

# Chapter 6

## Research and future directions

### Research on outcomes

6.1 Intersex is a term that embraces a range of biological traits and medical conditions, some requiring medical treatment and some not, with some of the medical treatment being complex and highly specialised. The numbers of people who are intersex are relatively small, and the numbers with any particular variety of intersex smaller still. Knowledge of their needs and experiences is limited, and gaining understanding of intersex has been severely impaired by stigma, ignorance and misunderstanding.

6.2 Despite some excellent studies in the field in relation to long-term outcomes and cancer management, there is a serious shortage of quality information, not only about medical treatment, but about the non-medical dimensions of intersex life. This is most evident in relation to sex assignment, including by surgery, as discussed in chapter three.

6.3 Even where studies are conducted, many suffer from significant methodological problems, some of which were discussed in more detail in chapters three and four. There are very few longitudinal studies following intersex individuals over their life course, and these studies face sampling problems:

Study bias or methodological problems are frequently encountered. Studies may experience poor patient participation or low numbers because these disorders are so rare. Selection bias is likely to be problematic because of the rare prevalence of the conditions or of the complexities of accruing research subjects.<sup>1</sup>

6.4 All studies face significant risks that the participants as a group may have different features from those who decline to participate, creating a biased sample.

6.5 The 2006 Consensus Statement indicated that there was still much to be learned to address treatment decisions for which it is currently hard to find good guidance. The Statement observed:

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 and take cognisance of guidelines relevant to all chronic conditions. These should preferably be prospective in nature and designed to avoid selection bias. Several countries already have registers of DSD cases but there could be added benefit from pooling such

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1 William G. Reiner, 'Gender identity and sex-of-rearing in children with disorders of sexual differentiation', *Journal of Pediatric Endocrinology & Metabolism*, Vol. 18, 2005, p. 552.

resources to enable prospective multicentre studies to be undertaken on a larger number of cases that are clearly defined.<sup>2</sup>

6.6 Research since that time has continued to argue for the importance of larger and better studies. Pleskacova and others, for example, dealing with cancer risk and gonadectomy, stated:

Of course, large series of patients are required for such an ambitious vision [of identifying which patients would benefit from gonadectomy]. As DSD is relatively rare, multi-centric studies and international cooperation are indispensable.<sup>3</sup>

6.7 The importance of high quality studies was echoed by OII, which argued:

We still lack sound, clear evidence of both necessity and good outcomes, and we lack longitudinal or control studies. Clinical practice is still based on inconsistent assertions of psychosocial risks and benefits, and cancer risk.<sup>4</sup>

6.8 In this context, OII favoured not only better quality studies, but also the development of capacity to track patients:

The lack of good data is a common theme in studies on intersex health, including the lack of useful sample sizes, non-standardised measures, lack of control groups, and selection bias in research. We wish for children to continue to receive a male or female assignment with recognition that this is mutable but, independent of this, there is a need for children and adults with an intersex status to be tracked through the health system, and more broadly.<sup>5</sup>

6.9 The concerns of OII were very similar to those of APEG, who called for a patient registry and better studies of long-term outcomes:

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

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2 Peter A. Lee, Christopher P. Houk, S. Faisal Ahmed, Ieuan A. Hughes et al, 'Consensus Statement on Management of Intersex Disorders', *Paediatrics*, Vol. 118, No. 2, 2006. <http://pediatrics.aappublications.org/content/118/2/e488.full#xref-ref-2-1> (accessed 26 July 2013).

3 J. Pleskacova, R. Hersmus, J.W. Oosterhuis, B.A. Setyawati, S.M. Faradz, M. Cools, K.P. Wolffenbuttel, J. Lebl, S.L. Drop, and L.H. Looijenga, 'Tumor Risk in Disorders of Sex Development', *Sexual Development*, Vol. 4, No. 4–5, 2010, p. 268.

4 Organisation Intersex International Australia, *Submission 23.3*, p. 3.

5 Organisation Intersex International Australia, *Submission 23.1*, p. 16.

research to improve care and guide decision making for individuals with DSD.<sup>6</sup>

6.10 APEG recommended that the Commonwealth fund a review of long-term outcomes and management.<sup>7</sup>

### **Recommendation 13**

**6.11 The committee recommends that the Commonwealth Government support the establishment of an intersex patient registry and directly fund research that includes a long-term prospective study of clinical outcomes for intersex patients.**

#### **Research on hormone intervention**

6.12 The committee's attention was drawn to one particular issue regarding research in the field of intersex. This concerned the administering of hormones, specifically dexamethasone, to pregnant women as a treatment for CAH in their foetus.

6.13 CAH is a group of conditions, the most common of which is of women who experience a deficiency of the enzyme 21-hydroxylase. Foetuses with CAH:

[a]re exposed to unusually high levels of androgens during fetal development, which variably masculinize the genitalia and presumably also the brain and later behaviour.<sup>8</sup>

6.14 Commencing in the mid-1980s, medicine has sought to use hormone treatment to counteract this androgen exposure. The treatment involves treating pregnant women with a steroid, dexamethasone, throughout the pregnancy.<sup>9</sup>

6.15 Research on people with CAH has led to a number of observations around sex and behaviour in CAH women, such as those made by Meyer-Bahlburg in 1999:

CAH women as a group have a lower interest than controls in getting married and performing the traditional child-care/housewife role. As children, they show an unusually low interest in engaging in maternal play with baby dolls, and their interest in caring for infants, the frequency of daydreams or fantasies of pregnancy and motherhood, or the expressed

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6 Australasia Paediatric Endocrine Group, *Submission 88*, p. 7.

7 Australasia Paediatric Endocrine Group, *Submission 88*, p. 9.

8 Heino F.L. Meyer-Bahlburg, Curtis Dolezal, Susan W. Baker and Maria I. New, 'Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess', *Archives of Sexual Behavior*, Vol. 37, 2007, p. 87.

9 Alice Dreger, Ellen K. Feder, and Anne Tamar-Mattis, 'Prenatal dexamethasone for congenital adrenal hyperplasia', *Bioethical Inquiry*, Vol. 9, No. 3, 2012, p. 277.

wish of experiencing pregnancy and having children of their own appear to be relatively low in all age groups.<sup>10</sup>

6.16 Because some of the research (such as that quoted above) has examined non-medical gender stereotypical behaviours, and considered the consequences of treatment for sexual orientation, it has been intensely controversial.

6.17 The controversy is particularly important because some research suggests the administration of prenatal hormones to treat foetal CAH carries with it health risks for the foetus.<sup>11</sup> OII was critical of the idea that:

The prevention of homosexuality and physical masculinisation is considered to be of greater benefit than the established *cognitive and physical risks* to treated children. These are substantial risks that mean that doctors in Sweden have discontinued treatment. Despite these published, reported risks, dexamethasone treatment is still being sold to parents in the US as 'safe and effective'.<sup>12</sup>

6.18 A 2012 paper from a Swedish team working in the field reported a number of adverse effects of prenatal hormone treatment, to the point where the researchers concluded:

As a consequence of our findings of possible adverse effects, we have addressed the Regional Ethics Committee in Stockholm in November 2010 and stated that we wish to put further recruitment of patients on hold for the ongoing prospective study of prenatal DEX treatment of CAH in Sweden. Hence, until larger and more conclusive studies are published, we do not consider it ethical to initiate further treatment. The patients who have entered the study during 1999–2010 will continue to be followed according to the study protocol.<sup>13</sup>

6.19 It has been reported that a major review of research in this area has found much of the research to be of relatively poor quality:

A systematic review and meta-analysis of this intervention, published in 2010 in *Clinical Endocrinology*, indicated that a search of the literature 'identified 1083 candidate studies for review; of which, only four studies were confirmed eligible' for serious scientific consideration (Fernández-Balsells et al. 2010, 438). That is to say, as late as 2010, less than one half

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10 Heino Meyer-Bahlburg, 'What Causes Low Rates of Child-Bearing in Congenital Adrenal Hyperplasia?', *The Journal of Clinical Endocrinology Metabolism*, Vol. 84, No. 6, 1999, pp 1844–1847, cited in Organisation Intersex International Australia, *Submission 23.4*, p. 14.

11 See, for example, Tatja Hirvikoski, Anna Nordenström, Anna Wedell, Martin Ritzén, and Svetlana Lajic, 'Prenatal Dexamethasone Treatment of Children at Risk for Congenital Adrenal Hyperplasia: The Swedish Experience and Standpoint', *Journal of Clinical Endocrinology and Metabolism*, Vol. 97, No. 6, 2012.

12 Organisation Intersex International Australia, *Submission 23*, p. 13.

13 Tatja Hirvikoski, Anna Nordenström, Anna Wedell, Martin Ritzén, and Svetlana Lajic, 'Prenatal Dexamethasone Treatment of Children at Risk for Congenital Adrenal Hyperplasia: The Swedish Experience and Standpoint', *Journal of Clinical Endocrinology and Metabolism*, Vol. 97, No. 6, 2012.

of one percent of published 'studies' of this intervention were regarded as being of high enough quality to provide meaningful data for a meta-analysis. Even these four studies were of low quality:

All the eligible studies were observational and were conducted by two groups of investigators (one from the US and one from Europe)...Studies lacked details regarding the use of methodological features that protect against bias. None of the studies reported blinding of the outcome assessors to the exposure (i.e., the researchers estimating each patient's degree of virilization). Loss to follow-up was, in most cases, substantial (Fernández-Balsells et al. 2010, 438).<sup>14</sup>

6.20 A 2010 statement by specialists in the field on treatment of CAH recommended:

We recommend that prenatal therapy continue to be regarded as experimental. Thus, we do not recommend specific treatment protocols. We suggest that prenatal therapy be pursued through protocols approved by Institutional Review Boards at centres capable of collecting outcomes data on a sufficiently large number of patients so that risks and benefits of this treatment be defined more precisely.<sup>15</sup>

6.21 The committee is aware of a recent peer-reviewed analysis of the research and regulatory approvals process in the United States, which argues that the regulation of the research was poor and that some of the research undertaken 'has been so scientifically weak as to be both clinically uninformative and profoundly unethical'.<sup>16</sup>

6.22 The committee understands from conversations with stakeholders that dexamethasone is being used in Australia. It notes the following information on the CAH support group website:

If your baby has CAH, your doctor can give you medicine to treat your baby even before he or she is born. Treatment should begin as soon as possible once CAH is diagnosed.<sup>17</sup>

6.23 The committee cannot be certain if this refers to hormone treatment. OII stated:

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14 Alice Dreger, Ellen K. Feder, and Anne Tamar-Mattis, 'Prenatal dexamethasone for congenital adrenal hyperplasia', *Bioethical Inquiry*, Vol. 9, No. 3, 2012, pp 277–294, citing M.M. Fernández-Balsells, K. Muthusamy, and G. Smushkin et al, 'Prenatal dexamethasone use for the prevention of virilization in pregnancies at risk for classical congenital adrenal hyperplasia because of 21-hydroxylase (CYP21A2) deficiency: A systematic review and meta-analyses', *Clinical Endocrinology*, Vol. 73, No. 4, 2010, pp 436–444.

15 Phyllis W. Speiser et al, 'Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline', *Journal of Clinical Endocrinology and Metabolism*, Vol. 95, 2010, p. 4138.

16 Alice Dreger, Ellen K. Feder, and Anne Tamar-Mattis, 'Prenatal dexamethasone for congenital adrenal hyperplasia', *Bioethical Inquiry*, Vol. 9, No. 3, 2012, p. 291.

17 Congenital Adrenal Hyperplasia Support Group Australia, What is CAH?, <http://www.cah.org.au/education/about-cah/> (accessed 24 September 2013).

We have attempted for some time to discover whether or not dexamethasone is prescribed 'off-label' in Australia. The Department of Human Services is now assisting, from late 2012, via their LGBTI Working Group, however we do not yet have any data.<sup>18</sup>

6.24 Given the controversial research around pre-natal hormone treatment for CAH, as well as the concerning results regarding possible adverse side-effects, the committee believes that the government should review the use of dexamethasone for prenatal CAH treatment, to determine its safe application. The committee will write to the Minister seeking a briefing on this issue.

#### **Recommendation 14**

**6.25 The committee recommends that the Commonwealth government investigate the appropriate regulation of the use of dexamethasone for prenatal treatment of CAH.**

6.26 In the interim, the committee believes that all hospitals and medical professionals must act to ensure that the use of dexamethasone for prenatal CAH treatment takes place only in a controlled research context.

#### **Recommendation 15**

**6.27 The committee recommends that, effective immediately, the administration of dexamethasone for prenatal treatment of CAH only take place as part of research projects that have ethics approval and patient follow-up protocols.**

#### **Conclusion**

6.28 Intersex presents a number of challenges. Best understood is the need, in some cases urgent, for an intersex person to receive medical treatment from birth. Not so well understood, but gaining more attention, is the need for specialised and on-going psychological support and access to counselling for both intersex people and their parents, where appropriate, to assist in addressing issues that arise in the course of growth and development.

6.29 Least well understood is the challenge that intersex variation presents to the rest of society. It is the challenge involved in recognising that genetic diversity is not a problem in itself; that we should not try to 'normalise' people who look different, if there is no medical necessity. It is the challenge of understanding that everyone does not have to fit into fixed binary models of sex and gender, and that nature certainly does not do so.

6.30 A key example of our lack of understanding of how to respond to intersex diversity can be seen in the clinical research on sex and gender of intersex people. The medical understanding of intersex is so strongly focussed on binary sex and gender that, even though its subjects have some sort of sex or gender ambiguity, the committee is unaware of any evidence to show that there are poor clinical or social

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18 Organisation Intersex International Australia, *Submission 23*, p. 13.

outcomes from *not* assigning a sex to intersex infants.<sup>19</sup> Why? Because it appears never to have even been considered or researched. Enormous effort has gone into assigning and 'normalising' sex: none has gone into asking whether this is necessary or beneficial. Given the extremely complex and risky medical treatments that are sometimes involved, this appears extremely unfortunate.

6.31 This report has addressed some of the specific issues relating to the medical (and particularly surgical) treatment of intersex people. However there are broader questions around sex and gender identity upon which the committee hopes this report will encourage further reflection.

**Senator Rachel Siewert**

**Chair**

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19 Martine Cools, Arianne Dessens, Stenvert Drop, Jacqueline Hewitt and Gary Warne, answers to questions on notice (received 27 September 2013).

