Article:
Lucas-Herald, AK, Bryce, J, Kyriakou, A et al. (55 more authors) (2021) Gonadectomy in conditions affecting sex development: a registry-based cohort study. European Journal of Endocrinology, 184 (6). pp. 791-801. ISSN 0804-4643

https://doi.org/10.1530/eje-20-1058

Gonadectomy in conditions affecting sex development: a registry-based cohort study

Angela K Lucas-Herald[1], Jillian Bryce[1], Andreas Kyriakou[1], Marie Lindhardt Ljubicic[2], Wiebke Arlt[3,4], Laura Audi[5], Antonio Balsamo[6], Federico Baronio[6], Silvano Bertelloni[7], Markus Bettendorf[8], Antonia Brooke[9], Hedi L Claahsen van der Grinten[10], Justin H Davies[11], Gloria Hermann[12], Liat de Vries[13,14], Ieuan A Hughes[15], Rieko Tadokoro-Cuccaro[15], Feyza Darendeliler[16], Sukran Poyrazoglu[16], Mona Ellaithi[17], Olcay Evliyaoglu[18], Simone Fica[19], Lavinia Nedelea[19], Aneta Gawlik[20], Evgenia Globa[21], Nataliya Zelinska[21], Tulay Guran[22], Ayla Güven[23], Sabine E Hannema[24,25], Olaf Hiort[26], Paul-Martin Holterhus[27], Violeta Iotova[28], Vilhelm Mladenov[28], Vandana Jain[29], Rajni Sharma[29], Farida Jennane[30], Colin Johnston[31], Gil Guerra Junior[32], Daniel Konrad[33], Odile Gaisl[33], Nils Krone[34], Ruth Krone[35], Katherine Lachlan[36], Dejun Li[37], Corina Lichiardopol[38], Lidka Lisa[39], Renata Markosyan[40], Inas Mazen[41], Klaus Mohnike[42], Marek Niedziela[43], Anna Nordenstrom[44], Rodolfo Rey[45], Mars Skaeil[46], Lloyd J W Tack[47], Jeremy Tomlinson[48], Naomi Weintrob[13,49], Martine Cools[47] and **S Faisal Ahmed[1]**

[1]Developmental Endocrinology Research Group, University of Glasgow, Glasgow, UK, [2]Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [3]Institute of Metabolism and Systems Research (IMSR), University of Birmingham, Birmingham, UK, [4]Centre for Endocrinology, Diabetes and Metabolism, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK, [5]Department of Pediatrics and Pediatric Endocrinology Unit, Vall d'Hebron Research Institute (VHIR), Hospital Vall d'Hebron, Barcelona, Spain, [6]Department of Pediatrics, University of Bologna Hospital of Bologna Sant Orsola-Malpighi, Bologna, Italy, [7]Department of Pediatrics, University Hospital Pisa, Pisa, Italy, [8]Division of Paediatric Endocrinology and Diabetes, Department of Paediatrics, University Hospital Heidelberg, Heidelberg, Germany, [9]Macleod Diabetes and Endocrine Centre, Royal Devon and Exeter Hospital, Exeter, UK, [10]Department of Pediatrics, Radboud University Medical Center, Nijmegen, the Netherlands, [11]Department of Paediatric Endocrinology, Faculty of Medicine, University of Southampton, Southampton, UK, [12]Department of Pediatrics and Adolescent Medicine, University Medical Centre, Ulm, Germany, [13]Paediatrics, Tel Aviv Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [14]Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Centre of Israel, Petah Tikvah, Israel, [15]Department of Paediatrics, University of Cambridge, Cambridge, UK, [16]Department of Pediatric Endocrinology, Istanbul University, Istanbul Medical School, Istanbul, Turkey, [17]Faculty of Medical Laboratory Sciences, Al-Neelain University, Khartoum, Sudan, [18]Department of Pediatric Endocrinology, Istanbul University – Cerrahpasa, Cerrahpaşa Medical School, Istanbul, Turkey, [19]Endocrinologie, Universitatea de Medicina si Farmacie Carol Davila Facultatea de Medicine, Bucharest, Romania, [20]Department of Pediatrics and Pediatric Endocrinology, Medical University of Silesia, Katowice, Poland, [21]Ukrainian Research Center of Endocrine Surgery, Endocrine Organs and Tissue Transplantation, MOH of Ukraine, Kyiv, Ukraine, [22]Department of Pediatric Endocrinology, Marmara University, Istanbul, Turkey, [23]Pediatric Endocrinology Clinic, Zeynep Kamil Women and Children Hospital, Istanbul, Turkey, [24]Pediatric Endocrinology, Erasmus Medical Centre, University Medical Centre Rotterdam, Rotterdam, the Netherlands, [25]Department of Pediatrics, Leiden University Medical Center, Leiden, the Netherlands, [26]Division of Paediatrics, University of Lübeck, Lübeck, Germany, [27]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University Hospital of Schleswig-Holstein Campus Kiel/Christian-Albrechts-University of Kiel, Kiel, Germany, [28]UMHAT 'Sveta Marina', Medical University of Varna, Varna, Bulgaria, [29]Division of Pediatric Endocrinology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India, [30]Unité d'Endocrinologie/Diabétologie et Gynécologie de l'Enfant et de l'Adolescent, Hôpital d'Enfants, Casablanca, Morocco, [31]Department of Endocrinology, St Albans City Hospital, West Hertfordshire Hospitals Trust, St Albans, UK, [32]Disciplina de Endocrinologia e Metabologia, Faculdade deo Ciencias Medicas da Universidade de Campinas, Departamento de Pediatria e Departamento de Clinica Medica, Sao Paolo, Brazil, [33]Division of Pediatric Endocrinology and Diabetology and Children's Research Center, University Children's Hospital, Zürich, Switzerland, [34]Department of Oncology and Metabolism, Academic Unit of Child Health, University of Sheffield, Sheffield, UK, [35]Endocrinology, Birmingham Children's Hospital, Birmingham, UK, [36]Department of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK, [37]Centre for Prenatal Diagnosis, Jilin University First Hospital, Jilin, China, [38]Endocrinology, University of Medicine and Pharmacy Craiova, Craiova, Romania, [39]Endocrinology, Institute of Endocrinology, Prague, Czech Republic, [40]Endocrinology, Yerevan State Medical University Endocrinology Clinic, Yerevan, Armenia, [41]Department of Clinical Genetics, National Research Centre, Cairo, Egypt, [42]Department of Pediatrics, Otto-von-Guericke University, Magdeburg, Germany, [43]Department of Pediatric Endocrinology, Poznan University of Medical Sciences, Poznan, Wielkopolskie, Poland, [44]Dept of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden, [45]CONICET – FEI – División de Endocrinología, Centro de Investigaciones Endocrinológicas 'Dr. César Bergadá' (CEDIE), Buenos Aires, Argentina, [46]Department of Paediatric Endocrinology, Royal Manchester Children's Hospital, Manchester, UK, [47]Pediatric Endocrinology Service, University Hospital Ghent, Ghent, Belgium, [48]Oxford Centre for Diabetes, Endocrinology & Metabolism, NIHR Oxford Biomedical Research Centre, Churchill Hospital, University of Oxford, Oxford, UK, and [49]Pediatric Endocrinology, Dana Dwek Children's Hospital, Tel Aviv Medical Centre, Tel Aviv, Israel

Correspondence should be addressed to S F Ahmed
Email
faisal.ahmed@glasgow.ac.uk

European Journal of Endocrinology

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE10.1530/EJE

Abstract

Objectives: To determine trends in clinical practice for individuals with DSD requiring gonadectomy.
Design: Retrospective cohort study.
Methods: Information regarding age at gonadectomy according to diagnosis; reported sex; time of presentation to specialist centre; and location of centre from cases reported to the International DSD Registry and who were over 16 years old in January 2019.
Results: Data regarding gonadectomy were available in 668 (88%) individuals from 44 centres. Of these, 248 (37%) (median age (range) 24 (17, 75) years) were male and 420 (63%) (median age (range) 26 (16, 86) years) were female. Gonadectomy was reported from 36 centres in 351/668 cases (53%). Females were more likely to undergo gonadectomy (n = 311, $P < 0.0001$). The indication for gonadectomy was reported in 268 (76%). The most common indication was mitigation of tumour risk in 172 (64%). Variations in the practice of gonadectomy were observed; of the 351 cases from 36 centres, 17 (5%) at 9 centres had undergone gonadectomy before their first presentation to the specialist centre. Median age at gonadectomy of cases from high-income countries and low-/middle-income countries (LMIC) was 13.0 years (0.1, 68) years and 16.5 years (1, 28), respectively ($P < 0.0001$) with the likelihood of long-term retention of gonads being higher in LMIC countries.
Conclusions: The likelihood of gonadectomy depends on the underlying diagnosis, sex of rearing and the geographical setting. Clinical benchmarks, which can be studied across all forms of DSD will allow a better understanding of the variation in the practice of gonadectomy.

European Journal of Endocrinology (2021) **184**, 791–801

European Journal of Endocrinology

Introduction

Differences or disorders of sex development (DSD) are a heterogeneous group of conditions, that can be associated with gonadal dysfunction and germ cell cancers (1). The estimated prevalence of germ cell tumours ranges from 0.8 to 40% depending on age and underlying diagnosis (2, 3). To mitigate this tumour risk, as well as for avoiding the possibility of hormone production that is discordant to the gender, children and adolescents with DSD have often undergone gonadectomy (4, 5). However, when counselling patients as well as their parents in case of a child with DSD, a careful balance must be sought, between mitigating this risk, preserving any residual gonadal function and encouraging patient participation in decisions regarding gonadectomy (4). Whilst single centre and single condition reports of the experience of gonadectomy in cases of DSD do exist (5, 6, 7, 8), there is little information on variations in care as well as any emerging trends in the timing of gonadectomy. More recently, there has been an increasing emphasis on delaying gonadectomy in a range of conditions associated with DSD (9) especially when there is a possibility that informed consent cannot be obtained from the young patient (10). The primary aim of the current study was to use the I-DSD Registry to investigate recent trends in gonadectomy internationally for a wider range of conditions associated with DSD. In addition, the use of objective outcomes including age at gonadectomy, sex of rearing and time of presentation was explored.

Methods

The I-DSD Registry was interrogated for information regarding year of birth, age at presentation to a specialist centre, the diagnosis, karyotype and sex of rearing of all cases who were over the age of 16.0 years in January 2019 and who had a disorder of androgen action, androgen synthesis or gonadal development; Leydig cell hypoplasia; persistent Müllerian duct syndrome or a non-specific DSD. The I-DSD registry is an international database of pseudo-anonymised information on patients with DSD and is approved by the National Research Ethics Service in the United Kingdom (IRAS 269776 and Research Ethics Committee reference 19/WS/0131) as a research database of information that is collected as part of routine clinical care at specialist DSD centres (11) and further details are

available at www.i-dsd.org. Throughout the manuscript, the terms male/female refer to reported sex at the time of the study, as reported by clinicians on the I-DSD Registry. The cut-off of 16 years was chosen to enable a reasonable time-lapse between diagnosis and gonadectomy to better understand when gonadectomies were performed. For eligible cases, the reporting clinicians were approached for information on gonadectomy, and in those cases that had undergone gonadectomy, additional data were collected on age at gonadectomy, indication for gonadectomy and histology result, if available.

Data management and statistical analysis

The data received from each centre were collated and stored on Microsoft Excel version 16.4 and accessed only by ALH and SFA, as the principal investigators who planned the original data analysis. Where incomplete data were available, for example lack of information regarding indication or histology, this was indicated. Data were quality checked to ensure no duplicate patients were entered, for example in the case of a patient moving care from one I-DSD centre to another. To assess temporal differences, comparisons were performed between individuals born before 1999 and after 1999, to approximate with the increasing awareness of the John vs Joan case (12, 13). For assessment of geographical differences in practice, participating centres were categorised as those from a low- or middle-income country (LMIC) or from a high-income country (HIC) as defined by the 2019 World Bank classification (14). Continuous variables were described as median and ranges and normality was assessed via the Shapiro–Wilk test. Inter-group comparison for these variables was performed by the Mann–Whitney *U* test or one way ANOVA as appropriate. The Fisher exact test was performed to compare proportions in different groups. Linear regression was performed to assess associations between trends of gonadectomy and odds ratios calculated for likelihood of gonadectomy. The level of $P < 0.05$ was considered to be statistically significant and all analyses were performed using Graphpad Prism 8 (San Diego, CA, 2018).

Results

Description of cases in the registry

At the time of the study, there were 3618 records on the I-DSD Registry. Of these, 757 (21%) met the study inclusion criteria and in 668 (88%) of these cases, information on gonadectomy status was available (Supplementary Fig. 1, see section on supplementary materials given at the end of this article). These cases were registered from 44 different centres in 21 different countries, over five continents with a median number of cases per centre of 5 (range 1, 215). Of the 668 cases, 248 (37%) with a median age of 24 years (17, 75) were registered as male and 420 (63%) with a median age of 26 years (17, 86) were registered as female. The karyotype was 46,XY in 520 (78%), 45,X/46,XY in 44 (7%), 46,XX in 35 (5%), 47,XXY in 34 (5%), 46,XX/46,XY in 8 (1%) and other in 27 (4%). Of those with 46,XX karyotypes, 12 (34%) had a diagnosis of ovotesticular DSD, 8 (23%) had testicular DSD, 5 (14%) had partial gonadal dysgenesis, 5 (14%) had complete gonadal dysgenesis, 2 (6%) had gonadal regression and 3 (9%) had non-specific DSD (NS-DSD). The most common conditions that were reported included complete androgen insensitivity syndrome (CAIS) ($n = 161$, 24%) and partial gonadal dysgenesis ($n = 94$, 14%).

Description of cases of gonadectomy

Of the 668 cases, gonadectomy was reported in 351 (53%) (Table 1) in 36 centres from 18 countries, and of these, 15 (42%) centres were located in 9 (50%) countries categorised as LMIC. In those cases that had gonadectomy, the karyotype was 46,XY in 302 (86%); 46,XX in 7 (2%); 45,X/46,XY in 28 (8%); 46,XX/46,XY in 4 (1%); 47,XXY in 1 (0.5%) and other in 9 (2.5%). Of the 420 females in the cohort, 311 (74%) had a history of bilateral gonadectomy compared to 40 of the 248 males who had gonadectomy, and in whom 19 (48%) had bilateral gonadectomy ($P < 0.0001$). The most common diagnoses in the females who had gonadectomy were CAIS (n=129) and partial gonadal dysgenesis ($n = 28$) but approximately 30% of females with these conditions had not had gonadectomy and their median age at the time of the study was 25 (17, 69) (Table 1 and Supplementary Fig. 1). In males, the highest rates of gonadectomy were reported in those with partial gonadal dysgenesis ($n = 15$), but even in this group, the majority had no history of gonadectomy ($n = 34$).

Of the 351 cases with gonadectomy, the primary indication was reported in 246 (70%) cases with mitigation of tumourigenesis risk in 172 (70%) and concordance to sex assignment in 74 (30%). Of the 172, who had gonadectomy for mitigation of tumourigenesis risk, 73 (42%) had a disorder of gonadal development, 68 (40%) had CAIS, 14 (8%) had a disorder of androgen synthesis, 11 (6%) had PAIS and 6 (4%) had NS-DSD. Of those who had gonadectomy for concordance to sex assignment, 22 (30%) had a disorder of androgen synthesis, 20 (27%) had

Table 1 The number and median age of females and males according to diagnosis. Data are presented as *n* (%) or as median (range).

	CAIS	PGD	CGD	NS-DSD	17β HSD 3 def	PAIS	5α RD 2 def	Other	Whole cohort
Females									
All									
n	161	36	80	7	37	29	15	55	420
Cases of gonadectomy	129 (80%)	28 (78%)*	62 (78)*	7 (100%)*	24(65%)	24 (83%)*	11 (73%)	26 (53%)	311 (74%)*
Age (years) at presentation	15 (0, 32)	0.1 (0.1, 30)	14 (0.1, 21)	0.1 (0.1, 12)	7 (0.1, 38)	11 (0.1, 20)	3 (0.1, 33)	13 (0.1, 34)	13 (0, 38)
Cases of Gonadectomy									
Age (years) at gonadectomy	16 (0.3, 68)	6 (0.1, 21)	14 (0.1, 25)	22 (18, 42)*	9 (0.5, 28)	8 (0.5, 24)	6 (2, 17)	13 (0.4, 26)	15 (0.1, 68)*
Prior to presentation at specialist centre†	6 (38%)	0 (0%)	4 (25%)	0 (0%)	1 (5.5%)	2 (13%)	1 (5.5%)	2 (13%)	16 (94%)
Cases with retained gonads									
n (%)	32 (20%)	8 (22%)*	18 (22%)*	0 (0%*	13 (35%)	5 (17%)*	4 (17%)	29 (47%)	109 (26%)
Age (years) at presentation	14 (0.1, 51)	9 (0.1, 17)	13 (0.1, 20)	n/a	14 (0.1, 17)	1 (0.1, 12)	24 (17, 28)*	12 (0.1, 39)*	14 (0.1, 51)
Current age	27 (17, 86)	34 (17, 61)	28 (17, 48)	n/a	28 (24, 47)	23 (18, 28)	27 (18, 37)	22 (17, 58)	27 (17, 86)
Males									
All									
n	0	58	11	33	2	50	10	84	248
Cases of gonadectomy	0 (0%)	15 (26%)	2 (18%)	5 (15%)	0 (0%)	3 (6%	0 (0%)	15 (17%)	40 (16%)
Age (years) at presentation	n/a	0.5 (0.1, 4)	3 (2, 4)	12 (9,15)	n/a	29 (3, 54)	n/a	0.3 (0.1, 19)	0.3 (0.1, 53)
Cases of Gonadectomy									
Age (years) at gonadectomy	n/a	17 (0.1, 13)	5 (4, 5)	12 (3, 42)	n/a	41 (5, 75)	n/a	19 (4, 28)	9 (0.1, 75)
Prior to presentation at specialist centre†	n/a	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (6)
Cases with retained gonads									
n (%)	0 (0%)	43 (74%)	9 (82%)	28 (85%)	2 (100%)	47 (94%)	10 (100%)	69 (83%)	208 (84%)
Age (years) at presentation	n/a	13 (0.1, 51)	1 (0.1, 34)	0.1 (0.1, 15)	16 (13, 19)	0.3 (0.1, 20)	3 (0.1, 25)	1 (0.1, 59)	2 (0.1, 59)
Current age	n/a	32 (17, 72)	29 (24, 48)	19 (17, 47)	26 (23, 28)	24 (18, 44)	29 (17, 57)	25 (17, 75)	27 (17, 75)

*$P < 0.05$ compared to males. Analysis via one way ANOVA or Chi-square as appropriate; †The number of cases of gonadectomy prior to presentation to the specialist centre was calculated according to date of presentation and date of first presentation at the specialist centre.

17β HSD 3 def, 17β hydroxysteroid deficiency type III; 5α RD 2 def, 5α reductase deficiency type 2; CAIS, Complete Androgen Insensitivity Syndrome; CGD, Complete Gonadal Dysgenesis; NS-DSD, non-specific DSD; PAIS, Partial Androgen Insensitivity Syndrome. PGD, Partial Gonadal Dysgenesis.

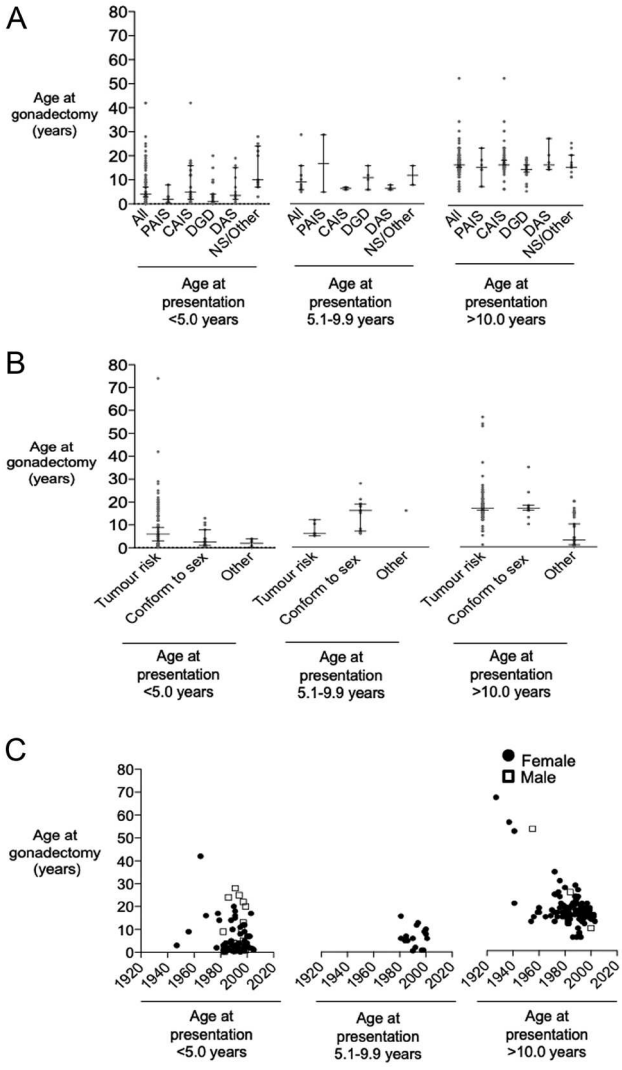

Figure 1

Age at gonadectomy according to diagnosis, year of birth and age at presentation to specialist centre. (A) Age at gonadectomy according to diagnosis and age at presentation to specialist centre. There was no difference in age at gonadectomy according to diagnosis. Analysis via linear regression. The lines represent the median and 95% CI. PAIS, Partial Androgen Insensitivity Syndrome; CAIS, Complete Androgen Insensitivity Syndrome; DGD, disorder of gonadal development; DAS, disorder of androgen synthesis; NS/other, non-specific DSD or other disorder type. (B) Age at gonadectomy according to indication for gonadectomy and age at presentation to specialist centre. There was no difference in age at gonadectomy according to diagnosis. The lines represent the median and 95% CI. (C) Age at gonadectomy according to year of birth and age at presentation. Age at presentation did affect age at gonadectomy. The lines represent the median and 95% CI.

CAIS, 18 (24%) had a disorder of gonadal development, 9 (12%) had PAIS and 5 (7%) had NS-DSD. There was no correlation between year of birth and indication for gonadectomy (P=0.6).

Age at gonadectomy

Of the 351 cases who had gonadectomy, data on both, age at gonadectomy and age at reported time of presentation, was available in 296 (79%) (Table 1). As expected, age at gonadectomy was associated with the age at presentation ($P<$ 0.0001) with the age at gonadectomy increasing with an increasing age at presentation, irrespective of the underlying diagnosis (Fig. 1A). However, the underlying diagnosis when coupled with the sex of rearing, did influence the interval between age at presentation and age at gonadectomy such that females with CAIS were more likely to be older at gonadectomy compared to age at presentation (Fig. 1A). Overall, females had gonadectomy later, at a median age of 15 years (0.1, 68), compared to males who had gonadectomy at a median age of 9 years (0.1, 54) (P= 0.047) (Table 1). There were no statistically significant differences between diagnoses. There were no statistically significant trends for a change in the age at gonadectomy according to indication for gonadectomy (Fig. 1B) or over time (Fig. 1C). Of those who were diagnosed under the age of 10 yrs, there was no difference in age at gonadectomy in those who were born prior to 1990 compared to those who were born between 1990 and 1999 (median age 5 years vs 6 years, P= 0.2).

Gonadectomy prior to presentation to specialist centre

Of the 351 cases of gonadectomy where information on age at gonadectomy was available, 17 (5%) (16 females and 1 male), had gonadectomy performed before presentation to the specialist centre (Fig. 2A). Of these 17 patients, 6 (38%) had CAIS; 4 (24%) had CGD; 3 (18%) had PAIS and there was one case each of 17β-dehydrogenase type 3 deficiency, 5-α-reductase type 2 deficiency, Leydig cell hypoplasia and non-specific XY DSD. The median reported age at presentation for these individuals was 16 years (3, 38) with a median period of 4 years (0.2, 23) from gonadectomy to presentation to specialist centre. Only 6 of these 17 (35%) cases were born after 1990 but linear regression analysis did not identify

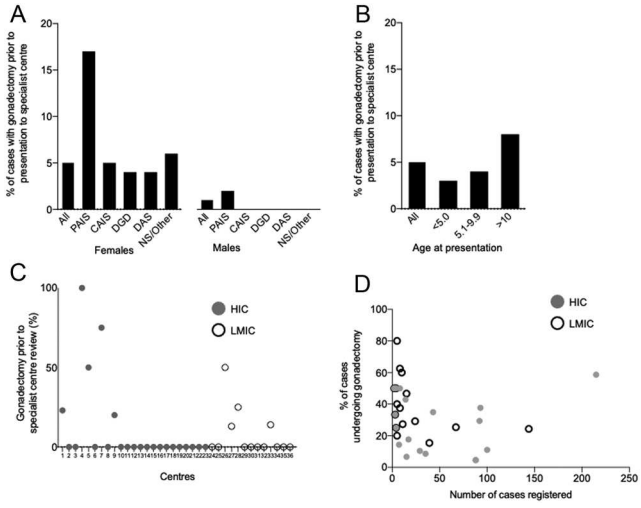

Figure 2

Proportion of individuals undergoing gonadectomy prior to presentation at the specialist centre according to sex, underlying diagnosis, year of birth, age at presentation and location of specialist centre. (A) Proportion of individuals undergoing gonadectomy prior to presentation at the specialist centre for females (left) and males (right) according to underlying diagnosis. (B) Proportion of individuals undergoing gonadectomy prior to presentation at the specialist centre according to age at presentation. (C) Proportion of individuals undergoing gonadectomy prior to presentation at the specialist centre, with LMIC and HIC countries highlighted. (D) The number of registered participants undergoing gonadectomy compared to the number of participants registered from that specialist centre. The symbols with the white circle and black outline represent LMIC and HIC centres. CAIS, Complete Androgen Insensitivity Syndrome; DGD, disorder of gonadal development; DAS, disorder of androgen synthesis; HIC, high-income country; LMIC, low- to middle-income country; NS/other, non-specific DSD or other disorder type; PAIS, Partial Androgen Insensitivity Syndrome.

a statistically significant temporal trend for a change in the number of individuals with gonadectomy prior to presentation according to the year of birth (P= 0.3) (Fig. 2B). The 17 cases that had gonadectomy prior to reported presentation to the specialist centre were from 9/36 (34%) centres (Fig. 2C). The proportion of registered patients from each centre who underwent gonadectomy prior to presentation to the specialist centre varied from 0 to 100% (Fig. 2D). There was a wide range of variability in the number of gonadectomies performed per centre, with the median being 1 (1, 126) although there was no statistically significant difference in the number of cases with gonadectomy before specialist presentation in those centres that reported more cases of gonadectomy (Fig. 2E).

Geographical differences

Of the 327 cases from LMIC centres, 95 (29%) had undergone gonadectomy whilst of the 341 cases from HIC, 256 (75%) had undergone gonadectomy (P < 0.0001). The median age at diagnosis of cases from HIC and LMIC was 6 years (0.1, 53) and 14 years (0.1, 38), respectively (P= 0.015) and the median age at gonadectomy of cases from HIC and LMIC was 13 years (0.1, 68) years and 16.5 years (1, 28), respectively (P< 0.0001). Of the 95 cases in LMIC centres, a disorder of gonadal development was the commonest condition in 43 cases (45%). In HIC, the commonest group of conditions was a disorder of androgen action in 131 cases (51%) (Table 2). Compared to HIC centres, the likelihood of retaining gonads was greater in LMIC centres for CAIS (OR (95% CI): 18.5 (7.3–47.5), P< 0.0001), CGD (OR (95% CI): 31.1 (8.3–91.8, P< 0.0001), 17β HSD 3 deficiency (OR (95% CI): 28 (3.2, 31.8), P< 0.01) and PAIS (OR (95% CI): 4.1 (1.5–11.9, P< 0.01). There were no significant differences in age at presentation or age at gonadectomy according to underlying diagnosis in LMIC centres vs HC centres. There was no statistically significant difference in the number of cases with gonadectomy prior to presentation to the specialist centre in those from LMIC centres vs HIC centres. Of the 17 cases with gonadectomy prior to specialist presentation, 5 (29%) were from 4 LMIC centres and 12 from 5 HIC centres.

Histology

Of the 351 cases of gonadectomy, histology data were available in 266 (76%), and of these, tumours were detected in 11 (4%) with a median age of 14 years (5, 74); 6 (55% of those with tumours; 8% of CGD cases with gonadectomy) had complete gonadal dysgenesis; 2 (18% of those with tumours; 6% of PGD cases with gonadectomy) had partial gonadal dysgenesis; 1 (9% of those with tumours; 1% of CAIS cases with gonadectomy) had CAIS; 1 (9% of those with tumours; 8% of ovotesticular DSD cases with gonadectomy) had ovotesticular DSD and 1 (9% of those with tumours; 100% of Persistent Müllerian Duct Syndrome (PMDS) cases with gonadectomy) had PMDS. The tumours were germ cell neoplasia *in situ* in 3 (27%) (1 case each of CGD, partial gonadal dysgenesis and PMDS); gonadal germ cell tumours in 6 (55%) (5 cases of CGD and

Table 2 The number and median age of individuals from LMIC and HIC according to diagnosis. Data are presented as *n* (%) or as median (range).

	CAIS	PGD	CGD	NS-DSD	17β HSD 3 def	PAIS	5α RD 2 def	Other	Whole cohort
LMIC									
All									
n	42	38	33	13	22	34	19	126	327
Cases of gonadectomy	18 (43%)	16 (42%)	10 (30%)	3 (23%	8 (36%)	6 (18%)	6 (30%)	28 (22%)	95 (29)
Age (years) at presentation	15 (0.1, 25)	4 (0.1, 16)	14 (0.3, 16)	14 (11, 15)	16 (3, 38)	12 (0.1, 17)	14 (0.1, 33)	8 (0.1, 23)	14 (0.1, 38)
Cases of Gonadectomy									
Age (years) at gonadectomy	17 (13, 27)	14 (9, 21)	17 (10, 19)	15 (14, 16)	17 (7, 28)	14 (7, 18)	13 (8, 17)	16 (1, 28)	16 (1, 28)
Prior to presentation at specialist centre[†]	1 (6%)	0 (0%)	1 (3%)	0 (0%)	1 (13%)	1 (17%)	0 (0%)	1 (4%)	5 (3%)
Cases with retained gonads									
n (%)	24 (57%)	22 (58%)	23 (70%)	10 (77%)	14 (64%)	28 (82%)	13 (70%)	98 (78%)	232 (71%)
Age (years) at presentation	25 (18, 49)	4 (0.1, 27)	16 (2, 20)	12 (0.1, 12)	19 (3, 19)	4 (0.1, 20)	11 (0.1, 28)	12 (0.1, 25)	25 (0.1, 49)
Current age	15 (5, 51)	17 (17, 34)	24 (17, 36)	24 (16, 40)	30 (18, 35)	23 (16, 34)	22 (16, 42)	22 (16, 37)	15 (16, 51)
HIC									
All									
n	119	56	58	27	17	45	6	13	341
Cases of gonadectomy	111 (93%)	27 (48%)	54 (93%)	9 (33%)	16 (94%)	21 (47%)	5 (100%)	13 (100%	256 (75%)
Age (years) at presentation	14 (0, 32)	0.1 (0.1, 30)	10 (0.1, 21)	9 (0.1, 14)	3 (0.1, 32)	11 (0.1, 54)	0.1 (0.1, 3)	1 (0.1, 17)	6 (0.1, 53)
Cases of Gonadectomy									
Age (years) at gonadectomy	16 (0.3, 68)	1 (0.1, 18)	12 (0.1, 25)	14 (3, 42)	6 (0.5, 19)	13 (0.5, 75)	3.5 (2, 7)	13 (0.5, 34)	13 (0.1, 68)
Prior to presentation at specialist centre[†]	5 (5%)	0 (0%)	3 (6%)	0 (0%	0 (0%)	2 (10%)	1 (20%)	1 (8%)	12 (5%)
Cases with retained gonads									
n (%)	8 (7%)	29 (52%)	4 (7%)	18 (67%)	1 (6%)	24 (53%)	1 (0%)	0 (0%)	85 (25%)
Age (years) at presentation	15 (1, 51)	0.1 (0.1, 51)	0.1 (0.1, 34)	11 (0.1, 15)	9 (0.1, 12)	3 (0.1, 13)	2 (0.1, 28)	11 (1, 59)	27 (0.1, 59)
Current age	32 (16, 86)	28 (16, 72)	27 (16, 48)	20 (17, 47)	29 (16, 47)	26 (16, 44)	24 (16, 57)	24 (16, 75)	11 (16, 86)

17β HSD 3 def, 17β hydroxysteroid deficiency type III; 5α RD 2 def, 5α reductase deficiency type 2;CAIS, Complete Androgen Insensitivity Syndrome; CGD, Complete Gonadal Dysgenesis; HIC, high-income country; LMIC, low- to middle-income country; NS-DSD, non-specific DSD; PAIS, Partial Androgen Insensitivity Syndrome; PGD, Partial Gonadal Dysgenesis.

1 case of partial gonadal dysgenesis) and dysgerminoma in 2 (18%) (1 case each of ovotesticular DSD and CGD). Data on histology were available for 9 out of 17 cases (53%) who had gonadectomy prior to presentation to the specialist centre and none of these had any histological evidence of tumourigenesis.

Discussion

This study demonstrates differences that exist in the practice of gonadectomy and that are dependent on the underlying diagnosis, the sex of rearing and the age at presentation. Clear patterns have previously been reported for conditions such as CAIS, where high rates of affected women have undergone gonadectomy (15) and these were reinforced in the current study. However, previous reports of gonadectomy in other forms of DSD, for example 17-β dehydrogenase type 3 deficiency, 5-α reductase type 2 deficiency or non-specific XY DSD are rare. In some of these conditions that are associated with a disorder of androgen synthesis, the indication for early gonadectomy was the avoidance of pubertal virilisation in an XY girl. Given that more children with XY DSD are being raised as boys (12), there is a greater prospect of preserving gonadal function and fertility (16, 17) and there is a greater emphasis on the patient's own views on gonadectomy (4, 18, 19), there has been an increased emphasis on retaining gonads until the age when patients with DSD can decide for themselves (20).

Mitigation of tumour risk was the commonest reported indication for performing gonadectomy and therefore as expected, in the current study, the number of cases that actually had any evidence of tumour development was very small. It is also noteworthy, that the conditions that were associated with a tumour included a case of PMDS and ovotesticular DSD, two conditions where the risk of gonadal tumourigenesis has generally been considered to be low (21, 22). Thus, the study emphasizes the need for ongoing monitoring of these outcomes in those conditions that are traditionally thought to be low risk. The study also demonstrated that a substantial proportion of cases continued to retain gonads into adulthood, even in conditions such as gonadal dysgenesis, where the risk of germ cell tumours is particularly high (18, 23).

With the shifts in societal attitudes, it would be useful to prospectively monitor the age at presentation and the age at gonadectomy. The current study showed that, in about 1 in 20 cases, the age at gonadectomy was prior to the age at presentation to a specialist DSD centre. There may be many reasons why this was the case. It is assumed that all of these individuals had specialists involved in their care outwith the DSD reference centre but a prospective study would allow this to be monitored and it is hoped that with improved awareness of DSD conditions, fewer affected individuals are being referred late to specialists in this field. It was also noteworthy that there were variations in practice between LMIC and HIC centres with the proportion of cases that had a gonadectomy being lower in LMIC countries. The older age at gonadectomy at the LMIC centres may be secondary to an older age at presentation in these cases but the lower proportion of cases undergoing gonadectomy may be due to difficulties in access to specialist diagnostic or surgical services (19, 24) or due to differences in cultural and societal attitudes to gonadectomy (25). These aspects as well as the surveillance measures that are used for monitoring retained gonads will need to be explored in future studies.

Over the last few decades, it has become increasingly clear that the risk of tumour development in conditions associated with DSD is dependent on the underlying condition. It is likely that the decision to perform gonadectomy is influenced by this knowledge as well as other variables, as above. Thus, the management of gonads requires a detailed understanding of all these factors which can only be provided by a specialist team that can call on this multidisciplinary expertise (4). The I-DSD Registry represents a valuable resource that can facilitate the study of clinical practice in this large heterogenous group of rare conditions. Studies using this resource have previously revealed the global shift in the practice of sex assignment (12) and more recent studies have shown how practices vary in the management of the testes in people with AIS (15). The current study has taken this further by showing how these differences can be described objectively to study temporal and regional variations for a wide range of conditions associated with DSD. We would recommend that all cases of gonadectomy should be recorded in a registry such as the I-DSD Registry for the purpose of long-term audit and surveillance.

In the process of performing this study, we believe that we have identified simple, yet effective, clinical benchmarks, that is, the number of individuals undergoing gonadectomy prior to review at a specialist centre or the age of presentation compared to the age at gonadectomy. Benchmarking represents a continual and collaborative effort at measuring and comparing the results of key processes that are directly relevant to patients with an eventual aim of improving clinical outcomes (26). Gaps in the professional development of

service providers have been reported before (27, 28) and it is possible that targeting simple observations such as these leads to greater local awareness of the pros and cons of early gonadectomy. It is likely that there is an optimal balance to be achieved between timely gonadectomy and a well-informed patient or parent and further exploration of these measures may allow the identification of this optimal range. Identification of benchmarks that target specific points in the care pathway of the patient with gonadectomy may lead to improvement of this pathway but this will require further exploration. For instance, most specialist centres that participate in the I-DSD Registry act as regional centres of referral and it is possible that greater outreach links and education programmes between such specialist centres and the referral catchment area may lead to greater informed decision making. Knowledge and awareness can be promoted locally through participating in joint clinics or local educational activities within the referral network and the availability of such opportunities has been previously reported by DSD centres to be variable (27).

There are, however, some limitations to using the number of individuals undergoing gonadectomy prior to review at a specialist centre as a clinical benchmark. The definition of a specialist centres was based on the centre participating in the I-DSD Registry and it is of course possible that the centre prior to presentation to the I-DSD centre was also an expert centre. Future work should examine the complete pathway of care of the patient who undergoes gonadectomy more comprehensively. With only 1 in 20 individuals undergoing gonadectomy prior to presentation to a specialist centre, the need for further research and prospective monitoring of timing of gonadectomy is important to confirm whether the findings in the current study were simply a chance finding.

It is possible that this study may suffer from some selection bias, as not every patient at a centre may have been included in the Registry. On the other hand, the structured manner of real-world data collection within the Registry, the size of the cohort and its potential to represent global practice were clear strengths. In addition, as with any large database, errors may occur with data entry; however, in all data that were analysed were checked with the centres at the time of the study to ensure it matched with the source data. Although, the investigators did not have recourse to source data, the data that have been collected have previously been reported to have a high degree of reliability (29). Comparison of the case mix that exists in the I-DSD Registry (30) to the range of cases that may exist in a specialist service (31) also shows remarkable similarities. For a greater understanding of the practice of gonadectomy, it would be helpful to have further information on gonadal position, post-operative complications, patient and parental decisional regret, complications of gonads that are left in situ, geographical and temporal differences in social attitudes, local health care resources and, very importantly, the extent of information provision to patients and parents. These aspects were beyond the scope of the Registry but deserve further study. The current study was aimed at studying individuals older than 16 years at the time of data collection. Data from younger individuals would also be of interest, particularly in conditions for which the risk of germ cell tumour is high early in life. A prospective study, condition-specific study would also allow more valuable information on condition-specific trends which has not been possible in the current study due to the small numbers.

To conclude, this global collaborative effort has clearly demonstrated that although the timing of gonadectomy depends on the condition and the age of the patient, there is considerable variation between centres. Objective parameters that have been identified as part of this work may serve as benchmarks of practice that can be prospectively monitored.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-20-1058.

Declaration of interest

Wiebke Arlt, Hedi L Claahsen van der Grinten and Jeremy Tomlinson are on the editorial board of EJE. They were not involved in the review or editorial process for this paper, on which they are listed as the authors.

Funding

The I-DSD Registry was developed using support from the Medical Research Council (G1100236), the Seventh European Union Framework Program (201444) and the European Society for Paediatric Endocrinology Research Unit.

Data availability

The datasets generated or analysed during the current study are not available publicly but available to access through a data sharing agreement with the I-DSD Registry (www.i-dsd.org).

Author contribution statement

Angela Lucas-Herald designed the study and data collection instruments, drafted the manuscript, undertook statistical analyses and reviewed and

revised the manuscript. Jillian Bryce designed the study, coordinated and supervised data collection, designed the data collection instruments and reviewed and revised the manuscript. Syed Faisal Ahmed conceptualised the study, supervised data collection and analysis and drafted the initial manuscript and reviewed and revised the manuscript. Martine Cools performed initial analyses, drafted the initial manuscript and approved the final manuscript after review. Andreas Kyriakou, Marie Lindhardt Ljubicic, Wiebke Arlt, Laura Audi, Antonio Balsamo, Federico Baronio, Silvano Bertelloni, Markus Bettendorf, Antonia Brooke, Hedi L Claahsen van der Grinten, Justin H Davies, Gloria Hermann, Liat de Vries, Ieuan A Hughes, Rieko Tadokoro-Cuccaro, Feyza Darendeliler, Sukran Poyrazoglu, Mona Ellaithi, Olcay Evliyaoglu, Simone Fica, Lavinia Nedelea, Aneta Gawlik, Evgenia Globa, Nataliya Zelinska, Tulay Guran, Ayla Güven, Sabine E Hannema, Olaf Hiort, Paul-Martin Holterhus, Violeta Iotova, Vilhelm Mladenov, Vandana Jain, Rajni Sharma, Farida Jennane, Colin Johnston, Gil Guerra Junior, Daniel Konrad, Odile Gaisl, Nils Krone, Ruth Krone, Katherine Lachlan, Dejun Li, Corina Lichiardopol, Lidka Lisa, Renata Markosyan, Inas Mazen, Klaus Mohnike, Marek Niedziela, Anna Nordenstrom, Rodolfo Rey, Mars Skae, Lloyd J W Tack, Jeremy Tomlinson, Naomi Weintrob contributed to data acquisition, revision of the manuscript and have read and approved the final report.

Acknowledgements

This work would not be possible without the patients whose data have been included in the I-DSD Registry. R C C, I A H acknowledge the support of NIHR Cambridge Biomedical Research Centre. We would also like to thank the support of the following reference centres that participate in the European Reference Network for Rare Endocrine Conditions (Endo-ERN): Ghent University Hospital; MHAT Sveta Marina, Varna; Copenhagen University Hospital, Rigshospitalet; Universitätsklinikum Schleswig-Holstein; Azienda Ospedaliera Sant'Orsola Malpighi, Bologna; Leiden University Medical Centre; Radboud University Nijmegen Medical Centre; Erasmus Medical Centre Rotterdam; Karolinska University Hospital, Stockholm; University Hospitals Birmingham NHS Foundation Trust; NHS Greater Glasgow and Clyde Board; Central Manchester University Hospitals NHS Foundation Trust; University Hospital Southampton NHS Foundation Trust.

References

1 Cools M, Looijenga LH, Wolffenbuttel KP & T'Sjoen G. Managing the risk of germ cell tumourigenesis in disorders of sex development patients. *Endocrine Development* 2014 **27** 185–196. (https://doi.org/10.1159/000363642)

2 Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW & Looijenga LH. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. *Endocrine Reviews* 2006 **27** 468–484. (https://doi.org/10.1210/er.2006-0005)

3 van der Zwan YG, Biermann K, Wolffenbuttel KP, Cools M & Looijenga LH. Gonadal maldevelopment as risk factor for germ cell cancer: towards a clinical decision model. *European Urology* 2015 **67** 692–701. (https://doi.org/10.1016/j.eururo.2014.07.011)

4 Lee PA, Nordenström A, Houk CP, Ahmed SF, Auchus R, Baratz A, Baratz Dalke K, Liao LM, Lin-Su K, Looijenga 3rd LHJ *et al*. Global disorders of sex development update since 2006: perceptions, approach and care. *Hormone Research in Paediatrics* 2016 **85** 158–180. (https://doi.org/10.1159/000442975)

5 Wünsch L, Holterhus PM, Wessel L & Hiort O. Patients with disorders of sex development (DSD) at risk of gonadal tumour development: management based on laparoscopic biopsy and molecular diagnosis. *BJU International* 2012 **110** E958–E965. (https://doi.org/10.1111/j.1464-410X.2012.11181.x)

6 Jiang JF, Xue W, Deng Y, Tian QJ & Sun AJ. Gonadal malignancy in 202 female patients with disorders of sex development containing Y-chromosome material. *Gynecological Endocrinology* 2016 **32** 338–341. (https://doi.org/10.3109/09513590.2015.1116509)

7 Chen K-T, Tai Y-S, Chiang I-N, Chang H-C & Huang K-H. Gonadectomy in patients with disorder of sexual development. *Urological Science* 2018 **27** 243–251. (https://doi.org/10.4103/UROS.UROS_35_18)

8 Chaudhry S, Tadokoro-Cuccaro R, Hannema SE, Acerini CL & Hughes IA. Frequency of gonadal tumours in complete androgen insensitivity syndrome (CAIS): a retrospective case-series analysis. *Journal of Pediatric Urology* 2017 **13** 498.e1–498.e6. (https://doi.org/10.1016/j.jpurol.2017.02.013)

9 Wolffenbuttel KP, Hersmus R, Stoop H, Biermann K, Hoebeke P, Cools M & Looijenga LHJ. Gonadal dysgenesis in disorders of sex development: diagnosis and surgical management. *Journal of Pediatric Urology* 2016 **12** 411–416. (https://doi.org/10.1016/j.jpurol.2016.08.015)

10 Döhnert U, Wünsch L & Hiort O. Gonadectomy in complete androgen insensitivity syndrome: why and when? *Sexual Development* 2017 **11** 171–174. (https://doi.org/10.1159/000478082)

11 Ali SR, Lucas-Herald A, Bryce J & Ahmed SF. The role of international databases in understanding the aetiology and consequences of differences/disorders of sex development. *International Journal of Molecular Sciences* 2019 **20** 4405. (https://doi.org/10.3390/ijms20184405)

12 Kolesinska Z, Ahmed SF, Niedziela M, Bryce J, Molinska-Glura M, Rodie M, Jiang J, Sinnott RO, Hughes IA, Darendeliler F *et al*. Changes over time in sex assignment for disorders of sex development. *Pediatrics* 2014 **134** e710–e715. (https://doi.org/10.1542/peds.2014-1088)

13 Diamond M. Sexual identity and sexual orientation in children with traumatized or ambiguous genitalia. *Journal of Sex Research* 1997 **34** 199–211. (https://doi.org/10.1080/00224499709551885)

14 World Bank Country and lending groups. (available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups). Last accessed on 1/6/20.

15 Tack LW, Maris E, Looijenga LJ, Hannema SE, Audi L, Köhler B, Holterhus PM, Riedl S, Wisniewski A, Flück CE *et al*. Management of gonads in adults with androgen insensitivity: an international survey. *Hormone Research in Paediatrics* 2018 **90** 236–246. (https://doi.org/10.1159/000493645)

16 Islam R, Lane S, Williams SA, Becker CM, Conway GS & Creighton SM. Establishing reproductive potential and advances in fertility preservation techniques for XY individuals with differences in sex development. *Clinical Endocrinology* 2019 **91** 237–244. (https://doi.org/10.1111/cen.13994)

17 Johnson EK, Finlayson C, Finney EL, Harris CJ, Tan SY, Laronda MM, Lockart BA, Chen D, Rowell EE, Cheng EY *et al*. Gonadal tissue cryopreservation for children with differences of sex development. *Hormone Research in Paediatrics* 2019 **92** 84–91. (https://doi.org/10.1159/000502644)

18 Pyle LC & Nathanson KL. A practical guide for evaluating gonadal germ cell tumor predisposition in differences of sex development. *American Journal of Medical Genetics: Part C, Seminars in Medical Genetics* 2017 **175** 304–314. (https://doi.org/10.1002/ajmg.c.31562)

19 Odundo GO, Ngwiri T, Otuoma O & Chanzu NM. Developing equity in capacity of paediatric endocrinology subspecialists worldwide. *Lancet: Diabetes and Endocrinology* 2016 **4** 204–205. (https://doi.org/10.1016/S2213-8587(16)00035-8)

20 MacMahon JM, O'Sullivan MJ, McDermott M, Quinn F, Morris T, Green AJ, Betts DR & O'Connell SM. Early bilateral gonadoblastoma in a young child with mosaicism for Turner syndrome and trisomy 18 with Y chromosome. *Hormone Research in Paediatrics* 2017 **87** 130–135. (https://doi.org/10.1159/000448172)

21 Pleskacova J, Hersmus R, Oosterhuis JW, Setyawati BA, Faradz SM, Cools M, Wolffenbuttel KP, Lebl J, Drop SL & Looijenga LH. Tumor

risk in disorders of sex development. *Sexual Development* 2010 **4** 259–269. (https://doi.org/10.1159/000314536)
22 Wood HM & Elder JS. Cryptorchidism and testicular cancer: separating fact from fiction. *Journal of Urology* 2009 **181** 452–461. (https://doi.org/10.1016/j.juro.2008.10.074)
23 Cools M. Germ cell cancer risk in DSD patients. *Annales d'Endocrinologie* 2014 **75** 67–71. (https://doi.org/10.1016/j.ando.2014.04.003)
24 Butler EK, Tran TM, Nagarajan N, Canner J, Fuller AT, Kushner A, Haglund MM, Smith ER & OSAS 4 Country Research Group. Epidemiology of pediatric surgical needs in low-income countries. *PLoS ONE* 2017 **12** e0170968. (https://doi.org/10.1371/journal.pone.0170968)
25 Yarhere I & Ahmed SF. Chapter 5 – Disorders of sexual development in resource-limited settings. In *Practical Pediatric Endocrinology in a Limited Resource Setting*, pp. 123–134. Ed M Zacharin. San Diego: Academic Press, 2013.
26 Thonon F, Watson J & Saghatchian M. Benchmarking facilities providing care: an international overview of initiatives. *SAGE Open Medicine* 2015 **3** 2050312115601692. (https://doi.org/10.1177/2050312115601692)
27 Kyriakou A, Dessens A, Bryce J, Iotova V, Juul A, Krawczynski M, Nordenskjold A, Rozas M, Sanders C, Hiort O *et al*. Current models of care for disorders of sex development – results from an International Survey of Specialist Centres. *Orphanet Journal of Rare Diseases* 2016 **11** 155. (https://doi.org/10.1186/s13023-016-0534-8)
28 Rolston AM, Gardner M, van Leeuwen K, Mohnach L, Keegan C, Délot E, Vilain E, Sandberg DE, members of the DSD-TRN Advocacy & Advisory Network Accord Alliance. Disorders of sex development (DSD): clinical service delivery in the United States. *American Journal of Medical Genetics: Part C, Seminars in Medical Genetics* 2017 **175** 268–278. (https://doi.org/10.1002/ajmg.c.31558)
29 Kourime M, Bryce J, Jiang J, Nixon R, Rodie M & Ahmed SF. An assessment of the quality of the I-DSD and the I-CAH registries – international registries for rare conditions affecting sex development. *Orphanet Journal of Rare Diseases* 2017 **12** 56. (https://doi.org/10.1186/s13023-017-0603-7)
30 Cox K, Bryce J, Jiang J, Rodie M, Sinnott R, Alkhawari M, Arlt W, Audi L, Balsamo A, Bertelloni S *et al*. Novel associations in disorders of sex development: findings from the I-DSD Registry. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** E348–E355. (https://doi.org/10.1210/jc.2013-2918)
31 Nixon R, Cerqueira V, Kyriakou A, Lucas-Herald A, McNeilly J, McMillan M, Purvis AI, Tobias ES, McGowan R & Ahmed SF. Prevalence of endocrine and genetic abnormalities in boys evaluated systematically for a disorder of sex development. *Human Reproduction* 2017 **32** 2130–2137. (https://doi.org/10.1093/humrep/dex280)

Received 15 September 2020
Revised version received 10 March 2021
Accepted 29 March 2021