Chapter 4
The Early Care of the Infant with a Suspected Disorder of Sex Development

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Abstract Disorders of sex development (DSD) are a wide range of relatively rare conditions with diverse pathophysiology that are most often present in the newborn or the adolescent. Given their rarity and the need for multidisciplinary input, the management of the child with a complex form of DSD may be quite complex, and the situation is worsened by the lack of evidence of many diagnostic and interventional procedures that are undertaken. It is, therefore, not surprising that there will be variation in management as well as outcome of patients with this group of conditions. Whilst variation in clinical practice may reflect on the quality of care, this link still needs careful exploration in the field of DSD. By working as a network of clinical and research centers, it is possible that these variations can themselves be better managed and studied. This chapter will concentrate on outlining the variation in the early care and evaluation of infants with suspected DSD.

4.1 Introduction

Truly ambiguous genitalia on expert examination are a particularly challenging problem, but this situation is relatively rare and reported to occur in about 1:4,500 births (Thyen, Lanz, Holterhus, & Hiort, 2006). However, a concern about the development of the external genitalia may exist in 1 in 300 newborn infants, and, in over 80 % of cases, the affected infants are raised as boys and are likely to have a chromosome complement of 46,XY (Ahmed et al., 2004). Thus, it is estimated that in a country such as Scotland with 58,000 births per year, 200 infants are born with atypical genitalia and 160 are raised as boys. In girls with 46,XY karyotype, the

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most common known genetic condition that leads to a DSD is congenital adrenal hyperplasia due to 21α-hydroxylase which occurs approximately in 1:14,000 infants, and each year Scotland would expect to have approximately two affected girls. Unlike infants with XX DSD, who are most likely to be clinically investigated comprehensively and, in over 90 % of cases, shall have congenital adrenal hyperplasia, many infants with XY DSD who are raised as boys are investigated to a variable extent and the etiology remains unclear in the majority of them.

4.2 Variation in Terminology and the Chicago Consensus

The use of terminology which is clear and easy to use and understand by all health professionals, patients, and their families is fundamental to the understanding, investigation, and management of affected newborns and children. In addition, terminology should respect the individual and avoid terms which might cause offense. The term "intersex" has had variable connotations even within professionals; some employed it as a term that covered all affected newborns whilst, at the other end of the spectrum, some believed that the term should only apply to those in whom there is complete mismatch between chromosomal and anatomic sex. The consensus reached at the meeting of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology in 2005 in Chicago on the management of these patients, stressed the importance of terminology, and recommended the substitution of the term "intersex" with "DSD," which is defined as any congenital condition in which development of chromosomal, gonadal, or anatomic sex is atypical (Hughes, Houk, Ahmed, Lee, & The LWPES/ESPE Consensus Group, 2006). It also recommended the abandonment of terms such as "pseudohermaphroditism" and "true hermaphroditism." One of the greatest strengths of the new nomenclature is that it guides the clinician in reaching a definitive diagnosis in a stepwise manner. For instance, a child with a small phallus and penoscrotal hypospadias who has a 46,XY karyotype may initially be labeled as 46,XY DSD, but, as he undergoes investigations, he is suspected to have a disorder of testosterone synthesis. The biochemical tests may point toward a deficiency of 17βHSD, and the diagnosis is confirmed by genetic investigations.

Although the DSD nomenclature (see Table 4.1) is easier to use and understand, and helps the professional in planning investigations, it will nevertheless evolve over time as our understanding of long-term outcome, as well as molecular etiology, improves in the future. The structure of the nomenclature has been developed in such a way that there is scope for it to incorporate such developments. Given that genital anomalies may occur as commonly as 1 in 300 births and may not always be associated with a functional abnormality, some have advocated the use of "differences" in preference to the term "disorder" (Diamond, 2009). The use of phrases such as "differences" or "variations" in sex development may help to introduce the concept of the range of variation that may occur in sex development. The strength of the acronym "DSD" is that it can be used to cover both differences and disorders

Table 4.1 The range of disorders of sex development that may be associated with a male sex of rearing

Disorder type	Diagnosis
XX or XY disorder of gonadal development	Complete gonadal dysgenesis
	Partial gonadal dysgenesis
	Gonadal regression
	Ovotesticular DSD
	Testicular DSD
XY disorder of androgen synthesis	Lipoid congenital adrenal hyperplasia*
	P450 side chain cleavage enzyme deficiency*
	3β-Hydroxysteroid dehydrogenase 2 deficiency
	17,20-Lyase deficiency
	17β-Hydroxysteroid dehydrogenase 3 deficiency
	5α-Reductase-2 deficiency
	P450 oxidoreductase deficiency
XY disorder of androgen action	Complete androgen insensitivity syndrome
	Partial androgen insensitivity syndrome
XX disorder of androgen excess	21α-Hydroxylase deficiency*
	11β-Hydroxylase deficiency*
	P450 aromatase*
	P450 oxidoreductase deficiency*
XY Leydig cell defect	Leydig cell hypoplasia
	LH deficiency
XY persistent Mullerian duct syndrome	AMH low
	AMH normal
XY isolated disorders of genital development	Isolated hypospadias
	Isolated bilateral cryptorchidism
	Isolated micropenis
XY complex disorders of genital development	Cloacal anomaly
	Bladder exstrophy
	Complex syndromes
	Complex combined anomalies

Conditions marked with an asterisk are more likely to be associated with a female sex of rearing. Further clinical details of the commonly encountered conditions are available in Ahmed et al. (2011)

of sex development. However, the likelihood of this difference existing as a disorder will depend on the functional implications of the condition, which may also be heavily influenced by the social and cultural framework within which the child exists.

4.3 Variation in Investigating Infants at Initial Presentation

While there is no doubt that investigations are required in all infants with clearly ambiguous genitalia in whom the sex of rearing is uncertain, there is less clarity about when investigations should be performed in those situations in which the genitalia are less ambiguous. This is particularly the case in those infants who are considered to be boys. Although there are some guidelines to inform the clinician's decision to investigate, these are mostly based on expert opinion (Hiort, 2011; Keir, O'Toole, Robertson, Wallace, & Ahmed, 2009; Viner, Teoh, Williams, Patterson, & Hughes, 1997). These guidelines suggested that groups of infants who should be evaluated include those with female genitalia with atypical features, such as an enlarged clitoris, or those with male genitalia with atypical features, such as abnormal penile development or impalpable testes. An evaluation may also be necessary in those with a family history of DSD or when there is a discordance between genital appearance and a prenatal karyotype.

In suspected cases of DSD, a karyotype check is often the first test that is undertaken; studying the practice of performing a karyotype in cases of atypical genitalia may be one way of assessing the variation in the practice of investigating new infants. A review by Rodie et al. (2011) of the practice of performing karyotype in Scotland, using the register kept by the Scottish DSD Network, showed that of 572 affected cases presenting between 2002 and 2007, 153 had a karyotype. This was more likely in the presence of a low masculinization score, bilateral impalpable testes, proximal hypospadias, or associated malformations. This study had primarily collected data from two Scottish cities with a combined birth rate of 16,500/year. Of the 572 cases, 52 had a karyotype within the first 10 days of birth and 20 of these 52 cases had it performed urgently, suggesting that there was a question about sex assignment in these 20 cases. Thus, these data also suggest that approximately three out of 16,500 births per year require further tests for sex assignment. The study also showed that 20 % of boys with bilateral impalpable testes did not have a karyotype, and in most karyotyped cases, this was performed after the age of 10 days.

4.4 Variation in Diagnostic Investigations

Reaching a diagnosis in DSD requires thorough delineation of the external and internal anatomy, as well as biochemical and molecular genetics. Not only are these procedures dependent on the skills and knowledge of the operators, but they are also highly resource intensive and continue to evolve over time. Biochemical tests are highly dependent on the method used to perform the test (Tomlinson, Macintyre, Dorrian, Ahmed, & Wallace, 2004). By identifying the etiology more precisely, molecular genetic analysis has the potential to tailor the rationale for long-term therapy and management in many cases of DSD, but there is a need to show this more clearly by reporting long-term outcome (Camats et al., 2012; Tantawy et al.,

2012). Notwithstanding these challenges, it is clear that the range of tests that are performed in cases of DSD can be quite variable. This was illustrated when studying a research database of over 700 cases of XY DSD that was held in Cambridge in 2000 (Ahmed, Cheng, & Hughes, 1999). This database consisted primarily of cases from a wide range of clinicians in the UK. Of 153 cases suspected of having partial androgen insensitivity syndrome, approximately one third did not undergo stimulation with human chorionic gonadotrophin (hCG), a test which is performed to study the production of testosterone so that conditions which are associated with poor testosterone synthesis can be identified. Furthermore, a range of doses of hCG were administered in those who did have an hCG stimulation test (Ahmed et al., 1999). The regimen of hCG stimulation and the timing of the blood samples may be important in the interpretation of the test, as reported by Dixon, Wallace, O'Toole, and Ahmed (2007). The definition of an optimal testosterone response to hCG stimulation has also been variable (Kolon & Miller, 2001).

4.5 Variation in the Support Available to New Parents

Child behavior, life events, and parental personality characteristics can raise parenting stress which, in turn, can adversely affect the quality of caregiving, parent–child interactions, and child behavior (Dawson, Ashman, & Carver, 2000). Coping is used to mediate stress, and a family can utilize specific cognitive and behavioral coping strategies to reduce this stress. It is likely that parenting stress and coping patterns may influence the child's long-term psychological outcome. Whilst there are many published reports of the role of chronic disease as parental stressors, there is little published evidence on the needs of parents of children with atypical genitalia and how best to support them. As it is important to understand potential stressors that parents may face and the methods they use to cope with their child's condition, the Scottish DSD network performed a study in 2004 examining stress and coping patterns among parents of affected children using quantitative psychological assessment tools, as well as a semi-structured qualitative interview. Quantitative assessment results indicated that parents did not generally seem to display abnormal levels of stress or coping (Duguid et al., 2007). However, the semi-structured interview provided further information about the parents' level of coping and potential for stress and highlighted the need for more effective exchange of clinical information. The study also raised a question about the reliability of using standardized quantitative questionnaires for the purpose of identifying parents with clinical levels of stress or problems with coping. Of the 19 parents who were interviewed, 95 % reported receiving suboptimal information at birth, 84 % had concerns about sexual function and fertility, 80 % found relatives a helpful source of support, and approximately 75 % found senior hospital-based clinical staff a useful source of support. However, about 65 % also reported that they found the subject difficult to discuss with relatives and friends, and approximately 60 % coped with the condition by thinking that it could be completely treated. In addition, four parents admitted that

the condition was even difficult to discuss between the mother and father, and four wished for greater support in explaining the condition to the affected child. Eleven (58 %) parents reported that they were unclear about the expected appearance of the genitalia following the operation. Five (26 %) parents raised concerns about recurrence of the condition either in their own future offspring or those of the affected child or the affected child's siblings. A substantial number of parents reported the need for written information on general issues such as the condition. The need for gradual and steady information about the condition following the initial presentation was also reported, as was the need for some illustrative examples of the expected appearance postoperatively. Eight (42 %) parents reported the desire to have a local network of families with children affected with similar conditions. Other sources of support such as a website and a link person who would be available at the initial presentation were also highlighted by some parents.

In 2011, a revised survey was performed to assess similar outcomes. The questionnaire was administered, by post, to all parents of children between the ages of 6 months and 24 months on the Scottish DSD Network register. Of the 56 questionnaires sent to families whose children had been managed in four centers in Scotland, 17 (21 %) completed questionnaires were received from parents with babies delivered in 10 maternity hospitals in Scotland. The sample was largely made up of boys with hypospadias, and only one parent was aware of a delay in sex assignment of their child. For most outcomes, the care received was rated favorably, but the availability of emotional support and information through websites and support groups was rated low by many parents (unpublished observations).

4.6 UK Guidance on the Initial Approach to an Affected Infant

Based on the above findings, a UK taskforce representing the wide range of professionals who are often involved in a complex case of DSD developed and published some guidance that was aimed at supporting clinical professionals in the initial evaluation and diagnosis of children with suspected disorders of sex development and providing a framework to standardize clinical practice throughout the UK. The consensus that was reached in Chicago in 2005 on the general principles of managing patients with DSD represented a historic milestone for international and multidisciplinary collaboration in this area. However, some areas of care, such as the initial approach to evaluating the infant or young person with suspected DSD, were not covered in detail as that was beyond the scope of the exercise. In addition, guidance on the initial evaluation of a complex condition is often colored by local provision of health care, and it was felt that reaching a consensus at a national, United Kingdom, level would be the most effective means of proceeding further. The guidance was subjected to a lengthy period of open consultation before its publication (Ahmed et al., 2011). The main recommendations are summarized as follows:

- Infants with a suspected DSD should be treated by an experienced multidisciplinary team, accessible through a regional center. At a minimum, this team should include specialists in endocrinology, surgery and/or urology, clinical psychology, radiology, nursing, and neonatology.
- One main contact person should be assigned to each family; in most cases, this will be the pediatric endocrinologist. The family should be told of the range of support available to them and provided with contact details for these personnel. They should also be made aware of the stepwise process used to diagnose and manage DSD, with the ultimate goal of achieving long-term well-being.
- Access to specialist psychological support during and after the diagnostic process is essential for both the affected person and their parents. The pace of how information is shared should be set by the family and issues of confidentiality discussed and respected.
- The exact tests used to diagnose a DSD will vary among patients. However, at a minimum, the multidisciplinary team should take into account the patient's external appearance, internal anatomy, genetic makeup, and hormone profile.
- The most important goals of the initial assessment period are to support the affected child and parents, assign a sex of rearing, and exclude the possibility of any early medical problems.
- Patient groups can provide important psychological support and information to affected individuals and their families. Contact details of relevant support groups should be provided as routine by healthcare professionals upon diagnosis.
- All medical personnel involved in the care of a patient with a DSD should have access to a regional DSD team. The team has a responsibility to educate other healthcare staff and should have a regular forum where they meet to discuss the case and review its own performance.
- By contributing to national and international disease registers, regional DSD teams have an important role in performing audit and research into the long-term outcome of these rare conditions.

4.7 Clinical Networks for Managing Complex Conditions

It is unrealistic to expect that every major clinical center can possess a comprehensive, multidisciplinary DSD team as outlined earlier. Furthermore, in many cases, care at a local hospital may be more appropriate for reasons of both convenience and necessity (e.g., adrenal crisis in CAH). For the less complex case of hypospadias, immediate multidisciplinary input may not be necessary, and initial discussion and explanation of the condition with the parents do not require urgent transfer of the baby at an emotionally sensitive period. Similarly, some investigations can also be performed at local centers that are affiliated to a regional center. It is, however, important that all personnel who may be involved in the care of an affected person have access to the regional DSD team and have the opportunity to develop themselves professionally. Some regions have overcome these hurdles with the

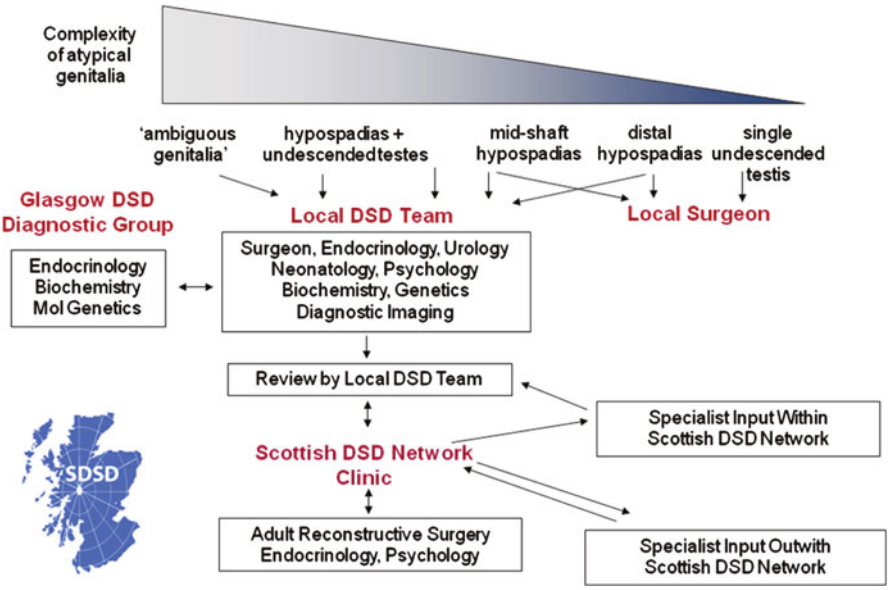

Fig. 4.1 Structure of the service that the Scottish DSD Network aims to deliver in Scotland. Depending on the complexity of the condition and the individual needs of the patient, the patients flow between clinics where healthcare professionals with appropriate skills are available. The network is supported by a diagnostic group which meets separately, channels cases for molecular genetic evaluation, and interprets the results

development of a national managed clinical network (http://www.sdsd.scot.nhs.uk). A service model such as this attempts to provide an equitable state-of-the-art service for all affected children and adolescents in a region. A formal organization allows a structured referral pathway within the region, as well as beyond, and provides the infrastructure for better long-term care of the patient as close to home as possible (see Fig. 4.1). A network can also facilitate the creation of agreed protocols for the care of the affected newborn, setting and monitoring of national standards of care, and rational utilization of other services such as molecular genetics and clinical biochemistry and provides a forum for education and professional development.

Research and audit are vital for the management of DSD, and clinical networks have a strong potential to drive these activities. The 2005 Consensus Meeting on DSD stressed the need for the creation and maintenance of a database in centers of expertise. Clinical audit systems that collect information on clinical activity and outcome should be an integral component of national specialist services and need to be seen as a tool for management, as well as audit. Such databases may exist at a less formal level in many other regional centers but until recently have lacked international uniformity and the ability to cross talk. A Web-based register (http://www.i-dsd.org) has been approved by the UK National Research Ethics Service as a multicenter research database which does not require any further local research approvals but does require the approval of the patient or parent. The development of

this Web-based virtual research environment was initially supported by the European Society of Paediatric Endocrinology in 2007 as the European DSD Registry. Following this, it was further developed between 2008 and 2011 by the EuroDSD project (Ahmed, Rodie, Jiang, & Sinnott, 2010), and it is now supported by the Medical Research Council of the UK as the International DSD Registry. Clinicians from 28 countries from the 5 continents have now registered as users of this Registry, and, currently, 19 clinicians from 14 countries in 3 continents (Europe, Asia, and Africa) have contributed clinical details in 1,098 cases. It is anticipated that the Registry will act as a long-term resource that supports the development of an international clinical and research network.

4.8 Conclusion

The last decade has seen enormous strides toward the development of multicenter collaboration—a willingness of experts in the field of DSD to reach a consensus and develop clinical and research networks. This has coincided with major advances in our knowledge of the underlying etiology as well as the diagnostic technology that is currently available now. It is anticipated that these developments that focus on the early care of the affected child will lead to an improvement in long-term outcome. The ground is now set for the wider community of healthcare professionals and patients to agree on the long-term outcomes that need to be assessed. Finally, while there is a high level of agreement on the importance of communication within clinical teams, as well as between the teams and the patients and their parents, there is a need to improve our understanding of effective methods of communication.

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