



**Submission of the Australasian Paediatric Endocrine Group to the
Senate Inquiry Into the Involuntary or Coerced Sterilization of People with
Disabilities in Australia:
Regarding the Management of Children with Disorders of Sex Development.**

27 June, 2013

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About the Australasian Paediatric Endocrine Group (APEG)

The Australasian Paediatric Endocrine Group (APEG) is the professional body in Australia and New Zealand which represents clinicians involved in management and/or research for children with disorders of the endocrine system, including disorders of sex development. The great majority of children with disorders of sex development in Australia are under the primary clinical care of members of APEG. A key focus of our organisation is to promote and maintain the highest standards of diagnosis and treatment of paediatric endocrine disorders.

Disorders of sex development (DSD)

Disorders of sex development (DSD) are defined as conditions where the development of the sex chromosomes, the testes/ovaries, or the genital anatomy are atypical. There are many different types of DSD, and the incidence of this group of disorders range from 1 in 125 boys for a mild variant, to 1 in 4,500 babies where the genitalia appear significantly ambiguous at birth such that the sex of the infant is unable to be immediately determined.

Some patient groups in Australia prefer to use the term 'intersex' to refer to individuals with a DSD, however other patient groups in Australia find this term pejorative and offensive, and do not want to be termed or referred to as 'intersex'. We acknowledge that all individuals with DSD should be referred to in the manner in which they identify with regard to their gender. This includes those who identify as male or female and who do not identify as intersex, and who find the term 'intersex' offensive. Furthermore, the definition of 'intersex' is medically, and therefore legally ambiguous. We therefore recommend against use of the term 'intersex' in medical legislation. We use the term 'disorders of sex development', as this is the medically recognised and defined term for these conditions internationally, however we acknowledge that some prefer not to use medical terminology.

The various forms of DSD are summarized in Table 1. Each of these diagnoses are associated with varying risks of gender identification distress, hormonal deficiencies, infertility, or cancer of the testes or ovaries.



Table 1. Types of disorders of sex development.

| | 46, XY chromosomes | 46, XX chromosomes | Mixed sex chromosomes (e.g. XXY, X, X/XY) |
|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Abnormal testis or ovary development | Gonadal dysgenesis Complete, mixed and partial gonadal dysgenesis Ovotesticular DSD Testicular regression syndrome | Gonadal dysgenesis Testicular and ovotesticular DSD Premature ovarian failure due to gonadal dysgenesis | Gonadal dysgenesis Partial, mixed and complete gonadal dysgenesis Ovotesticular DSD |
| Abnormal testosterone action | Androgen biosynthesis defect e.g. 17 β -hydroxysteroid dehydrogenase deficiency, 5 α -reductase deficiency Androgen insensitivity Androgen insensitivity syndrome (partial or complete) | Increased synthesis Congenital adrenal hyperplasia Maternal/placental androgen excess Placental aromatase deficiency | |
| Syndromic | Cloacal exstrophy, simple hypospadias | Cloacal exstrophy, vaginal agenesis | |

History and Trends

In the past, it was thought that adequate penis size was the main determinant of whether an infant with ambiguous genitalia should be assigned male or female at birth. Following gender assignment, surgery was performed to normalise the appearance of the external genitalia, and to remove testes in children raised female. There was, however, very little follow-up data published to support this management approach.

Indeed some individuals who were assigned female but later identified as male and who had tissue removed from their clitoris/phallus, as well as those who continued to identify as female but feel they have poor genital outcomes following removal of tissue from the enlarged clitoris, are angry about surgery which was performed in their childhood. These concerns were brought into the public and policy spotlight by patient support groups such as ISNA (Intersex Society of North America), which has now been renamed Accord Alliance following international disuse of the term 'intersex' to refer to all people with DSD.

The trend with time has been toward assigning male sex where there is evidence of androgen action, particularly for those with a 46,XY karyotype. There has also been a trend toward consideration of less genital and gonadal surgery in infants assigned female, or delaying surgery. It is important to note that current practice has changed significantly from the past.

A major concern in medical management, both in Australasia and internationally, is with deficient psychosocial support, particularly as the young person with DSD becomes older.

These considerations have been synthesised in various consensus statements which describe recommended indications for genital and gonadal surgery in specific types of DSD, and strong recommendations for improved psychosocial support.

It is becoming clear that specific diagnoses lead to different health risks and different considerations with regard to surgery. Consensus statements therefore call for improved accuracy of the specific diagnosis, or type of DSD, for this reason.



Hormonal and surgical management of DSD

Hormonal management

Some forms of DSD are associated with deficiencies of critical hormones required for survival, or of sex hormones testosterone and oestrogen. Replacement of the critical hormones is necessary throughout life, and replacement of the sex hormones is required occasionally briefly after birth or during childhood, but usually from the time of puberty to allow physiological development, growth, and development of bone strength.

Surgical management

Indications for surgery in DSD involve management of high cancer risk in the testes or ovaries, management of dysfunctional urine flow, creation of a vagina, or surgery for the purpose of appearance including reduction of an enlarged clitoris or repair or construction of a urinary outlet to the end of the penis.

a. Surgery for cancer risk

Cancer risk is stratified by the underlying diagnosis in high-risk and low-risk groups, described in Table 2. In high-risk groups the recommendation is to remove the gonads before the individual develops cancer, which can occur in childhood. It would be negligent to expose these children to cancer by leaving the testes/ovaries in when the high risk is known.

Table 2. Cancer risk and treatment recommendations. From Looijenga LHJ et al. Tumor risk in disorders of sex development (DSD). Best Practice and Research: Clinical Endocrinology and Metabolism 2007;21(3):480–95.

| Risk group | Disorder | Malignancy risk (%) | Recommended action | Studies (n) | Patients (n) |
|--------------|---------------------------------------------------|---------------------|--------------------------------------|-------------|--------------|
| High | GD ^a (+Y) ^b intra-abdominal | 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 |
| | 17 β -HSD | 28 | Monitor | 2 | 7 |
| | GD (+Y) ^c | Unknown | Biopsy ^d and irradiation? | 0 | 0 |
| | PAIS scrotal gonad | Unknown | Biopsy ^d and irradiation? | 0 | 0 |
| Low | CAIS | 2 | Biopsy ^d and ??? | 2 | 55 |
| | Ovotestis DSD | 3 | Testis tissue removal? | 3 | 426 |
| | Turner (– Y) | 1 | None | 11 | 557 |
| No (?) | 5 α -reductase | 0 | Unresolved | 1 | 3 |
| | Leydig cell hypoplasia | 0 | Unresolved | 2 | |

CAIS, complete androgen insensitivity syndrome; 17 β -HSD, 17 β -hydroxysteroid dehydrogenase deficiency; PAIS, partial androgen insensitivity syndrome.

^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, with diagnosis preferably based on OCT3/4 immunohistochemistry.



The Senate has unfortunately received misleading information in submissions on this issue. We are concerned that some of the information presented appears to have been either misunderstood, or misrepresented in error, leading to inaccurate conclusions. Some authors have misunderstood the difference between high-risk and low-risk cancer groups within DSD, and in particular, one submission incorrectly implied that the cancer risk for a diagnosis in the highest-risk group ("PAIS with non-scrotal/intra-abdominal testes") was quoted by Warne and Hewitt as being the cancer risk for a diagnosis in the low-risk group ("CAIS"), as outlined in Table 2. The implication is that testes or ovaries are being removed from patients with diagnoses at low-risk of cancer, such as CAIS, however this is incorrect. The recommendation of Warne and Hewitt, and in the current medical literature, is for preventative surgical removal only in the high-risk and intermediate-risk cancer group, as outlined in Table 2. It is not recommended that testes/ovaries are removed from patients in the low-risk cancer group, although these patients remain at elevated risk for cancer above the general population, and ongoing cancer monitoring is essential.

International medical guidelines exist to define high-risk and low-risk cancer groups, and recommend treatment for each group. APEG recommends that treatment for cancer risk follows these international best practice guidelines. The way to ensure that clinicians are quoting accurate cancer risks and correctly following these guidelines nationally would be to establish properly funded specialist multidisciplinary management teams, with expert peer review of management decisions.

Of significant concern is that of individuals who are not in the high-risk cancer group, there remains an elevated risk for cancer, even if the risk is not high enough to indicate removal of the testes/ovaries at an early age. At present there is no national system or registry for the life-long monitoring of these patients. Establishment of such a registry is strongly recommended by APEG.

b. Surgery for dysfunctional urine flow

When the genital anatomy is complex, there may be obstruction to urine flow, or pooling of urine in the vagina or uterus. Surgery is medically indicated in these cases, in order to correct urine flow and prevent infection or organ damage.

c. Surgery for creation of a vagina

Surgery may be performed to create a vagina where there was none present at birth. This surgery also involves separating the labial/scrotal folds which may be fused together, but no removal of tissue.

d. Reconstructive reduction of an enlarged clitoris or repair or construction of a urinary outlet to the end of the penis

The purpose of these procedures is for functional reasons such as to allow a male individual to urinate while standing, and for psychosocial reasons such as to allow the child to develop without the psychosocial stigma or distress which is associated with having genitalia incongruous with the sex of rearing. Surgery for psychosocial indications remains in contention both within Australasia and internationally, particularly for reduction of an enlarged clitoris, as tissue is being removed which the individual may wish was not removed later on.

There is limited evidence reporting long-term outcomes of early surgical management for reasons of appearance. The few outcome studies reported have conflicting results of good and poor outcomes (cosmetic, sexual, or psychological), with particular concern regarding sexual function and sensation. Surgical techniques have differed over time, with clitorrectomy no longer performed, and clitoral reduction now being favoured by surgeons. Some individuals are unhappy with their childhood treatment and have formed advocacy groups or pursued litigation. Other patients report satisfaction with early surgery. Best practice



treatment relies on current consensus statements endorsed by learned bodies, and consideration of medical ethics.

International medical guidelines exist to define the level of genital ambiguity at which surgery is indicated, however the guidelines state that the optimal timing of surgery remains debatable. This is because there is a lack of strong evidence to either support or refute specific recommendations on timing. According to current consensus guidelines, surgery for the purposes of appearance can ideally be recommended either during infancy, or later at the time of adolescence, when the child can be involved in the decision to operate.

Controversy exists with regard to surgery in infancy, as consent for surgery is provided by the parents on behalf of the child. For girls with a specific diagnosis of congenital adrenal hyperplasia there can be spontaneous reduction in the size of the clitoris with adequate hormone replacement therapy, and some specialists recommend that surgery be delayed until no further shrinkage is expected, before considering any surgery to further reduce size. In some cases, with adequate hormone treatment, there can be enough natural regression in size during infancy such that surgery is not indicated any more. However, other specialists argue that very early surgery in the first months of life is optimal, and that there is no need to wait for any natural regression in clitoral size.

APEG acknowledges the contention in this area, and recommends that until further evidence becomes available, surgery for the purposes of appearance should only occur if consistent with international medical guidelines on degree of ambiguity, and that in terms of timing, parents should be thoroughly counselled about the options of very early surgery, delay until later in infancy or delay until the child can be involved themselves in the decision to operate. We are in the process of performing a study of the recommendations on surgical timing across the clinicians in our organisation.

In the setting of the controversy regarding timing of surgery, and with fully informed consent, APEG recommends that parents be able to provide consent to either early or late surgery after discussion with an expert specialist multidisciplinary team and consideration of ethical principles (see later in this document).

Multidisciplinary management groups

Current consensus recommends expert specialist multidisciplinary management groups to be established to case conference the accurate diagnosis and management of children with DSD. Multidisciplinary groups have now been established and properly funded throughout the world. The composition of the multidisciplinary group may include endocrinologists, urologists, gynaecologists, psychologists, geneticists, biochemists, and bioethicists amongst others.

Informal multidisciplinary management groups have been established in Australia, however unlike those established overseas, none have received discrete health funding, and they often do not have participation of all the specialists listed above. At present there is no formal process requiring expert multidisciplinary management team review of children with DSD, and thus not all patients receive review by such an expert group.

APEG supports the funding of formal specialist multidisciplinary DSD management groups as a priority, and recommend that all cases of DSD should be discussed with a specialist DSD management group.



Ethical issues in DSD management

Due to the high significance of management decisions on long term outcome, ethical implications of decisions must be considered. An ethical framework for clinical management decisions has been developed by Gillam, Hewitt and Warne at the Royal Children's Hospital Melbourne, recommending that the following are considered:

- (1) Minimising physical risk to child.
- (2) Minimising psycho-social risk to child.
- (3) Preserving potential for fertility.
- (4) Preserving or promoting capacity to have satisfying sexual relations.
- (5) Leaving options open for the future.
- (6) Respecting the parents' wishes and beliefs.

Unfortunately these principles are not always compatible with each other in clinical decision making. However, APEG recommend that each principle is considered individually for each patient.

Legal issues in DSD management

In recent years, some doctors have brought cases of DSD to the Family Court for approval of planned gonadectomy. This was under the Special Medical Procedures Act, which outlines the requirement for 'non therapeutic' treatments to be approved by the court.

The ruling of *Re: Sally* FCA 2010 found that gonadectomy could occur in a young person who had a cancer risk of 28%, but that similar cases should be brought before the court. The subsequent ruling of *Re: Sean and Russell* 2010 found that gonadectomy could occur in two children who had a cancer risk of 40%, but that similar cases should be decided with the parents and doctor, and should not be brought before the court, i.e. they were therapeutic.

At present it appears that the Family Court of Australia consider a cancer risk of >28% as 'therapeutic'. Although gonadectomy in cases with cancer risk of 28% was also deemed therapeutic, further involvement of the Family Court was recommended for all such cases. International guidelines, however, recommend surgery for some diagnoses where the cancer risk is below 28% (see Table 2).

The stress and considerable financial cost to families in seeking legal approval for medical care of their children is detrimental to the health of the family unit, and is not consistent with holistic or equitable health care. It is also unnecessary if the approval for surgery occurs in conjunction with appropriate discussions with an expert multidisciplinary team.

APEG recommends that the classification of surgery for cancer risk in DSD as a 'special medical procedure' is urgently clarified, and recommend that the definition of 'therapeutic' treatment should be that which is defined as such by the current medical literature.



National and international guidelines

Following lengthy consultation and inquiry, the Victorian Department of Health published a framework for the management of DSD in 2012. These guidelines support the recommendations made in this submission to the senate.

International treatment guidelines exist for hypospadias repair, feminising genitoplasty, and for gonadectomy for high cancer risk. Each of these guidelines recommends a level of severity above which surgery is indicated, and recommendation on when surgery should be performed (including mention of controversies on timing).

APEG believes that medical best practice would be adherent to these guidelines, which represent current international medical consensus, and which have been endorsed by specialist medical professional learned bodies.

Requirement for patient registry and follow-up

In view of the significant health risks associated with DSD, and the significance of decision making on the affected individual's lives, it is essential that individuals with DSD are closely monitored and followed up, with data collected and analysed to determine the best treatment and improve medical management.

Current international guidelines recommend long-term follow-up of children with DSD who have early surgery. This does not occur in Australia, as there is no co-ordinated registry regarding the management and outcomes for people with DSD.

APEG strongly recommends that governmental funding is made available to create a patient registry to ensure adequate follow-up of patients with DSD who may develop gender dysphoria, sexual dysfunction as a result of surgery, and cancer in any testes/ovaries left in the body, and to support research to improve care and guide decision making for individuals with DSD.



Conclusion

The management of DSD in children remains highly complex, and although international recommendations exist for clinical decision-making, some areas remain contentious. APEG recommend that treatment be consistent with international practice guidelines as well as ethical principles, with all decisions made with the full informed consent of the parents and the assent of the young person if they are old enough to be able to become involved in decision making.

Urgent clarification is required regarding interpretation of the law with regard to 'special medical procedures'. APEG urges the senate to define which cases require court approval and which do not.

There are currently no discretely funded multi-disciplinary medical services for children with DSD in Australia, unlike the funded clinics in the UK, the US, and many countries in Europe. APEG recommends that funded multidisciplinary clinics be established in Australia.

It is very important that a patient registry is established for long-term follow-up of individuals with DSD. This is because of the significance of early decision making on long-term patient outcomes, including gender identity change, psychosexual dysfunction, and risk of cancer. These are very strong arguments for establishment of a patient registry. Patient registries exist for other significant disorders in Australia, however due to stigma and perceived rarity of DSD, funding has not previously been allocated for a patient registry for DSD.

Improvements in care for individuals with DSD will not occur without improvements in clinical service provision and research. We appreciate the effort the Senate is making into improving the situation for individuals with DSD in Australia.

Recommendations

1. APEG has adopted the established guidelines developed by the Victorian Department of Health, which it feels are safe, responsible and respectful and are currently the best practice internationally.
2. APEG recommends that children deemed to have an elevated cancer risk need to have a process of co-ordinated follow-up if a decision is made not to perform gonadectomy, thereby leaving the testes/ovaries at elevated risk of cancer in the body. Furthermore, as there is no system of centralised care for children with DSD, and major long-term implications of early management decisions, there is a need for long-term monitoring of medical and surgical management.

Current international guidelines recommend long-term follow-up of any patient who has early surgery, however this is not occurring in Australia. A national patient registry should be established for this purpose.

3. APEG agrees with the Family Court that a cancer risk of more than 28% is sufficient to perform a therapeutic removal of the gonadal tissue without recourse to Family Court decision. However the process to be followed for cancer risk considered to be less than 28% is not clear and requires urgent clarification. APEG recommends a non-adversarial approach is best for families in the majority of cases.

APEG feels that management should in the first instance follow international guidelines with full informed consent of the parents, with involvement of an expert specialised DSD medical service rather than go to the Family Court. APEG endorses the method which has been employed in developed countries internationally, via the establishment of properly funded, expert specialist multidisciplinary teams or a national expert panel, which reviews individual cases in conjunction with local care providers, and considers the relative risks of cancer versus loss of fertility or hormone production.



4. APEG recognises that there are ongoing difficult decisions regarding genital surgery in minors with DSD raised female, specifically regarding reduction in size of the clitoris/phallus i.e., at what degree of ambiguity is surgery indicated and when is the best time to perform such procedures? It will not be possible to legislate on this matter and APEG recommends that properly funded specialist medical services following international guidelines and recommendations, along with ethical considerations and fully informed parental consent are the best way to deal with such matters.
5. APEG recommends that specialised services with wide expertise (clinical/surgical/ psychological/ ethical/ legal) are important for the ongoing care of people with DSD, and that the Commonwealth and the States discuss the funding and development of such specialised services to be available to all with DSD.
6. APEG recommends that there should be a review of the clinical management and long-term outcome for people with DSD. This review should be funded by the Department of Health and Ageing and will help inform future decision making.

We thank the Senate Committee for its consideration of this submission.

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