Testosterone Therapy and Its Monitoring in Adolescent Boys with Hypogonadism: Results of an International Survey from the I-DSD Registry

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Abstract: It is unclear whether testosterone replacement therapy (TRT) in adolescent boys, affected by a range of endocrine diseases that may be associated with hypogonadism, is particularly common. The aim of this study was to assess the contemporary practice of TRT in boys included in the I-DSD Registry. All participating centres in the I-DSD Registry that had boys between 10 and 18 years of age and with a condition that could be associated with hypogonadism were invited to provide further information in 2019. Information on 162 boys was collected from 15 centres that had a median (range) number of 6 boys per centre (1.35). Of these, 30 (19%) from 9 centres were receiving TRT and the median (range) age at the start was 12.6 years (10.8–16.2), with 6 boys (20%) starting at ≤12 years. Median (range) age of boys not on TRT was 11.7 years (10.7–17.7), and 69 out of 132 (52%) were ≤12 years. TRT had been initiated in 20 of 71 (28%) boys with a disorder of gonadal development, 3 of 14 (21%) with a disorder of androgen synthesis, and all 7 (100%) boys with hypogonadotropic hypogonadism. The remainder who did not have TRT included 15 boys with partial androgen insensitivity, 52 with non-specific XY DSD, and 3 with persistent Müllerian duct syndrome. Before starting TRT, liver function and blood count were checked in 19 (68%) and 18 boys (64%), respectively, a bone age assessment was performed in 23 (82%) and bone mineral density assessment in 12 boys (43%). This snapshot of contemporary practice reveals that TRT in boys included in the I-DSD Registry is not very common, whilst the variation in starting and monitoring therapy is quite marked. Standardisation of practice may lead to more effective assessment of treatment outcomes.

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Testosterone Therapy and Its Monitoring in Adolescent Boys with Hypogonadism: Results of an International Survey from the I-DSD Registry

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Keywords
Adolescent boys · DSD · Hypogonadism · Testosterone

Abstract
It is unclear whether testosterone replacement therapy (TRT) in adolescent boys, affected by a range of endocrine diseases that may be associated with hypogonadism, is particularly common. The aim of this study was to assess the contemporary practice of TRT in boys included in the I-DSD Registry. All participating centres in the I-DSD Registry that had boys between 10 and 18 years of age and with a condition that could be associated with hypogonadism were invited to provide further information in 2019. Information on 162 boys was collected from 15 centres that had a median (range) number of 6 boys per centre (1.35). Of these, 30 (19%) from 9 centres were receiving TRT and the median (range) age at the start was 12.6 years (10.8–16.2), with 6 boys (20%) starting at <12 years. Median (range) age of boys not on TRT was 11.7 years (10.7–17.7), and 69 out of 132 (52%) were <12 years. TRT had been initiated in 20 of 71 (28%) boys with a disorder of gonadal development, 3 of 14 (21%) with a disorder of androgen synthesis, and all 7
(100%) boys with hypogonadotropic hypogonadism. The remainder who did not have TRT included 15 boys with partial androgen insensitivity, 52 with non-specific XY DSD, and 3 with persistent Müllerian duct syndrome. Before starting TRT, liver function and blood count were checked in 19 (68%) and 18 boys (64%), respectively, a bone age assessment was performed in 23 (82%) and bone mineral density assessment in 12 boys (43%). This snapshot of contemporary practice reveals that TRT in boys included in the I-DSD Registry is not very common, whilst the variation in starting and monitoring therapy is quite marked. Standardisation of practice may lead to more effective assessment of treatment outcomes.

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Introduction

Hypogonadism in adolescent boys may be due to several diseases [Dwyer et al., 2015], and hormone replacement therapy with testosterone (T) is considered one of the cornerstones of the clinical management. In a routine tertiary hospital setting in the United Kingdom, approximately 10–15% of boys reviewed for suspected hypogonadism may proceed to testosterone therapy [Lucas-Herald et al., 2018]. In childhood, the majority of children with suspected DSD are raised as boys [Rodie et al., 2011], and within a routine clinical setting it is estimated that a quarter of the boys with DSD may have biochemical evidence of hypogonadism [Nixon et al., 2017]. Given that a child with XY DSD and profound hypogonadism is more likely to be raised as a boy nowadays [Kolesinska et al., 2014], it is increasingly likely that there will be more hypogonadal boys who will require androgen replacement in the future. However, currently, unlike girls, there is a relative lack of guidance on sex steroid replacement in affected boys who are reaching the age of puberty [Berteloni et al., 2008; Stancampiano et al., 2019].

In the absence of clear guidelines for testosterone therapy in boys, the relative rarity of this indication, especially in boys with a DSD and some evidence of variations in practice [Lucas-Herald et al., 2018], there is a need to understand the current practice in more detail. Registered users of the I-DSD Registry have previously participated in surveys of practice [Kyriakou et al., 2016]. Therefore, to understand the variations in practice at an international level, I-DSD centres that had registered boys of a pubertal age with a range of endocrine diseases that may be associated with hypogonadism were approached and invited to participate in a survey of contemporary practice with regard to testosterone replacement therapy.

Patients and Methods

Between February and May 2019, those centres that had registered patients in the I-DSD Registry who were male, between the ages of 10 and <19 years, and who had a condition that could be associated with hypogonadism were approached to participate in an electronic survey. At the time of the study, there were a total of 1,144 cases categorised as male in the I-DSD Registry, and of these, 225 boys (20%) from 29 centres were within the suitable age band for inclusion. Of the 29 centres that were approached, 14 (48%) centres with a total of 174 boys (77%) agreed to participate, and of these, follow-up data were available in 127 (73%). In addition to these 127 boys, routinely collected clinical data on a further 35 boys were available from an additional centre, providing a total of 162 cases from 15 centres. The median (range) number of boys per centre was 6 (1–35).

The questionnaire that was used to collect study data was divided into 2 sections. The first section obtained information on year of birth (YOB), disorder type, diagnosis, karyotype, gonadectomy, and testosterone replacement therapy (TRT) status. Testosterone therapy received in infancy or topical dihydrotestosterone therapy on genitalia were not regarded as TRT. As the I-DSD Registry did not collect the date of birth to estimate the age of each boy at the time of recruitment, all cases were assigned an arbitrary birthday of July, 1st. The second section of the questionnaire was reserved for the subset of patients who were on TRT, and this questionnaire collected information on age at starting hormone therapy, type of therapy, route of administration, dosage, length of treatment, and occurrence of adverse events during testosterone treatment. In addition, the centres were asked to report on any investigations performed at initiation and during therapy. This included auxology, Tanner stage, FSH, LH, testosterone, SHBG, AMH, inhibin B, full blood count, liver function tests, bone mineral density, bone age, sperm count, metabolic, glucose, and bone profile.

The I-DSD Registry is an international database of pseudo-anonymized information deposited by clinicians following informed consent from the patient or their guardian. Details of the development of the Registry and its recent use have been previously reported [Ahmed et al., 2010; Ali et al., 2019], and its standard operating protocol is available at idsdorg.files.wordpress.com/2019/09/the-i-dsd-i-cah-registry-data-access-policy-v1-290719-1.docx (last accessed, April 9, 2020). The Registry is approved by the National Research Ethics Service in the UK as a research database of information that is collected as part of routine clinical care. Statistical analysis was performed using GraphPad software package (Prism 8 for macOS version 8.0.2, GraphPad Software Inc, San Diego, CA, USA). All data were described as median and range, and comparison of continuous variables was performed using the Mann-Whitney test. A p value of less than 0.05 was considered significant.

Results

Description of Cases

The study cohort of 162 boys included 71 (44%) cases of a disorder of gonadal development (DGD), 15 (9%) cases of a disorder of androgen action (DAA), 14 (9%)

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cases of a disorder of androgen synthesis (DAS), 7 (4%) cases of hypogonadotropic hypogonadism, 3 (2%) cases of persistent Müllerian duct syndrome (PMDS), and 52 (32%) cases of non-specific XY DSD (Table 1). The median age (range) of the entire population was 12.7 years (10.7–17.7). Among the 71 boys with a DGD, 29 (41%) had partial gonadal dysgenesis (PGD), 19 (27%) had Klinefelter syndrome, 12 (17%) had gonadal regression, 7 (10%) had ovotesticular DSD, and the remaining 4 (5%) included 3 boys with XX testicular DSD and 1 boy with mixed gonadal dysgenesis. All cases of DGD were confirmed by one or more diagnostic methods, including biochemistry, genetics, and gonadal histology. All 15 boys with a DAA were diagnosed as partial androgen insensitivity syndrome (PAIS) with a confirmed pathogenetic variant in the androgen receptor gene. Among the 14 boys with a DAS, 7 (50%) had 5α-reductase deficiency, 3 (21%) had isolated 17,20-lyase deficiency or combined with 17α-hydroxylase deficiency, 2 (14%) had 3β-hydroxysteroid dehydrogenase deficiency, and there was 1 boy each with P450 oxidoreductase deficiency and 17β-hydroxysteroid dehydrogenase type 3 deficiency. All these cases were confirmed by biochemistry and/or genetic investigations. The initial presenting features among the 52 boys with non-specific XY DSD included a combination of genital anomalies with a total external masculinisation score (EMS) [Ahmed et al., 2000] of <9 out of 12 in 29 (56%) boys, isolated proximal hypospadias in 12 (23%) boys, complex genital anomalies in 6 (15%), and isolated bilateral undescended testes in 1 boy.

**Testosterone Replacement Therapy**

Of the 162 boys, 30 (19%) were receiving TRT at the time of the study (Table 1), and these boys were from 9 centres from 9 countries. Of these 30 boys, 24 (80%) from 9 centres had data available at follow-up. The me-
Median (range) age at the start of TRT was 12.6 years (10.8–16.2), and the median age at last assessment was 15.6 years (12–17.5). Median (range) age of boys not on TRT was 11.7 years (10.7–17.7), and 69 out of 132 (52%) were <12 years. Of the 30 boys, 6 (20%) started TRT before the age of 12 years: 4 with gonadal regression, 1 with 3β-hydroxysteroid dehydrogenase deficiency, and 1 with hypogonadotropic hypogonadism (Fig. 1). All those with hypogonadotropic hypogonadism were on TRT, and a substantial proportion of those with DGD (n = 20; 28%) and DAS (n = 3; 21%) were also on TRT (Table 1). However, none of the boys with PAIS, PMDS, or non-specific XY DSD were on TRT. Among the 15 boys diagnosed with PAIS, EMS at first presentation was available in 14, and 12 of these (86%) had an EMS ≥5. The 3 boys with PGD who had started TRT included 2 who had undergone bilateral gonadectomy. There were another 2 boys with PGD with a median age of 11.7 years who had bilateral gonadectomy prepubertally and who had not started TRT at the time of study. The median age at starting therapy was broadly similar in the 3 subgroups of disorders (Fig. 1). However, the extent of variation in age at starting therapy was greater for those with DGD, and this was primarily because this group consisted of boys with gonadal regression who started at a younger age (Fig. 1).

**Testosterone Formulation**

The formulation of testosterone the 30 boys were started on included Sustanon®, a blend of intramuscular testosterone esters (T decanoate 40%, T phenylproprionate 24%, T isocaproate 24%, T propionate 12%) in 14 (47%) patients, intramuscular testosterone enanthate in 12 (40%), oral testosterone undecanoate in 2 (7%), and transdermal 2% testosterone gel in 2 (7%). Of the 24 boys who had follow-up data, 10 (42%) were on intramuscular Sustanon®, 8 (33%) were on intramuscular testosterone enanthate, and 6 (25%) were on transdermal 2% testosterone gel. One boy who was originally on oral testosterone undecanoate changed to intramuscular Sustanon®, 1 changed from intramuscular Sustanon® to intramuscular testosterone enanthate, and 5 boys who were on intramuscular testosterone enanthate changed to transdermal 2% testosterone gel; these 5 boys were all at 1 centre.

**Monitoring of Therapy**

Before starting treatment, liver function and blood count were checked in 19 (68%) and 18 boys (64%), respectively. In addition, at start of therapy a radiological assessment of skeletal age was performed in 23 boys (82%), and an assessment of bone mineral density (BMD) was performed by dual energy X-ray absorptiometry in 12 boys (43%). In the 24 boys with follow-up data, serum testosterone, liver function, and blood count had been
monitored in 19 (79%), 16 (67%), and 15 boys (63%), respectively, at either 12 or 18 monthly intervals. BMD had been performed in 8 boys (33%) at an interval of 24 months. Adverse effects that were reported to be related to TRT included acne or oily skin in 3 boys, including 2 on intramuscular testosterone esters blend and 1 on oral testosterone undecanoate, aggressive behaviour in 1 boy on intramuscular testosterone esters blend, pain on injection in 1 boy on intramuscular testosterone esters blend, and a self-limiting episode of testicular pain in 1 boy on oral testosterone undecanoate.

Discussion

The current study represents the largest survey of TRT in boys with hypogonadism due to DSD or hypogonadotropic hypogonadism. It was designed to obtain a snapshot of contemporary practice, and boys within an age bracket where they would be currently receiving TRT were selected.

The occurrence of hypogonadism in boys and men with XY DSD has rarely been studied in detail. On systematic investigation of all boys presenting to an expert clinic with atypical genitalia, it is estimated that about a quarter may have an endocrine abnormality that may predispose them to long-term hypogonadism [Nixon et al., 2017]. However, it is possible that in some cases, hypogonadism may not be present in early childhood but develops over time with spontaneous testicular degeneration such as that observed in disorders of gonadal development associated with NR5A1-related partial gonadal dysgenesis [Tantawy et al., 2012] or Klinefelter syndrome. In some conditions such as undescended testes, hypogonadism may not be evident until adulthood [Rohayem et al., 2017] or may present after a procedure such as orchiopexy [Tseng et al., 2019]. Single-centre studies of adolescents suggest that in conditions such as partial gonadal dysgenesis, the occurrence of hypogonadism that presents overtly as pubertal delay may be as common as 40% [Gomes et al., 2018].

In the current study that included 15 centres, about a fifth of adolescent boys with a range of conditions were hypogonadal to such an extent that they required testosterone therapy for induction and maintenance of puberty. Within this large group of diverse conditions, about a quarter of those with a disorder of gonadal development or disorder of androgen synthesis were on testosterone. In addition, all boys who had hypogonadotropic hypogonadism were also on testosterone therapy. This latter finding is interesting to note given that opinion varies amongst specialists on whether to induce puberty with gonadotropins or testosterone [Han and Bouloux, 2010]. It is also possible that the availability of gonadotropins and the priority placed on fertility outcomes may have also influenced the therapeutic rationale. It was also important to note that none of the adolescents with PAIS were on testosterone therapy, and neither were those that had non-specific XY DSD who had normal gonadal function. Previous studies suggest that in adolescence, TRT may only be required by those who are severely undermasculinized as described by an EMS <5 [Lek et al., 2018]; most of the cohort in the current study had a greater EMS. Interestingly, in young adulthood, almost 50% of men with PAIS with a wide range of EMS receive testosterone supplementation [Lucas-Herald et al., 2016]. The findings of these studies in combination suggest that androgen supplementation in PAIS is more likely to be initiated for pubertal induction in boys who are particularly undermasculinised at first presentation, while a greater proportion of men with PAIS receive TRT in adulthood, perhaps for inadequate virilisation.

Whilst the age at starting TRT has been reported to be as low as 12 years in cases of permanent hypogonadism [Lucas-Herald et al., 2018], a fifth of the boys in the current cohort had initiation of therapy at an age <12 years and as early as 10 years. The practice of starting testosterone as early as 10 years was particularly evident in boys with gonadal regression. Given that there is unequivocal evidence of primary hypogonadism in these cases and the mean age for genital stage 2 has been reported in some population studies to be as young as 9.5 years [Herman-Giddens et al., 2001], there is a possible rationale for starting testosterone early. However, most studies show that the age of attainment of genital stage 2 is between 11 and 12 years [Juul et al., 2006]. Some who are concerned about pubertal growth have suggested that TRT should be initiated after a bone age of 10.5 years [Mason et al., 2020]. In conditions other than bilateral anorchia or gonadal regression, it is possible that the adolescent may have a state of partial hypogonadism where onset and/or progression through puberty may be affected to a variable extent. In such cases, it would be appropriate to monitor growth and pubertal development as well as biochemical markers of puberty and wait until there are clear signs that indicate that normal pubertal progress is unlikely to occur. It is likely that the timing of starting TRT is linked to the diagnosis, but to analyse this relationship, there is a need to study a larger group of boys with specific and confirmed diagnoses. The largest homogenous group of boys in the

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current study who had TRT was the group of boys with
gonadal regression, a condition which uniformly presents
at a very early age. However, even in this group, the range
of starting therapy was highly variable, ranging between
10.8 and 14.7 years. There is a need to gain further struc-
tured evidence of the rationale for the starting age of test-
osterone therapy as well as its relative benefits and harms.

It is clear that despite the availability of oral and topical
forms of testosterone [Stancampiano et al., 2019], the in-
tramuscular depot for testosterone remains the most
popular form of therapy, confirming literature data [Dro-
bac et al., 2006]. However, it was interesting to note that
over time, the topical form of testosterone may be gaining
popularity and there may be differences between centres.
Comparison of different forms of testosterone therapy
have rarely been performed [Ahmed et al., 2004; Chioma
et al., 2018], and it is likely that the choice of preparation
is based on local availability and preferences. However, in
adult men with DSD, it seems that a greater proportion
seem to be satisfied with non-parenteral forms of TRT
[Nordenström et al., 2018]. Satisfaction with testosterone
replacement has not been systematically assessed in ado-
lescents and, in addition to markers of clinical efficacy,
would benefit from being routinely assessed in the future.
Reports of adverse effects were infrequent, but given that
the study assessed these retrospectively, it is unclear
whether these are sought routinely and whether they in-
fluence practice. Testosterone therapy in transgender ad-
olescents has been associated with changes in metabolic
parameters [Stoffers et al., 2019]. While it is possible that
the likelihood of adverse effects of testosterone replace-
ment may depend on the underlying condition, as sug-
gested recently in a study of young men with thalassaemia
[De Sanctis et al., 2019], there is a need to assess these ef-
ffects systematically in all boys who embark on long-term
testosterone replacement. Clinical trials of testosterone
therapy that evaluate the efficacy and safety for pubertal
induction are very rare [Stancampiano et al., 2019] and
probably reflect the heterogeneity and the rarity of the
conditions for which boys require TRT. Although it
seems that liver function tests and haematology are as-
essed in the majority, this was not universal practice.
Previously, guidance on the topic of monitoring TRT in
adolescence has been published [Bertelloni et al., 2010;
Soliman et al., 2014], and these have been revised recent-
ly [Stancampiano et al., 2019]. However, our experience
from the current multicentre study, as well as previous
studies [Nahata et al., 2015; Lucas-Herald et al., 2018],
suggests that this guidance is not universally followed.
Perhaps, this may also reflect the lack of evidence that
supports the need for routine monitoring, as may be the
case for regular assessment of BMD [Stancampiano et al.,
2019]. In the absence of clinical trials and licensed forms
of TRT, there is a need to standardize the monitoring of
therapy of such infrequent practice and ensure system-
atic collection of real-world evidence.

For pragmatic reasons we chose to define hypogonad-
ism as those boys on testosterone therapy. In those pa-
ients with conditions such as gonadal regression or con-
genital hypogonadotropic hypogonadism, it is likely that
TRT was started before they developed any actual bio-
chemical or physical signs of hypogonadism. However, in
general, it is possible that the current study is an under-
estimate of the actual number of adolescents with hypo-
gonadism given that this condition is a very wide spec-
trum and can include patients with biochemical hypogo-
nadism [Grinspon et al., 2019]. The prevalence of overt
or sub-clinical hypogonadism in boys has not been sys-
tematically studied to date. Rodie et al. [2011] reported
that approximately 50 cases with suspected DSD may
present per year for a population of approximately 3 mil-
ion. Considering that in 2019 the estimated number of
boys aged 10–19 years in the same area was 30,000 and
that 24 boys included in the study were recruited from
West of Scotland (https://www.understandingglasgow.
com/indicators/population/trends/changing_age_struc-
ture, last accessed, May 2019), it could be considered that
boys with DSD were well represented. However, this may
not be valid for all centres, and there may have been some
selection bias. It is also possible that clinicians may have
chosen to report cases that were more severely affected or
the centres that chose to participate or not to may have
introduced a level of bias. However, the current study still
represents the largest assessment of the contemporary
practice of testosterone therapy in boys with a wide range
of conditions that cause permanent hypogonadism. The
results show that testosterone therapy in boys with DSD
is not a common occurrence and that there is a wide ex-
tent of variation in practice. It is possible that this vari-
ation is due to multiple factors, such as the needs of the
young person himself, the clinical outcomes that are con-
sidered important by the clinician, and the local availabil-
ity of drugs. The results also stress the need for ongoing
studies to monitor practice and highlight the need for
guidelines and standardized protocols that can be used at
the initiation and during maintenance of long-term tes-
tosterone therapy. Whilst the I-DSD Registry remains a
valuable resource of cases of DSD, the study has also high-
lighted the need for developing a specific module within
the Registry that focuses on capturing relevant informa-
tion on TRT in a standardized manner. These protocols and resources will allow us to understand the rationale as well as the short- and long-term effects of TRT in boys with DSD.

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Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The I-DSD Registry is an international database of pseudo-anonymized information deposited by clinicians following informed consent from the patient or their guardian. The Registry is approved by the National Research Ethics Service in the UK as a research database of information that is collected as part of routine clinical care.

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Conflict of Interest Statement

S.F.A. has received consultant fees from Acerus Pharma. M.R.S. has received consultant fees from Neurocrine Pharma.

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Author Contribution

S.F.A., M.R.S., A.K.L.-H., and J.B, designed the study. M.R.S. analysed and interpreted the data. S.F.A. and M.R.S. wrote the manuscript. A.K.L.-H., J.B., G.R., G.B., A.B., F.B., S.B., M.V., M.C., L.J.W.T., F.D., S.P., E.G., R.G., S.E.H., I.A.H., R.T.-C., A.T., C.I., V.M., D.K., I.M., M.N., Z.K., A.N., and S.F.A. revised the manuscript critically and approved the final version.

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).
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