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DOI:
10.1530/EJE-17-0862

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Document Version
Peer reviewed version

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

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Download date: 15. Jul. 2024
Gonadal Function in Adult Male Patients with Congenital Adrenal Hyperplasia

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Abstract

Context: Current knowledge on gonadal function in Congenital Adrenal Hyperplasia (CAH) is mostly limited to single center/country studies enrolling small patient numbers. Overall data indicate that gonadal function can be compromised in men with CAH. Gonadal function can be compromised in male patients with congenital adrenal hyperplasia (CAH), however previous studies have been limited to reports from a single center/country or small patient numbers.

Objective: To determine gonadal function in men with CAH within the European “dsd-LIFE” cohort.

Design: Cross-sectional clinical outcome study, including retrospective data from medical records.

Methods: Fourteen academic hospitals included 121 men with CAH aged 16-68 years. Main outcome measures were serum hormone concentrations, semen parameters, and imaging data of the testes.

Results: At the time of assessment, 19/83 (23%) patients had a serum testosterone concentration level below the reference range; 8 of those were hypogonadotropic, 10 normogonadotropic, and 1 hypergonadotropic. In contrast, in the presence of normogonadotropic, 54/69 (79%) patients were hypogonadotropic, 50 (73%) normogonadotropic, and 9 (13%) hypergonadotropic. The association of decreased testosterone with reduced gonadotropin concentrations (Odds Ratio (OR)=8.0 [2.7-29.6] 12.8 [2.9-57.3]) was weaker than the association between serum androstenedione/testosterone ratio ≥ 1 and reduced gonadotropin concentrations (OR=16.8 [2.0-142.5] 39.3 [2.1-732.4]). Evaluation of sperm quality revealed decreased sperm concentrations (15/39), decreased motility (13/37), and abnormal morphology (4/28) were also observed. Testicular adrenal rest tumor (TART) were present in 39/80 patients, with a higher prevalence in patients with the most severe genotype (14/18), and in patients with increased current 17-hydroxyprogesterone (12/18 20/35) or androstenedione (16/26 12/18) serum concentrations. Forty-three children were fathered by 26/113 patients.
Conclusions: Men with CAH have a high risk of developing hypothalamic-pituitary-gonadal disturbances and spermatogenic abnormalities. Regular assessment of endocrine gonadal function and imaging for TART development by imaging are recommended, in addition to measures for fertility protection.
**Introduction**

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder resulting in impaired adrenocortical steroid synthesis by several enzyme deficiencies. The most common form (>95%) is 21-hydroxylase deficiency (21OHD) with an incidence of 1:15 000, leading to glucocorticoid and often also mineralocorticoid deficiency in combination with androgen excess 1, 2.

Reported fertility and fecundity in men with CAH on routine steroid replacement therapy range from normal to severely impaired. Fertility can be compromised due to primary (hypergonadotropic) hypogonadism or central (hypogonadotropic) hypogonadism 3-11. In addition, reduced fertility and fecundity rates problems in CAH can be caused by psychosexual factors 4. One of the commonest complications in men with CAH is the presence of Testicular Adrenal Rest Tumor (TART)s, which can cause disturbances of gonadal function, including mechanical obstruction of the seminiferous tubules. The reported prevalence of TART ranges between 12.5% and 94% in the populations studied. Central or secondary hypogonadism is defined as decreased testosterone concentrations in combination with either low or low-normal LH or FSH concentrations. In patients men with CAH, secondary hypogonadism is most likely to be caused by the suppressive effect of elevated adrenal androgens (that are aromatized to estrogens) on the hypothalamic-pituitary-gonadal (HPG)-axis 6.

Differentiation between gonadal and adrenal testosterone is difficult, complicating the diagnosis of hypogonadism in patients men with CAH. One of the commonest complications in men with CAH is the presence of Testicular Adrenal Rest Tumor (TART)s, which can cause disturbances of gonadal function, including mechanical obstruction of the seminiferous tubules. The reported prevalence of TARTs ranges between 12.5% and 94% in the populations studied 4,10,12-22.

Until now, the data on fertility outcome in men with CAH are scarce. Available data are 3-11 and often derived from studies with patients from a single center or country. Our aim was to study gonadal function in a large European multi-center cohort of male patients with CAH by evaluating hormone concentrations, semen parameters, and TART frequency.
Subjects and Methods

Subjects

dsd-LIFE is a cross-sectional clinical outcome study of individuals with disorders/differences of sex development (DSD). Fourteen study centers in 6 European countries (France (n=4), Germany (n=4), United Kingdom (n=1), Poland (n=2), Sweden (n=1), and the Netherlands (n=2)) included former and current patients as participants from February 2014 - September 2015. In addition to DSD participants, 121 male participants with CAH (46XY karyotype) aged 16-68 years were recruited as they may face similar clinical challenges as DSD patients, including sex hormone imbalances and fertility problems, although male patients with CAH do not fit into the classification of DSD. Written informed consent was obtained from all participants and/or their parents, with assent of minors. Ethical approvals were obtained as appropriate for each country, e.g., Ethics Commission of the Charité Universitätsmedizin; reference number EA2/069/13. For. The theoretical and methodological framework of the dsd-LIFE study have been published in detail elsewhere see Röhle 2017 et al. 23. Patients were investigated in their local treatment center. Cross-sectional data were obtained for serum hormone concentrations, semen parameters and testicular imaging. The genotype of patients with 21OHD was classified into genotype groups null, A, B, and C 24. Patients were also classified into salt-wasting (SW), simple virilizing (SV) or non-classical (NC) based on their main symptoms and time of diagnosis. General patient characteristics and clinical parameters included: country of inclusion, age, age at diagnosis, CAH genotype and phenotype, socioeconomic status, and obesity, as well as height, weight, and BMI throughout the years (at diagnosis, 9 months old, 6 years old, Tanner stage 2, 16 years old, and current age). Patients’ educational levels was established according to the EU classification. We combined the standardized ES-ISCED (international standard classification of education) scale to Low (ES-ISCED I = less than lower secondary and ES-ISCED II = lower secondary); medium (ES-ISCED IIb = lower tier upper secondary; ES-ISCED IIIA = upper tier upper secondary; ES- ISCED IV = advanced vocational, sub-degree) and high (ES-ISCED V1 = lower tertiary education, BA
level; ES-ISCED V2 = higher tertiary education, >=MA level). Data was collected during medical examination at study inclusion (cross-sectional) and retrieved from medical records (retrospective data).

**Hormonal analysis**

Blood samples were taken during day time, but mostly in the morning, before intake of the glucocorticoid medication. Total testosterone, SHBG, LH, FSH, inhibin B, AMH, androstenedione, 17-hydroxyprogesterone (17OHP) concentrations, and renin/plasma renin activity were measured in the local hospital laboratory and compared to local references. Values are reported in SI or international units and reported as “below reference range”, “within reference range”, “above reference range up to twice the upper limit”, and "more than twice the upper limit of the reference range”. To increase the number of patients per category, we combined the latter 2 categories into the category "above reference range".

The serum androstenedione/testosterone ratio (AD/T) was calculated and divided into normal (<0.5; interpreted as testosterone mainly of testicular origin), ≥0.5 and <1 (significant fraction of testosterone is of adrenal origin), and ≥1 (testosterone mainly of adrenal origin ) as suggested by others.

Three patients were excluded from part of the analyses as they received testosterone substitution, which directly affects testosterone and gonadotropin concentrations. Two of these patients had data on TART available; these are described in the results section, but were otherwise excluded from further analyses.

**Semen analysis**

Semen analysis was performed by the local hospital laboratory and interpreted in accordance with the 2010 World Health Organization criteria, including sperm concentration (lower reference limit
(LRL): 15x10^6/mL, motility (LRL: 40%), morphology (LRL: 4%), vitality (LRL: 58%), and volume (LRL: 1.5 mL).

**Imaging of testes**

At the study visit, 68 patients (56.2%) underwent testicular ultrasound. The presence of TART at the age of 16 years was also reported retrospectively (in 30/68 patients with cross-sectional TART data).

In addition, retrospective data were available for 12 participants based on ultrasound findings or MRI (n=11) and on histological findings (n=1).

**Paternity**

Data about paternity and relationships were collected from the dsd-LIFE questionnaires.

**Medication and estimation of metabolic control in the past**

Patients used different formulations of glucocorticoids, including hydrocortisone, prednisone, prednisolone, and dexamethasone. Furthermore, we converted all glucocorticoid preparations were converted to hydrocortisone equivalents for comparison, using the following factors for the glucocorticoid equivalent dose: 1 (hydrocortisone), 4 (prednisone or prednisolone), 30 (dexamethasone), and 15 (fludrocortisone). We also calculated mineralocorticoid equivalent dose using the following factors: 1 (hydrocortisone), 0.8 (prednisone or prednisolone), 0 (dexamethasone), and 200 (fludrocortisone). In addition to the serum 17OHP concentrations presented in the section hormonal analysis, we also assessed metabolic control by a subjective rating of metabolic control of the local examining physician at 5 different time points: at diagnosis, at the age of 9 months, at Tanner stage 2, at age 16 years and at study inclusion, using the following scores: "poor", "moderate", "good", "excellent" or "unknown".

**Statistical Analysis**
SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) was used for all analyses. Descriptive analyses were performed for all variables. Depending on normality, mean and 95% confidence intervals (95%CI) or median and interquartile ranges (IQR) were calculated. We compared patients with values below or above reference range to patients with normal values (within the reference range). Odds ratios (OR) with 95%CI were calculated if at least 3 cases were present in both subgroups. If any cell count in the contingency table was zero, OR and 95%CI were calculated manually by using a continuity correction (+0.5 in each cell).

Missing data were evaluated for each variable and the total number of participants in a particular analysis was reported exactly. Analysis of the variables was only performed only if when the number of participants was at least 25% of the total cohort of male patients with CAH.

Three patients were excluded from part of the analyses as they received testosterone substitution, which directly affects testosterone and gonadotropin concentrations. Two of these patients had data on TART available; these are described in the results section, but were otherwise excluded from further analyses. Furthermore, we excluded 22 patients with missing genotype information and 2 patients with 11β-hydroxylase deficiency from all comparative analyses.
Results

General characteristics of the male CAH cohort

A total of 121 male patients were included in the CAH cohort in the dsd-LIFE study. General characteristics are shown in Table 1. The median age of the study population was 28 years (IQR: 18.5-37.5, range 16-68). Mean height was 170.7 (95%CI: 169.3-172.0) cm and median BMI was 25.6 (IQR: 22.0-29.2) kg/m² (data available for 119 patients). Nearly all patients had 21OHD (119/121), of which 97 were confirmed by molecular genetic analysis and 22 were based on phenotype alone. The remaining 2 patients had 11β-hydroxylase deficiency. Among the 97 patients with genetically confirmed 21OHD, genotype groups null, A, B, and C contained 19.8% 24.7% were classified as genotype null, 30.6% 38.1% as genotype A, 27.3% 34.0% as genotype B, and 2.5% 3.1% as genotype C. of the 97 patients with genotyping results. The majority of patients (62.0%) were classified as having the SW form of CAH, 31.4% had the SV form and 4.1% had the NC form.

Glucocorticoids were used by 116 (95.9%) patients, most commonly hydrocortisone, followed by prednisone or prednisolone, and dexamethasone. Fludrocortisone was used by 86 patients (71.1%). The patients’ education was intermediate or high in 54.5%, and 22.3% of the participants, respectively. Furthermore, 54.6% of the patients were in a relationship at the time of study.

We analyzed all variables mentioned in the method section, but we only present in detail the data that differed between the analyzed groups (no overlap in the confidence intervals). In the following sections we will present data regarding hormone concentrations, semen analysis and TART.

Hormone concentrations

Univariate descriptive analyses of hormone concentrations were performed. The proportion of patients with normal, decreased or increased serum testosterone, LH, FSH, inhibin B, AMH, and SHBG concentrations is illustrated in Figure 1A. Hormone concentrations were below the reference range in 19/97 (19.6%: testosterone), 8/43 (18.6%: inhibin B), 12/90 (13.3%: LH), 9/90 (10.0%: FSH), and
1/69 (1.4%: SHBG) of the participants. SHBG concentrations were above the reference range in 14.5% (10/69).

Table 2 shows compares testosterone and gonadotropin concentrations in all patients with data on T, LH, and FSH available. That in 7 patients (50%) with decreased testosterone concentrations (19/33), 8 (42.1%) had decreased gonadotropins, while 10 (52.6 42.9%) had normal LH and FSH concentrations, and 1 (5.3 7.1%) patient had gonadotropin concentrations above reference range. Normal testosterone concentrations were found in 64/83 (77.8%) patients, 50 (60) (78.1 80.0%) of whom had normal gonadotropin concentrations, whereas 9 (14 12.7%) had increased, and 5 (7.38%) had decreased concentrations. Decreased testosterone concentrations were clearly associated with decreased LH and/or decreased FSH concentrations (OR 8.0 12.8, 95%CI: 2.9 - 25.6 57.3).

A serum AD/T ratio was calculated in 49 patients, 22 of whom (44.9%) had an AD/T ratio ≥1. Ten patients (45.5%) with an AD/T ≥1 had decreased gonadotropins, while 11 (50.0%) patients had normal gonadotropins and only 1 (4.5%) patient had increased gonadotropins. Normal AD/T ratios were found in 27/49 (55.1%) patients, 21 of whom had normal gonadotropin concentrations (77.8%), 5 had increased concentrations, but none had decreased gonadotropin concentrations. was found in 7/8 patients (87.5%) with decreased testosterone and gonadotropins, while 4/5 patients (80.0%) with normal testosterone and decreased gonadotropins had an AD/T ratio ≥1. Moreover, 5/10 patients (50.0%) with decreased testosterone and normal gonadotropins had an AD/T ratio ≥1, whereas this was seen in only 11/50 patients (22.0%) with normal testosterone and gonadotropins. An AD/T ratio ≥1 was strongly associated with decreased LH and/or decreased FSH concentrations (OR 16.8 39.3, 95%CI: 2.10 - 142.5 732.4).

Semen analysis

Semen analysis was performed in approximately one third of the patients (Figure 1B). Normal values for all known (at least 3 out of 5) semen parameters (normozoospermia) were seen in 11/39 patients.
in which semen analysis was performed. Sperm concentration, motility, and volume were below the normal ranges in 38.5% (15/39), 35.1% (13/37), and 25.6% (10/39) of the patients, respectively, while morphology and vitality were both impaired in 14.3% (4/28 and 2/14) of the patients. Five of 8 patients (62.5%) with decreased testosterone and gonadotropin concentrations underwent semen analysis, with 4 (80.0%) of them showing abnormal semen parameters (Table 3). In only 2/10 patients with decreased testosterone, but normal gonadotropin concentrations, semen analysis was performed and both had decreased sperm concentrations (7.0 and 10.0 x10^6/mL). No statistically significant associations were found (data not shown).

Testicular adrenal rest tumors

TARTs were visualized by ultrasound or MRI at cross-sectional investigation in 28/68 patients. For 1 patient, the diagnosis was based on retrospective histology data. Furthermore, retrospective imaging data were available for 11 men: TARTs were present in 10 of these individuals. So, in the total population screened, TARTs were present in 39/80 patients (48.8%) of which 34 were bilateral TARTs (87.2%). Documented retrospective TARTs at age 16 years were reported in 16/30 patients (53.3%), all of which were bilateral. In only 2/16 patients (12.5%) with TART reported to be present at age 16, TART was no longer observed during the cross-sectional investigation: one patient was misdiagnosed with TART as it appeared to be a varicocele, and in the other patient TART (size 2 mm) disappeared after treatment with prednisone. This patient was still considered as a TART patient with TART in all analyses.

Comparison of patients with and without TART

Table 4 shows associations of TART with various variables in the 78 patients with gonadal imaging data (12 patients were excluded due to testosterone substitution, 11β-hydroxylase deficiency or unconfirmed 21-hydroxylase deficiency), comprising 47 patients with and 31 without TARTs. Genotype was clearly associated with the presence of TART: The null genotype group had the highest prevalence of TART (14/18: 77.8%), while the prevalence was 10/27 (37.0%) for genotype group A.
and 7/21 (33.3%) for genotype group B. The odds of having TART in the null genotype group was 6.0 [1.5-23.1] and 7.0 [1.7-29.4] times higher compared to the genotype groups A and B, respectively. TARTs were also present in both men in the genotype C group, and also in 1 CYP11B1-deficient patient (the other CYP11B1 patient did not undergo assessment for TART). The OR of having TART when having an serum androstenedione level concentration above the upper limit of normal at the time of the cross-sectional investigation was 3.6 [1.0 - 11.2] 12.7. Similar associations were found for serum 17OHP at the cross-sectional investigation, with an OR of 6.4 [1.7 3.1 - 24.7] 252.5 for having TART when 17OHP concentrations were more than twice the upper level of the reference range, and an OR of 4 18.7 [1.3 2.2 - 158.1 16.5] when these concentrations were above the reference range compared to concentrations within the reference range.

Paternity

Data on paternity were available for 113 of the 121 patients, 26 (23.0%) of whom (age range 26-68 years) had fathered a total of 43 children. Three couples had used assisted reproductive techniques (ART) resulting in 4/43 children. One of the men who had used ART had decreased testosterone concentrations, while another had increased FSH, decreased sperm concentration, and TART. No information was available about the third patient who had used ART. One man with impaired semen motility, increased FSH concentrations, and TART had adopted a child.

Discussion

This unique and relatively large European multicenter study shows that gonadal dysfunction is a common complication in male patients with CAH. Approximately half of the patients were affected by endocrine disturbances of the HPG axis at an adult age and TARTs were present in approximately half of the patients as well. The difficulty in diagnosing hypogonadism in men with CAH is related to the fact that testosterone measured in serum is a mixture of testosterone of gonadal and adrenal origin. 25. 28. Circulating
testosterone in male patients with well-controlled CAH is predominantly derived from testicular production, but when there is poor hormonal control, a relevant contribution arises from adrenal steroidogenesis. Until now, no method is able to discriminate between testosterone derived from the testes or the adrenal gland. Therefore, it has been suggested to use the serum AD/T ratio in male patients with CAH, as this precursor steroid is elevated in serum when serum androgens are predominantly of adrenal origin. Our data point toward an association between an AD/T ratio ≥1 (testosterone mainly of adrenal origin) and decreased LH and/or decreased FSH concentrations compared to testosterone concentrations alone, suggesting that adrenal androgens in men with CAH contribute to the suppression of gonadotropins. In approximately half of the patients, either aberrant testosterone or AD/T ratios, or aberrant gonadotropin concentrations, or a combination of both were found. In previous studies, the reported prevalence of endocrine HPG axis disturbances ranged from 20% to 52% 5-7, 9, 10. However, only one other report provided information on testosterone and gonadotropin concentrations in each patient, and also indicated endocrine disturbances hypogonadism in approximately half of the patients. We recommend to include the evaluation of the AD/T ratio in the regular follow-up androstenedione measurements in the gonadal evaluation of male patients with CAH to calculate the AD/T ratio, and interpret this ratio in combination with gonadotropin concentrations in order to detect a disturbance of the HPG axis. Our study does not include data information on 11-oxygenated androgens, that are generated through conversion of androstenedione, and are reported to be elevated concentrations are found in patients with CAH 29, 30. Recent studies indicate that 11-oxygenated androgens are almost entirely derived from the 11beta-hydroxylation of androstenedione in the adrenal, and as they are potent androgens they can contribute to suppression of the HPG axis31. However, their exact role in the evaluation of androstenedione associations with hormonal control and gonadal function in men with CAH has to be established in further studies. Serum AMH and inhibin B are also used as markers for male fertility32. However, literature already showed it has been demonstrated that serum AMH concentrations do not
correlate with sperm concentration and other male fertility parameters. Serum inhibin B, a marker of Sertoli cell function, is known to correlate with spermatogenesis in healthy men and was decreased in 18.3% of our cohort. Semen quality, assessed in one third of the study cohort, was reduced in 40% of the men. Except for the study of Urban et al., all other studies on fertility in male patients with CAH showed decreased sperm concentrations ranging from 47.8% to 66%.

More strikingly, in all studies only half of the participants participated in semen analysis. Taken together, these data indicate the need for increased awareness on fertility status in patients with CAH, and to start detecting disturbances early and allow semen preservation to be able to preserve semen for later fertility purposes.

Data from our cohort indicate, in agreement with previous studies, that TART is a common complication in male patients with CAH, with a prevalence of 48.8% and can have onset as early as in adolescence. In fact, Strikingly, 14 patients with TART at the time of the dsd-LIFE study already had TART at the age of 16 years. TARTs disappeared in only 1 patient, thus indicating that complete regression of TART might only be achieved in a small proportion of the patients. Hence, prevention of the development of TART should be pursued, by optimizing treatment strategies already in childhood. Current standard of care does not include imaging of testes, however we recommend incorporating testicular ultrasound in routine clinical practice.

In contrast to previous studies, several studies did not find an association between CAH severity and TART, we observed an association between the CYP21A2 genotype and the presence of TARTs, with the prevalence of this complication being highest in men with the null CYP21A2 genotype.
This likely confirms supports the current perception that TARTs are more frequently observed in patients with a more severe form of CAH, as these patients are exposed to higher concentrations of ACTH, already in utero, which is thought to be a possible causative factor for TART development \(^6\), \(^7\), \(^15\). However, a clinically relevant finding in this study is that TARTs occur even in less severe forms of 21OHD. In fact, in our study, 2 patients in genotype group C with NC-CAH (both compound heterozygous for deletion and P30L mutation) had TARTs. In our current dataset, we could not find an association between genotype and semen quality or genotype and hypogonadism. Both patients were compound heterozygous (deletion + P30L mutation). Only 1 patient in our cohort had the typical NC mutation, i.e. the V281 mutation (V281/I2Splice). No TARTs were detected in this patient.

In our study, we found an association between increased 17OHP concentrations at cross-sectional data assessment and the presence of TART. Although a single 17OHP measurement may not be representative of overall metabolic control, these results could be interpreted as a possible indicator of the patient’s metabolic control in the recent past. Therefore, our results seem to be in accordance with literature reporting higher TART prevalence in patients with poor hormonal control compared to patients with adequate hormonal control \(^5\), \(^7\), \(^13\), \(^35\)-\(^38\). The association between increased androstenedione concentrations at cross-sectional data assessment and the presence of TARTs adds evidence to this pathophysiologic concept, even if the AD/T ratios were not clearly associated with TART within this subgroup of patients. Primary gonadal dysfunction may be suggested by raised FSH concentrations. In our dataset, 10 patients (11.1%) had elevated FSH concentrations. Seven of these patients had data on the presence of TART, and 4 had evidence of TART. King et al. found that testicular failure was a consequence of TART in the majority of cases \(^10\). However, our data are limited and do not allow firm conclusions concerning this issue. We cannot confirm the findings of King as we have only very limited data available.

Despite this being the first international multicenter study describing gonadal function in male patients with CAH, the study also has some limitations. All centers included in this consortium are
tertiary care centers, therefore it is possible that the patient groups were selected and that the patients included were more severely affected. Furthermore, serum hormone concentrations were not measured centrally, but in various centers with a range of different assays. Accounting for this fact, only range variables were used in the data analyses. The median BMI in our patient cohort was 25.6 kg/m² (range 22.0-29.2), which is slightly overweight. It has been demonstrated that excess of total and abdominal body fat could represent one cause of fertility impairment in men with CAH.

Serum total testosterone can be decreased in patients with obesity, as a result of the decreased serum concentration of SHBG. In case of increased serum SHBG (induced by hepatitis, hyperthyroidism, or a genetic variant), total testosterone may be increased. Ideally, free testosterone should be measured in these cases, but this requires complex equilibrium dialysis. Free testosterone can also be calculated from the level of total testosterone, SHBG, and albumin concentrations, but it is crucial that the results of such calculations are compared with the normal range of each separate laboratory. Such data were not available. We are aware that assessment of fertility by paternity numbers in our study was incomplete, as many other factors, of which including female fertility, are important as well. However, these data were not available. Furthermore, participation in the medical examination was not obligatory for study inclusion. This may have led to even more selection, especially concerning the ultrasound examination and semen analysis. It is likely that only the very motivated patients and the more severely affected patients consented to these additional examinations. Due to the resulting low numbers of available data, multivariable logistic regression analyses were not possible.

In summary, impaired gonadal function is common in adult men with CAH. This is indicated by the presence of TART and/or hypogonadotropic or hypergonadotrophic hypogonadism. The risk of TART is highest in men with the most severe enzyme deficiencies underlying CAH. Our data suggest that an association with poor previous hormonal control is likely but has to be confirmed by further prospective studies. Determination of the serum AD/T ratio, in addition to serum concentrations of testosterone, androstenedione, LH, and FSH may help to differentiate...
between testicular and adrenal androgens in male patients with CAH and to estimate the degree of gonadal dysfunction. Routinely performed semen analysis, measurement of serum inhibin B, and testicular ultrasound investigation already in adolescence are recommended to detect upcoming reproductive problems and to allow for fertility preserving measures, such as sperm banking.
Disclosure

Funding
dsd-LIFE - The work leading to these results received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 305373. The following author received additional funding: NR: Else Kröner-Fresenius Stiftung (Grant 2011-EKMS.21), and the European Community (Marie Curie European Reintegration Grant PERG-GA-2010-268270).

Declaration Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Acknowledgements

We are grateful to the participants of dsd-LIFE and to all of the study centers for their enthusiasm and dedication in contacting potential participants and collecting high-quality data. We especially thank the support groups in the different countries for their help. For an overview of all contributors we refer to our study protocol 23.

References


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Andersson AM, Petersen JH, Jorgensen N, Jensen TK & Skakkebaek NE. Serum inhibin B and follicle-stimulating hormone levels as tools in the evaluation of infertile men: significance of


**Figure legends**

**Figure 1:** Hormone concentrations (A) and semen quality (B) in male patients with congenital adrenal hyperplasia to assess gonadal function. Stacked bars represent percentage of patients within a category. Numbers in the bars represent the specific number of patients within a category, while the total number of patients included in this analysis is stated underneath the x-axis. **A)** Hormone concentrations of each patient were measured in the local hospital and compared to the hospitals standard reference ranges. **B)** Semen analysis was performed and scored according to World Health Organization 2010 criteria: sperm concentration, motility, morphology, and vitality, and semen volume were assessed. Abbreviations: AMH, anti-Müllerian hormone; INHB, inhibin B; N, number of patients; T, testosterone.