA	Full term	3.5 ± 0.4	1.1 ± 0.1	0.52 (median)	26,27
M	Japan	Term -14yrs	2.9 ± 0.4 – 8.3 ± 0.8			28
M	Australia	24-36 wks GA	PL = 2.27 + (0.16 GA)			29
M	Chinese	Term	3.1 ± 0.3	1.07 ± 0.09		30
M	India	Term	3.6 ± 0.4	1.14 ± 0.07		30
M	N America	Term	3.4 ± 0.3	1.13 ± 0.08		30
M	Europe	10 years	6.4 ± 0.4		0.95 - 1.20	27,31
M	Europe	Adult	13.3 ± 1.6		16.5 - 18.2	27,31
Sex	Population	Age	Clitoral Length Mean (mm) ± SD	Clitoral Width Mean (mm) ± SD	Perineum Length* Mean (mm) + SD	Ref
F	USA	Full Term	4.0 ± 1.24	3.32 ± 0.78		32
F	USA	Adult Nulliparous	15.4 ± 4.3			33
F	USA	Adult	19.1 ± 8.7	5.5 ± 1.7	31.3 ± 8.5	34

Table 4 Risk of germ cell malignancy according to diagnosis

Risk group	Disorder	Malignancy Risk (%)	Recommended Action	Numbers: Studies (n)	Numbers: Patients (n)
High	GD[a] (+Y)[b] intra-abd.	15-35	gonadectomy[c]	12	>350
	PAIS non-scrotal	50	gonadectomy[c]	2	24
	Frasier	60	gonadectomy[c]	1	15
	Denys-Drash (+Y)	40	gonadectomy[c]	1	5
Intermediate	Turner (+Y)	12	gonadectomy[c]	11	43
	17β-HSD	28	monitor	2	7
	GD (+Y)[b] scrotal	unknown	biopsy[d] and irrad.?	0	0
	PAIS scrotal gonad	unknown	biopsy[d] and irrad.?	0	0
Low	CAIS	2	biopsy[d] and ???	2	55
	ovotest. DSD	3	testis. tissue removal ?	3	426
	Turner (–Y)	1	None	11	557
No (?)	5α-reductase	0	unresolved	1	3
	Leydig cell hypoplasia	0	unresolved	1	2

[a]Gonadal Dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete); [b]GBY region positive, including the *TSPY* gene; [c]at time of diagnosis; [d]at puberty, allowing investigation of at least 30 seminiferous tubules, preferentially diagnosis based on OCT3/4 immunohistochemistry.

Table 5 Genes known to be involved in DSD

Gene	Protein	OMIM	Locus	Inheritance	Gonad	Mullerian Structures	External Genitalia	Associated features/Variant phenotypes
46,XY DSD								
Disorders ***of gonadal (testicular) development: Single gene disorders***								
WT1	TF	607102	11p13	AD	Dysgenetic testis	+/-	Female or ambiguous	Wilms tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash & Frasier syndromes)
SF1 (NR5A1)	Nuclear receptor TF	184757	9q33	AD/AR	Dysgenetic testis	+/-	Female or ambiguous	More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis
SRY	TF	480000	Yp11.3	Y	Dysgenetic testis or ovotestis	+/-	Female or ambiguous	
SOX9	TF	608160	17q24-25	AD	Dysgenetic testis or ovotestis	+/-	Female or ambiguous	Campomelic dysplasia (17q24 rearrangements milder phenotype than point mutations)
DHH	Signaling molecule	605423	12q13.1	AR	Dysgenetic testis	+	Female	The severe phenotype of one patient included minifascicular neuropathy, other patients have isolated gonadal dysgenesis
ATRX	Helicase (?chromatin remodeling)	300032	Xq13.3	X	Dysgenetic testis	-	Female, ambiguous or male	α-thalassemia, mental retardation
ARX	TF	300382	Xp22.13	X	Dysgenetic testis	-	Ambiguous	X-linked lissencephaly, epilepsy, temperature instability
Disorders of gonadal (testicular) development: Chromosomal changes involving key candidate genes								
DMRT1	TF	602424	9p24.3	Monosomic deletion	Dysgenetic testis	+/-	Female or ambiguous	Mental retardation
DAX1 (NR0B1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Dysgenetic testis or ovary	+/-	Female or ambiguous	
WNT4	Signaling molecule	603490	1p35	dup1p35	Dysgenetic testis	+	Ambiguous	Mental retardation
Disorders in hormone synthesis or action								
LHGCR	G-protein receptor	152790	2p21	AR	Testis	-	Female, ambiguous or micropenis	Leydig cell hypoplasia
DHCR7	Enzyme	602858	11q12-13	AR	Testis	-	Variable	Smith-Lemli-Opitz syndrome: coarse facies, second-third toe syndactyly, failure to thrive, developmental delay, cardiac & visceral abnormalities
STAR	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	-	Female	Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	-	Female or Ambiguous	Congenital adrenal hyperplasia (primary adrenal failure), pubertal failure
HSD3B2	Enzyme	201810	1p13.1	AR	Testis	-	Ambiguous	CAH, primary adrenal failure, partial androgenization due to ↑ DHEA
CYP17	Enzyme	202110	10q24.3	AR	Testis	-	Female, ambiguous or micropenis	CAH, hypertension due to ↑ corticosterone & 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)
POR (P450 oxido-reductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	-	Male or ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency and aromatase deficiency; sometimes associated with Antley Bixler craniosynostosis
HSD17B3	Enzyme	605573	9q22	AR	Testis	-	Female or ambiguous	Partial androgenization at puberty, ↑ androstenedione:testosterone ratio
SRD5A2	Enzyme	607306	2p23	AR	Testis	-	Ambiguous or micropenis	Partial androgenization at puberty, ↑ testosterone:DHT ratio,
AMH	Signaling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal male	Persistent Mullerian duct syndrome (PMDS). Male

AMH-Receptor	Serine-threonine kinase transmembrane receptor	600956	12q13	AR	Testis	+	Normal male	syndrome (PMDS). Male external genitalia, bilateral cryptorchidism.
Androgen receptor	Nuclear receptor TF	313700	Xq11-12	X	Testis	-	Female, ambiguous, micropenis or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility
46,XX DSD								
Disorders of gonadal (ovarian) development								
SRY	TF	480000	Yp11.3	translocation	Testis or ovotestis	-	Male or ambiguous	
SOX9	TF	608160	17q24	dup17q24	ND	-	Male or ambiguous	
Androgen Excess								
HSD3B2	Enzyme	201810	1p13	AR	Ovary	+	Clitoromegaly	CAH, primary adrenal failure, partial androgenization due to ↑ DHEA
CYP21A2	Enzyme	201910	6p21-23	AR	Ovary	+	Ambiguous	CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal failure to simple virilizing forms with compensated adrenal function, ↑ 17-hydroxyprogesterone
CYP11B1	Enzyme	202010	8q21-22	AR	Ovary	+	Ambiguous	CAH, hypertension due to ↑ 11-deoxycortisol & 11-deoxycorticosterone
POR (P450 oxido-reductase)	CYP enzyme electron donor	124015	7q11.2	AR	Ovary	+	Ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency and aromatase deficiency; associated with Antley Bixler craniosynostosis
CYP19	Enzyme	107910	15q21	AR	Ovary	+	Ambiguous	Maternal androgenization during pregnancy, absent breast development at puberty, except in partial cases
Gluco-corticoid receptor	Nuclear receptor TF	138040	5q31	AR	Ovary	+	Ambiguous	↑ ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (NB patient heterozygous for a mutation in CYP21)

Key: AR, autosomal recessive; AD, autosomal dominant (often *do novo* mutation); Y, Y chromosomal; X, X-chromosomal; TF, transcription factor; ND, not determined; CAH, congenital adrenal hyperplasia; ACTH, adrenocorticotropin. Chromosomal rearrangements likely to include key genes are included. Modified from reference[88].