Changes Over Time in Sex Assignment for Disorders of Sex Development

WHAT’S KNOWN ON THIS SUBJECT: XY disorders of sex development have a diverse etiology and often present with atypical genitalia in the newborn period. Sex assignment in those cases in whom this is marked genital ambiguity is a rare, challenging situation that requires multidisciplinary input.

WHAT THIS STUDY ADDS: An international registry has shown temporal changes over the last 3 decades in the practice of sex assignment with a greater proportion of severely affected infants being raised as boys, raising the need for long-term monitoring of these children.

abstract

BACKGROUND AND OBJECTIVE: It is unclear whether the proportion of infants with a disorder of sex development who are raised as male or female has changed over time. The temporal trends in sex assignment of affected cases entered in the International Disorder of Sex Development (I-DSD) Registry were studied.

METHODS: Cases of disorders of sex development reported as partial androgen insensitivity syndrome (PAIS; $n = 118$), disorder of gonadal development (DGD; $n = 232$), and disorder of androgen synthesis (DAS; $n = 104$) were divided into those who were born before 1990, 1990–1999, and after 1999. External appearance of the genitalia was described by the external masculinization score.

RESULTS: The median (5th–95th percentile) external masculinization scores of those infants with PAIS, DGD, and DAS who were raised as boys were 6 (2–9), 6 (3–9), and 6 (1–12), respectively; this difference was maintained in the 3 temporal birth cohorts ($P < .01$). Of the 118 cases in the pre-1990 cohort, 41 (35%) were raised as boys; of the 148 cases in the 1990–1999 cohort, 60 (41%) were raised as boys; and of the 188 cases in the post-1999 cohort, 128 (68%) were raised as boys.

CONCLUSIONS: Although there is an association between the external appearance of the genitalia and the choice of sex assignment, there are clear temporal trends in this practice pointing toward an increased likelihood of affected infants being raised as boys. The impact of this change in practice on long-term health outcomes requires additional focus. 

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KEY WORDS
atypical, differences, DSD, gender, genitalia, intersex

ABBREVIATIONS
DAS—disorder of androgen synthesis
DGD—disorder of gonadal development
DSD—disorder of sex development
EMS—external masculinization score
I-DSD—International Disorder of Sex Development
PAIS—partial androgen insensitivity syndrome

(Continued on last page)
Disorders of sex development (DSDs) represent a wide range of rare congenital conditions with a diverse pathophysiology that alter the development of chromosomal, gonadal, or anatomic sex and that often require expert input from early infancy. Although the etiology may not be clear in a large proportion of cases, in many the condition may have occurred due to a disorder of gonadal development (DGD), a disorder of androgen synthesis (DAS), or a disorder of androgen action, such as partial androgen insensitivity syndrome (PAIS). Affected newborns often present with atypical genitalia, and these clinical situations can often be difficult to manage, particularly when the sex of rearing is uncertain.

In the face of genital ambiguity, the issue of sex assignment has been one of the most controversial aspects in the field of DSD management. The thinking in the 1950s and 1960s that humans are born tabula rasa and that gender identity was programmed during the first few years of life, mainly through social and environmental conditioning and reinforcement of gender role behavior, may have contributed toward the rationale for performing early sex assignment and sex-related surgery that conformed to the assigned sex in affected children. This theory was initially questioned by the report in the late 1970s of the XY girls with 5α-reductase deficiency who seemed content with changing to a male gender as they spontaneously virilized in puberty. The theory was also challenged by patient advocacy groups and research on long-term outcomes, which suggested that conditions such as micropenis may not necessarily be associated with a poor psychosocial outcome. In addition, the follow-up of the John versus Joan case in which a healthy boy was initially reported to be successfully raised as a girl after a severe injury to the penis only to be subsequently reported at a later stage in adulthood to be unhappy with this assigned sex further shook the confidence in the belief that “nurture” was dominant over “nature.” As late as 2002, female sex assignment was still being advocated in infants born with micropenis. However, around this time, studies using objective methods of assessing the appearance of external genitalia reported a large overlap in genital appearance of those raised as boys and those raised as girls, and the rationale for an optimal policy for sex assignment was increasingly being questioned. By 2006, experts in the field of DSD issued a wide-ranging consensus statement within which they acknowledged that sex assignment cannot solely be based on genital appearance but should include consideration of the diagnosis, surgical options, need for lifelong replacement therapy, the potential for fertility, views of the family, and circumstances relating to cultural practices.

A survey performed in 2010 suggested that a large number of European DSD centers had implemented policies and procedures in accordance with the recommendations that were issued after the above consensus meeting but since then it has not been clear whether there has been a measurable change in practice in the field of DSD. In 46,XY infants with bladder extrophy, a survey performed in 2004 and then repeated in 2011 suggested that clinicians were increasingly likely to consider a male sex assignment. A knowledge of current trends in the practice of sex assignment is not only important for understanding and improving clinical practice but also has an implication on long-term management including monitoring of long-term issues such as hypogonadism, subfertility, gonadal tumorigenesis, sexual function, gender identity, and quality of life. The consensus statement in 2006 on the management of DSD also stressed the need for creating and maintaining databases in centers of expertise. Such databases had existed at a less formal level in many regional centers but had lacked international uniformity and did not directly interoperate. An international Web-based registry, the International Disorder of Sex Development (I-DSD) Registry, was therefore created in 2008 with the promise to sustain research activity and address many unanswered questions on outcome in these rare conditions.

The aim of the current study was to use the I-DSD registry to assess whether there was any evidence for a change in the practice of sex assignment over the past few decades that have spanned important milestones in the field of DSD.

METHODS

Details of the I-DSD registry, including its development and current operation, have been previously reported and are also available from its Web site (www.i-dsd.org). Briefly, all specialist clinicians belonging to recognized professional medical and scientific societies and who are approved by the registry management group are eligible to register and report cases. There are no restrictions on the age requirement of the case, and there is no time limit between initial presentation or diagnosis and entry into the registry. Patient and/or parental consent is obtained before case registration, with the level of consent tiered according to the geographical extent of data sharing (own center, own country, European Union member states, international). The I-DSD registry is approved by the National Research Ethics Service of the United Kingdom, and the terminology used within the registry is based on the nomenclature initially developed at the Chicago consensus meeting and which has continued to evolve subsequently.
At the time of the study in September 2013, 1167 cases had been submitted from 24 centers in 15 different countries. Of these cases, there were 580 (50%) who were suspected to have a diagnosis of PAIS (n = 133), a DGD (n = 275), or a DAS (n = 172). All cases of complete androgen insensitivity in the registry had been raised as female and PAIS was therefore selected as the only diagnostic category representing a disorder of androgen action. Of these 580 cases, 454 (78%) had a sufficient level of consent to allow sharing of anonymized details regarding diagnosis, karyotype, sex of rearing, and clinical center. Of the 454 cases, 382 (84%) also had sufficient information about the external appearance of the genitalia at initial presentation and before any clinical intervention to calculate the external masculinization score (EMS), as previously described.15

In 7 of 454 (1.5%) cases, sex reassignment at a later stage was reported, and in these cases the initial sex assignment was used for the analysis. To analyze the influence of time, the cases were also divided according to the year of birth into 3 birth cohorts: before 1990, 1990–1999, and after 1999. The 1999 milestone was chosen to approximate with the increasing awareness of the John versus Joan case.7 The proportion of cases from individual centers was similar in all the subgroups.

Statistical analysis was performed by Statistica 10.0 (StatSoft, Tulsa, OK) and PQStat 1.4.8 (PQStat, Poznan, Poland). The Mann-Whitney U test was performed to assess the difference in EMS between male and female cases, the intergroup comparisons were performed by Kruskal-Wallis analysis of variance, and the χ² for trends test was performed to assess the significance of the temporal change in sex assignment. P < .05 was considered to be statistically significant.

RESULTS
Overall, of the 454 cases, 229 were raised as boys and 225 were raised as girls. Of the 118 cases in the pre-1990 cohort, 41 (35%) were raised as boys. Of the 148 cases in the 1990–1999 cohort, 60 (41%) were raised as boys; and of the 188 cases in the post-1999 cohort, 128 (68%) were raised as boys (Fig 1). In the sub-group of 382 cases in whom the EMS could be calculated, the median (5th–95th percentile) EMSs for those raised as boys and girls were 6 (2–11) and 1 (0–6) (P < .001). On categorization by temporal birth cohorts, the median EMS for those raised as boys was higher than that for girls, with a marked degree of overlap in the EMSs of the 2 sexes in all 3 cohorts (Fig 2).

PAIS
Of 118 cases reported as PAIS, 87 (74%) were raised as boys and 31 (26%) were raised as girls. The ratio of male to female sex assignment increased from 1.4 in the pre-1990 cohort, to 2.3 in the 1990–1999 cohort, to 6.3 in the post-1999 cohort, respectively (P = .021) (Table 1). Sufficient data were available to calculate the EMS in 72 (83%) male and 27 (87%) female cases. The median (5th–95th percentile) EMSs were 6 (2–9) in those raised as boys and 2 (0–6) in those raised as girls (P < .01). This difference in EMSs between the 2 sexes was present in all 3 temporal cohorts, and the change in proportion of cases assigned to male and female sex in these 3 temporal cohorts could not therefore be attributed to differences in EMS between cohorts (Table 1).

DGD
Of 232 cases reported as DGD, 102 (44%) were raised as boys and 130 (56%) cases were raised as girls. The ratio of male to female sex assignment increased from 0.4 in the pre-1990 cohort, to 0.6 in the 1990–1999 cohort, to 1.5 in the post-1999 cohort, respectively (P = .013) (Table 1). Sufficient data were available to calculate the EMS in 92 (90%) male and 112 (86%) female cases. The median (5th–95th percentile) EMSs were 6 (1–12) in those raised as boys and 0 (0–5) in those raised as girls (P < .01). This difference in EMSs between the 2 sexes was also present in all 3 temporal cohorts, and the change in proportion of cases assigned male and female sex in the 3 cohorts could therefore not be attributed to differences in EMS between cohorts (Table 1).

DAS
Of 104 cases reported as DAS, 40 (39%) were raised as boys and 64 (62%) cases
were raised as girls. Sufficient data were available to calculate the EMS in 30 (75%) male cases and 49 (77%) female cases. The median (5th–95th percentile) EMSs were 6 (3–9) in the group raised as boys and 2 (0–7) in those raised as girls \((P < .01)\). Although this difference in EMSs between the 2 sexes also seemed to be present in all 3 temporal cohorts, the difference did not reach statistical significance because of the smaller size of the cohorts. A clear trend in a change in the proportion of cases who were raised male and female was also not observed for this diagnostic group. Of the 22 cases of 5-\(\alpha\)-reductase deficiency and 17\(\beta\)-hydroxysteroid dehydrogenase deficiency, 3 (14%) were raised as male in the pre-1990 cohort. In the 1990–1999 cohort and the post-1999 cohort, the corresponding figures for those raised as male were 2 of 19 (11%) and 14 of 26 (54%), respectively.

**DISCUSSION**

The results from this analysis of the I-DSD registry clearly reveal that the practice of assigning female sex in newborns with 46,XY DSD seems to be decreasing. Previous reports highlighted the overlap that exists between the extent of masculinization of the external genitalia of children with PAIS raised as boys and those raised as girls. The current study confirms that this overlap also exists in infants with gonadal dysgenesis and DAS. Given that the phenotypic overlap remained similar in the 3 birth cohorts and that the proportion of children raised as boys increased, the results of this study reinforce the point that the change in practice was not due to a higher degree of masculinization of the cases raised as boys. Data in the I-DSD registry were entered from a number of centers but the majority were entered from countries in Western Europe, and it is likely that the observed trends primarily reflect practice in this region. With more widespread use of the registry, it is possible that geographical and regional trends can also be investigated in the future.

The change in practice that was observed in the current study seems to be gradual and the data suggest that it predates the meeting of the International Consensus Group in 2005, which, to an extent, was held in response to the changing tide of opinion. The change in practice is probably due to a number of reasons. In addition to a greater emphasis that clinicians are generally placing on the karyotype, the change in practice may be also due to reports of adequate long-term outcome in men with 46,XY DSD and conditions such as micropenis and an improved surgical outlook for penile reconstruction or neophallus construction. A survey of pediatric urologists recently reported an increasing preference for male sex assignment, especially among those clinicians who had practiced urology for a shorter duration, suggesting that part of the change may be due to a shift in social norms.

**TABLE 1** Number of Cases Assigned as Male or Female, Categorized by Reported Diagnosis and Birth Cohort

<table>
<thead>
<tr>
<th></th>
<th>PAIS</th>
<th></th>
<th>DGD</th>
<th></th>
<th>DAS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Male</td>
<td>Female</td>
<td>Male, %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pre-1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td>18</td>
<td>13</td>
<td>58</td>
<td>17</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>EMS, median (range)</td>
<td>6 (2–9)</td>
<td>1&lt;sup&gt;b&lt;/sup&gt; (0–5)</td>
<td>5 (0–12)</td>
<td>0&lt;sup&gt;b&lt;/sup&gt; (0–6)</td>
<td>3 (5–8)</td>
<td>2 (0–8)</td>
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<tr>
<td>1990–1999</td>
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<tr>
<td>(n)</td>
<td>25</td>
<td>11</td>
<td>69</td>
<td>31</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>EMS, median (range)</td>
<td>8 (2–11)</td>
<td>3&lt;sup&gt;b&lt;/sup&gt; (1–6)</td>
<td>6 (0–12)</td>
<td>0&lt;sup&gt;b&lt;/sup&gt; (0–6)</td>
<td>5 (5–5)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>Post-1999</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>(n)</td>
<td>44</td>
<td>7</td>
<td>86</td>
<td>54</td>
<td>37</td>
<td>59</td>
</tr>
<tr>
<td>EMS, median (range)</td>
<td>6 (2–9)</td>
<td>2&lt;sup&gt;b&lt;/sup&gt; (0–8)</td>
<td>6 (0–12)</td>
<td>0&lt;sup&gt;b&lt;/sup&gt; (0–6)</td>
<td>6 (2–8)</td>
<td>3&lt;sup&gt;b&lt;/sup&gt; (1–8)</td>
</tr>
</tbody>
</table>

The external appearance of the genitalia was described by the EMS.

<sup>a</sup> Percentage of cases raised as male.

<sup>b</sup> The median EMS was significantly different between male and female cases in that cohort \((P < .01)\).
attitudes. It is likely that practice has also been influenced by those cases of XY DSD who were raised as girls and who developed gender dysphoria, although other similar cases in which gender dysphoria was not encountered have received less attention. The etiology of 46,XY DSD is wide ranging, although at the moment, a confirmatory genetic diagnosis is rarely sought regularly for assisting with a decision for sex assignment, it is possible that in the future ongoing technological advances will lead to a turnaround time that is so short that it is possible that in the future ongoing technological advances will lead to a turnaround time that is so short that the knowledge of the genetic mutation may play a larger part in the sex assignment process as well as in the development of a plan for long-term surveillance. For instance, ~20% of boys with DSD may have a mutation in the androgen receptor gene, and it is possible that an early knowledge of this mutation will allow the clinician to differentiate a case of PAIS from partial gonadal dysgenesis. Boys with gonadal dysgenesis and retained gonads may show an age-related deterioration of testicular function, and suffer from suboptimal growth and pubertal development during adolescence. If more infants with 46,XY DSD are being raised as boys and retain their testes with an expectation of normal pubertal development and optimal long-term outcome including fertility, the need for long-term detailed clinical and biochemical surveillance as well as a reevaluation of the genetic etiology will become increasingly important in these affected boys. It is also possible that there may be more cases of complex hypospadias and micropenis that may require expert input for reconstructive surgery later in life. The I-DSD registry was not originally designed as an epidemiologic registry and neither does it collect detailed information on all cases that are entered. Other information that would provide more insight into the practice of sex assignment but was not captured includes factors such as age at sex assignment, the relative value of detailed endocrine and molecular genetic investigations, the contribution of the multidisciplinary clinical team, and the involvement of the parents in the sex assignment process. Registry users can also choose the extent of data sharing with other users for each individual case, and this sharing may depend on the patient’s or clinician’s preference. Based on the extent of access allowed to the investigators, only 85% of cases in the registry could be accessed for this study, thus introducing some selection bias. However, without the availability of this registry it is unlikely that trends in large numbers of these relatively rare conditions would have otherwise been studied. We chose to use the EMS as a method of describing and quantifying the extent of masculinization of the genitalia. Although this is an objective method of assessing genitalia, it is still possible that there may have been some interindividual variation in documenting the score. However, the large data set that was available through the I-DSD registry would have minimized the influence of any error. The I-DSD registry is increasingly becoming a powerful resource for studying trends in DSD and was recently used to study the patterns of associated malformations in DSD. Such rare disease resources have the potential to answer other questions that have been difficult to address with small sample sizes.

CONCLUSIONS

In summary, although the external appearance of genitalia continues to be associated with the choice of assigned sex, there are clear temporal trends in sex assignment that are independent of this external appearance and may reflect a shift away from the influence of genital appearance. Because infants with more profound hypogonadism may be raised as boys, there is a need to continue to improve our understanding of the underlying pathophysiology while intensifying the long-term follow-up of boys and men with DSD.

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(Continued from first page)

Dr Ahmed was involved in the design, development, and maintenance of the database; conceptualized and designed the study; was responsible as the local database
controller for the acquisition of the data and for interpreting the data; performed statistical analysis; produced the figures; and performed literature searches and
written revisions of the manuscript; Drs Kolesinska and Niedziela conceptualized and designed the study, analyzed the data, performed statistical analysis, produced the figures, performed literature searches, and contributed to revision of the manuscript; Dr Molinska-Glura performed the statistical analysis and
reviewed the manuscript critically for important intellectual content; Dr Bryce was involved in the design, development, and maintenance of the database; was responsible for coordinating the International Disorder of Sex Development (I-DSD) project; and was involved in drafting and revision of the manuscript; Drs Bertelloni, Hughes, Hiort, Jiang, Rodie, and Sinnott were involved in the design, development, and maintenance of the database; and were responsible as local
database controllers for the acquisition of the data and for interpreting the data and performing written and critical revision of the manuscript; Drs Alkhwari, Ariti,
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ponsible as local database controllers for the acquisition of the data and for interpreting the data and performing written and critical revision of the manuscript; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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