Experience in Optimising Fertility Outcomes in Men with Congenital Adrenal Hyperplasia due to 21 Hydroxylase Deficiency.

Thomas F. J. King[1,2], Marilyn Cheng Lee[1,2], Elizabeth E. J. Williamson[2], Gerard S. Conway[1,2]

Department of Endocrinology[1] and

Women's Health Institute[2]

University College London Hospitals

London, United Kingdom

Correspondence to:

Dr Thomas King

Department of Endocrinology

University College Hospital

250 Euston Road

London NW1 2PG

United Kingdom

Thomas.king@uclh.nhs.uk

Abstract

Objective:

Men with congenital adrenal hyperplasia (CAH) have impaired fertility. We aimed to assess the importance of hypogonadotropic hypogonadism, testicular failure and the presence of testicular adrenal rest tumours (TART) in men with CAH and to determine their relationship with fertility outcomes.

Design:

Retrospective analysis of men attending an adult CAH clinic in a tertiary centre.

Patients:

Fifty men with CAH due to 21 hydroxylase deficiency were identified of whom 35 were salt-wasting and 15 were non-salt-wasting.

Measurements:

Review of fertility history and parameters including luteinising hormone (LH), follicle stimulating hormone (FSH), androstenedione, 17-hydroxyprogesterone (17-OHP), semen analysis and the presence of testicular adrenal rest tissue (TART) on ultrasound.

Results:

TART were detected by ultrasound in 21 (47%) and their presence was associated with an elevated FSH ($p=0.01$). Severe oligospermia was present in 11/23 (48%), and this was associated with an elevated FSH ($p=0.02$), suppressed LH ($p<0.01$) and

TART (p=0.03) when compared to those with a sperm count >5 x 10^6 per ml. Of those that desired fertility, 10/17 (59%) required intensification of treatment prior to conception. The overall live birth rate was 15/17 (88%) with a median (range) time to conception of 8(0-38) months.

Conclusions:

Suppressed LH is a marker for subfertility and is often reversible. Testicular failure is closely associated TART formation. If TART are detected, sperm cryopreservation should be offered as there is a risk of progression to irreversible testicular failure. Male fertility in CAH can be improved by intensified treatment and assisted reproductive technology.

Introduction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive enzymatic defects in the adrenal steroidogenesis pathway, of which 21-hydroxylase deficiency is the most common form, leading to glucocorticoid and in more severe cases, mineralocorticoid deficiency (1). The compensatory increase in adrenocorticotropic hormone (ACTH) secretion in response to hypocortisolism stimulates overproduction of androgens and progesterone of adrenal origin, with subsequent suppression of pituitary luteinising hormone (LH) secretion.

While early papers quote a normal fertility rate in men with CAH(2), more recent studies from the UK, France and Germany have shown fertility rates of 67%, 51% and 23% respectively (3-5). Three phenotypes of male infertility in CAH are described, comprising hypogonadotropic hypogonadism, testicular adrenal rest tumours (TART) and testicular failure.

Hypogonadotropic hypogonadism results from negative feedback of excess adrenal androgens at the hypothalamic-pituitary level. This was the first feature of abnormal testicular function to be recognised in CAH. When cortisone treatment first became available in the 1950s, the reduction in negative feedback after commencing treatment enabled an increase in testicular size in boys with CAH (6). Suppression of LH secretion is usually reversible following improved compliance with glucocorticoid treatment (7, 8).

TART have received a great deal of attention over recent years. TART are thought to arise from aberrant adrenal cells in the testes, and their ACTH stimulated growth can cause compression of the seminiferous tubules leading to obstructive azoospermia (9). The prevalence of TART in several small series ranges from 45-94%; and that of low sperm count from 32-72% (5, 10-13). In the largest series to date of 219 male subjects, the reported prevalence of TART was 34% and low sperm count 66% (4).

Testicular failure, manifest by a raised FSH, may only emerge after the ACTH-dependent source of androgen is suppressed by glucocorticoids. Elevated FSH concentrations may persist even after 2 years of therapy, suggesting that testicular failure may be permanent (14). The pathogenesis of this testicular failure is less well characterised and may relate to local steroid production that has a toxic paracrine effect on Leydig and/or germ cells (5, 12).

Poor compliance and non-attendance in clinic are common in men with CAH and may contribute to infertility. Adult men with CAH may notice no adverse effects from adrenal testosterone excess, so much so that they commonly default from clinic. Although males and females are equally affected, in the UK CaHASE cohort only 33% were male (3). This is compounded by transition problems in chronic disease. In one paediatric cohort, half of all patients referred to adult services were lost to long term follow up (15). In the adult CAH clinic at our centre only 64/270 (24%) are males, inclusive of all forms of steroidogenic defects.

While recent literature has focused greatly on TART formation there are little data on overall fertility outcomes for men with CAH and the degree to which low sperm

count is reversible with focused treatment. In this report we collate our experience of managing subfertility and our aim is to investigate the relationships between the three fertility phenotypes in men with CAH. As previous reports of fertility in men with CAH have shown that biochemical profiles at a single time point are generally not informative, we have extended our observations to include all time points available during routine clinic assessments.

Subjects and methods

The case notes of all men with CAH that had attended the endocrinology clinic at the University College Hospital (UCH) within the last 10 years were reviewed. The paediatric diagnosis was assumed to be correct and access to earlier documentation including genetic testing was rarely successful in our healthcare system, depending on the route to adult services. Repeat genetic testing was only sought if couples were considering prenatal screening. Glucocorticoid dose was converted into prednisolone dose equivalent (PredEq) with a ratio of prednisolone:hydrocortisone:dexamethasone of 1:4:0.15 as per previous reports (16).

As part of routine care, all men attending clinic were offered a blood profile, semen analysis and testicular ultrasound scan to assess for the presence of TART. Ultrasonography was used as the majority (75%) of TART are clinically undetectable and only seen on imaging (17). Blood profiles at each visit included luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone, androstenedione and 17-hydroxyprogesterone (17-OHP).

If fertility was desired, treatment was intensified and subjects were seen every 3 to 6 months until conception. When subfertility was identified, our practice has been to intensify glucocorticoid treatment in a step-wise manner. Dose regimens and adjustment intervals were individualised depending on compliance, biochemical parameters and side effects of glucocorticoid excess. In general, hydrocortisone 5-20mg was used 6-8 hourly, followed by prednisolone 2-5mg 8-12 hourly, and then dexamethasone 0.25-1 mg daily in 1-2 divided doses. The dose of fludrocortisone was adjusted according to blood pressure and with the aim of suppressing plasma renin activity to the lower border of the reference range. The rationale for these regimens is to ensure suppression of ACTH over 24 hours to reduce the drive to TART, and to reduce adrenal testosterone production and resulting suppression of pituitary LH secretion.

Based on published guidelines, we defined a suppressed LH as less than 1.6 IU/L and a raised FSH level as greater than 8 IU/L, given that values above this level suggest primary spermatogenic failure (18, 19). As blood tests only give a snapshot of overall control and abnormal gonadotropin levels are often detected during the course of monitoring, we analysed outcomes based on those that ever had raised FSH or low LH at any time point.

Semen analysis was collected after 3-7 days of ejaculatory abstinence, with interpretation according to the 2010 World Health Organization (WHO) criteria (20). Severe oligospermia is defined as a sperm count of $< 5 \times 10^6$ per ml (21), and subjects with this finding are likely to require intra-cytosplasmic sperm injection (ICSI) for

conception. In view of this, we chose to compare subjects with severe oligospermia (sperm count of $< 5 \times 10^6$ per ml, including those with azoospermia) to the remainder of subjects with a sperm count $>5 \times 10^6$ per ml.

We report here the routine real life clinic data accepting that not all subjects consented to ultrasound or semen analysis. Female fertility factors were not formally assessed and partners were considered fertile unless otherwise documented. The data collection exercise was passed by the Ethics Committee of UCH and University College London.

Statistical analysis

The statistical software programme SPSS version 22 was used for analysis (SPSS Inc., Chicago, IL, USA) and a 5% level of significance was chosen. The Fishers exact test was applied to calculate the probability for differences between subgroups. The Mann-Whitney U test was used to test continuous variables. The influence of predictive factors for fertility outcomes were compared using the Phi coefficient.

Results

There were 64 men with CAH in total, 9 subjects were excluded as they had been lost to follow up or declined consent. Five other subjects were excluded: 4 with 11-β-hydroxylase deficiency and 1 with a 46,XXY karyotype. Therefore, 50 men with CAH caused by 21-hydroxylase deficiency were included in the analysis. Subjects attended for a median 5 years follow up (range 1-35 years) and there was a total

follow up of 416 patient-years. Baseline characteristics are shown in Table 1. Thirty-five were classified as salt wasting (SW) with the diagnosis of CAH in their first year of life and/or had at least one documented salt-losing crisis, and 15 were classified as non-salt wasting (NSW).

Forty-six subjects were taking regular glucocorticoid therapy at their last clinic visit, with 2 taking stress doses only and 2 not taking any medication. Median PredEq dose was 6.7 mg per day and 24 subjects were receiving prednisolone, 19 hydrocortisone, 2 dexamethasone and 1 betamethasone. Thirty-nine subjects were receiving mineralocorticoid replacement with fludrocortisone dose ranging from 25 to 300 microgrammes per day. The median number of gonadotropin measurements was 6 (range 1-27). During the course of monitoring, serum LH was suppressed at least once in 26/50 (52%), and FSH was elevated at least once in 13/50 (26%). Last recorded median (range) 17-OHP was 58 (1.1-564.9) nmol/L, testosterone 11.7 (2.9-32.2) nmol/L, and androstenedione 13.1(1-50) nmol/L, and these parameters were not informative for TART, semen analysis or fertility outcome.

Semen analysis

Twenty-three (46%) men consented to semen analysis, of which 11 (48%) revealed severe oligospermia (sperm count $<5 \times 10^6$ per ml) and 12 (52%) had a sperm concentration of $>5 \times 10^6$ per ml. Five men had successfully fathered children and completed their family so semen analysis was not performed. Semen analysis groups are shown in Table 2. The laboratory upper limit of normal (12.9nmol/L) was used to define an elevated androstenedione, and a median split was used for 17-OHP levels, with high being >58 nmol/L. When compared to those with a sperm count of $>5 \times 10^6$

per ml, the severe oligospermia group were more likely to have a TART on ultrasound ($p=0.03$) and a suppressed LH ($p<0.01$) and elevated FSH ($p=0.02$) during the course of monitoring. Out of these three parameters, suppressed LH had the strongest correlation with severe oligospermia (Table 2). When comparing continuous variables between the semen analysis groups, there were no statistically significant differences in height, BMI or PredEq dose.

Testicular Adrenal Rest Tumours (TART)

Testicular ultrasound was performed in 45 subjects, and 21 (47%) of those scanned had evidence of TART. Of those that had ever had an elevated FSH, 9 (82%) had evidence of TART and 2 (18%) had normal testicular ultrasound, Phi coefficient 0.401, $p<0.01$. There was no association between TART and suppressed LH, with TART found in 13 (52%) and normal ultrasound in 12 (48%) in those that had ever had a suppressed LH. There was also no difference in the prevalence of TART in the SW vs NSW groups. Figure 1 shows the distribution of highest recorded FSH in the TART vs. no TART groups, demonstrating that raised FSH was almost exclusively associated with the presence of TART.

Fertility

Eighteen subjects (36%) had attempted fertility, and the partner of one subject had premature ovarian insufficiency so he was therefore excluded from fertility outcome analysis. All but one had not previously fathered children (one subject presented with secondary infertility, having had a spontaneous conception 10 years previously). Median (range) age at conception was 32.9 (24-42) years. Seven subjects reported spontaneous fertility, having required no alteration in their routine treatment and

experiencing no delay in conception, and 10 subjects required intensification of treatment prior to conception.

Intensification of Treatment

Out of the 10 subjects that required intensification of treatment, 5 required a higher dose of steroid or a change to a more potent formulation, and 5 required recommencement of treatment. These 5 subjects had NSW CAH and had been off all treatment for a median duration of 15 (4-25) years, and steroid treatment was recommenced when they represented to the clinic desiring fertility. Glucocorticoids used in the intensification group were hydrocortisone in 2, prednisolone in 4 and dexamethasone in 4 subjects. Median (range) pre-intensification and peak intensification PredEq doses were 5mg (0-12.5) and 7.5mg (3.3-12.5) respectively. Intensification resulted in a rise in median LH (0.6 to 4.3 IU/L; p=0.01) and FSH (2.3 to 4.8 IU/L; p=0.01), but no significant change in testosterone or 17-OHP. Raised FSH appeared during intensification of treatment in 2 subjects, Figure 2.

Out of those that required intensification of treatment, 7 (78%) had severe oligospermia and 2 (22%) had a sperm count >5 million/ml. When comparing other factors in those who were spontaneously fertile and those that required intensification of treatment, there were no significant differences in salt wasting status, presence of TART, suppressed LH or raised FSH.

Four subjects underwent intra-cytoplasmic sperm injection (ICSI) and two of these subjects also required microscopic testicular sperm extraction (micro-TESE) for persistent azoospermia. Both micro-TESE procedures recovered spermatozoa, but

only one of them resulted in pregnancy. The two other ICSI procedures were successful, so the live birth rate for subjects that underwent vitro fertilisation (IVF) and ICSI was 3/4 (75%).

The time taken to achieve paternity is shown as cumulative fertility rate (figure 3) with 50% succeeding in 8 months and the maximum time taken was 38 months. Fertility was achieved in 4 out of the 5 subjects who had previously discontinued all treatment, after 8, 12, 14 and 35 months. All subjects with normal testicular ultrasound succeeded with conception. Two subjects failed to achieve conception despite intensive treatment, and both had evidence of TART on ultrasound. One had persistent hypogonadotropic hypogonadism and failed treatment with exogenous gonadotropins, and the other developed testicular failure with a rise of FSH up to 41.8 IU/L during intensification of treatment, and failed IVF with TESE. After exclusion of female factors, 15/17 (88%) subjects who sought fertility were successful.

Discussion

In this paper we confirm the frequent finding of low sperm counts and reduced fertility in men with CAH and extend the knowledge in the field by exploring the impact of three main factors that contribute to impaired testicular function. This relatively large cohort allows for comparison of suppressed LH, raised FSH and the presence of TART as associated factors influencing adverse fertility outcome.

We have previously reported low LH to be a useful marker of control of CAH in males and advocate recording this parameter at every visit (1). In the current series we found that a suppressed LH was the strongest predictor of severe oligospermia

although we did not find an association with the presence of TART or with reduced fertility outcome. We conclude that testicular failure was a consequence of TART in the majority of cases as raised FSH was almost exclusively found to exist with TART (Figure 1).

Intensification of treatment was required in over half of subjects who sought fertility. Recovery of hypogonadotropic hypogonadism was achieved in the majority of cases, however one of our subjects failed to respond to high dose steroid and had persistent azoospermia despite gonadotropin treatment. Exposure of an elevated FSH during intensification was observed in two subjects, Figure 2. This is consistent with previous reports of testicular failure unmasked by optimisation of glucocorticoid treatment (14).

The development of TART is generally taken to be the result of sustained elevation of plasma ACTH concentrations, usually associated with poor control of CAH. However, TART have also been reported in men with adequate control of CAH (5) and conversely, some subjects with poorly controlled CAH never develop TART despite chronically elevated ACTH levels (12). A recent longitudinal study found no association between TART and lifetime disease control parameters (22). We found no association between TART and levels of 17-OHP, androstenedione or with the finding of a suppressed LH during monitoring. TART have been reported to be more common in males with SW 21-hydroxylase deficiency compared to the NSW form (23). When comparing men with SW and NSW forms of CAH in our population, we found no differences in presence of TART, adverse biochemical parameters, or fertility outcome.

Growth of TART may cause infertility by compression of the rete testis and seminiferous tubules leading to obstructive azoospermia. This may be reversible in the early stages, however further growth can lead to irreversible damage to the surrounding testicular tissue (24). Claahsen-van der Grinten and colleagues demonstrated reduced tubular diameter, peritubular fibrosis and tubular hyalinization in testicular biopsies of CAH subjects with long standing TART, as well as a severe decrease in the number of germ cells (8). In addition to mechanical obstruction, there may be a toxic effect of local adrenal steroids or metabolites derived from adrenal rests, affecting the Sertoli or germ cells (12, 14, 25).

In the early stages of TART development, optimisation and intensification of glucocorticoid therapy can lower the ACTH drive, reduce TART size and improve testicular function and fertility (1, 26, 27). In the later stages of TART development, this approach may be ineffective in reducing tumour size and improving testicular function, but can help control further growth and testicular damage. Surgery for TART appears to be counterproductive offering no benefit and possibly contributing to further testicular damage, with one series showing a rise in FSH in 3/8 men after surgery (28).

In this report we found that subjects with no TART on ultrasound had normal fertility. Our data show that it is the relationship with testicular failure that confers the adverse effect of TART on fertility and therefore in the absence of successful treatment, prevention must be key to ensuring paternity in men with CAH. If ultrasonography

detects TART then sperm cryopreservation should be considered to safeguard future fertility.

Although we found that raised FSH was associated with a low sperm count, 6 men with raised FSH succeeded with paternity so the adverse effect of testicular damage is not absolute. In addition, micro-TESE successfully recovered sperm in 2 subjects with raised FSH in whom optimisation of glucocorticoids alone was not successful in retrieving azoopsermia.

After exclusion of female factors we found an overall 88% success rate in men who desired fertility. Whilst paternity took up to 38 months, the overall figure is much higher than previous reports of fertility in men with CAH and is equivalent to the prevalence of infertility in the general population.

There are potential forms of bias that could affect the data presented in this report. Firstly as a tertiary centre our cases may not be representative of all men with CAH and indeed some subjects are specifically referred to us for infertility. Secondly this is an observational report and may be affected by variable adherence and clinic attendance.

Conclusion

Men and women with CAH have similar successful fertility outcomes(29), but men have the possibility of progressing to irreversible testicular failure, which appears to be a consequence of TART formation. Early diagnosis and good disease control are key to preserving fertility, and we recommend routine gonadotropin monitoring in

subjects with CAH. Suppressed LH is a predictor of reduced sperm count, and raised FSH is associated with TART. Sometimes testicular failure can emerge only after intensification of therapy. Even if medical management fails to reverse azoospermia, micro-TESE can be successful in men with CAH. In men who require intensified treatment it may take up to 3 years of adjusted treatment to achieve paternity and this outcome has to be balanced against the side effects of higher dose glucocorticoids. We recommend that testicular ultrasound monitoring be a routine part of health surveillance for men with CAH starting in adolescence and that sperm cryopreservation be considered if TART are detected given the risk of progression to irreversible testicular failure.

References

1. Ogilvie CM, Crouch NS, Rumsby G, Creighton SM, Liao LM, Conway GS. Congenital adrenal hyperplasia in adults: a review of medical, surgical and psychological issues. Clin Endocrinol (Oxf). 2006;64(1):2-11.
2. Urban MD, Lee PA, Migeon CJ. Adult height and fertility in men with congenital virilizing adrenal hyperplasia. N Engl J Med. 1978;299(25):1392-6.
3. Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab. 2010;95(11):5110-21.
4. Bouvattier C, Esterle L, Renoult-Pierre P, de la Perrière AB, Illouz F, Kerlan V, et al. Clinical outcome, hormonal status, gonadotrope axis and testicular function in 219 adult men born with classic 21-hydroxylase deficiency. A French national survey. J Clin Endocrinol Metab. 2015:jc20144124.
5. Reisch N, Flade L, Scherr M, Rottenkolber M, Pedrosa Gil F, Bidlingmaier M, et al. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2009;94(5):1665-70.
6. WILKINS L, CARA J. Further studies on the treatment of congenital adrenal hyperplasia with cortisone. V. Effects of cortisone therapy on testicular development. J Clin Endocrinol Metab. 1954;14(3):287-96.
7. Wischusen J, Baker HW, Hudson B. Reversible male infertility due to congenital adrenal hyperplasia. Clin Endocrinol (Oxf). 1981;14(6):571-7.
8. Claahsen-van der Grinten HL, Otten BJ, Hermus AR, Sweep FC, Hulsbergen-van de Kaa CA. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia can cause severe testicular damage. Fertil Steril. 2008;89(3):597-601.
9. Claahsen-van der Grinten HL, Stikkelbroeck NM, Sweep CG, Hermus AR, Otten BJ. Fertility in patients with congenital adrenal hyperplasia. J Pediatr Endocrinol Metab. 2006;19(5):677-85.
10. Delfino M, Elia J, Imbrogno N, Argese N, Mazzilli R, Toscano V, et al. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. J Ultrasound Med. 2012;31(3):383-8.
11. Falhammar H, Nyström HF, Ekström U, Granberg S, Wedell A, Thorén M. Fertility, sexuality and testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia. Eur J Endocrinol. 2012;166(3):441-9.
12. Stikkelbroeck NM, Otten BJ, Pasic A, Jager GJ, Sweep CG, Noordam K, et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2001;86(12):5721-8.
13. Cabrera MS, Vogiatzi MG, New MI. Long term outcome in adult males with classic congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2001;86(7):3070-8.
14. Keely EJ, Matwijiw I, Thliveris JA, Faiman C. Congenital adrenal hyperplasia with testicular tumors, aggression, and gonadal failure. Urology. 1993;41(4):346-9.
15. Gleeson H, Davis J, Jones J, O'Shea E, Clayton PE. The challenge of delivering endocrine care and successful transition to adult services in adolescents with congenital adrenal hyperplasia: experience in a single centre over 18 years. Clin Endocrinol (Oxf). 2013;78(1):23-8.
16. Han TS, Stimson RH, Rees DA, Krone N, Willis DS, Conway GS, et al. Glucocorticoid treatment regimen and health outcomes in adults with congenital adrenal hyperplasia. Clin Endocrinol (Oxf). 2013;78(2):197-203.

17. Vanzulli A, DelMaschio A, Paesano P, Braggion F, Livieri C, Angeli E, et al. Testicular masses in association with adrenogenital syndrome: US findings. Radiology. 1992;183(2):425-9.
18. McLachlan RI. Approach to the patient with oligozoospermia. J Clin Endocrinol Metab. 2013;98(3):873-80.
19. Sikaris K, McLachlan RI, Kazlauskas R, de Kretser D, Holden CA, Handelsman DJ. Reproductive hormone reference intervals for healthy fertile young men: evaluation of automated platform assays. J Clin Endocrinol Metab. 2005;90(11):5928-36.
20. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231-45.
21. Foresta C, Garolla A, Bartoloni L, Bettella A, Ferlin A. Genetic abnormalities among severely oligospermic men who are candidates for intracytoplasmic sperm injection. J Clin Endocrinol Metab. 2005;90(1):152-6.
22. Reisch N, Rottenkolber M, Greifenstein A, Krone N, Schmidt H, Reincke M, et al. Testicular adrenal rest tumors develop independently of long-term disease control: a longitudinal analysis of 50 adult men with congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2013;98(11):E1820-6.
23. Claahsen-van der Grinten HL, Sweep FC, Blickman JG, Hermus AR, Otten BJ. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Eur J Endocrinol. 2007;157(3):339-44.
24. Claahsen-van der Grinten HL, Otten BJ, Stikkelbroeck MM, Sweep FC, Hermus AR. Testicular adrenal rest tumours in congenital adrenal hyperplasia. Best Pract Res Clin Endocrinol Metab. 2009;23(2):209-20.
25. Takihara H, Sakatoku J, Cockett AT. The pathophysiology of varicocele in male infertility. Fertil Steril. 1991;55(5):861-8.
26. Collet TH, Pralong FP. Reversal of primary male infertility and testicular adrenal rest tumors in salt-wasting congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2010;95(5):2013-4.
27. Claahsen-van der Grinten HL, Otten BJ, Sweep FC, Hermus AR. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. Fertil Steril. 2007;88(3):705.e5-8.
28. Claahsen-van der Grinten HL, Otten BJ, Takahashi S, Meuleman EJ, Hulsbergen-van de Kaa C, Sweep FC, et al. Testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia: evaluation of pituitary-gonadal function before and after successful testis-sparing surgery in eight patients. J Clin Endocrinol Metab. 2007;92(2):612-5.
29. Casteràs A, De Silva P, Rumsby G, Conway GS. Reassessing fecundity in women with classical congenital adrenal hyperplasia (CAH): normal pregnancy rate but reduced fertility rate. Clin Endocrinol (Oxf). 2009;70(6):833-7.

Table 1: Characteristics of 50 men with CAH (median (range)) or n (%).

Age	31 (18-55)
Years of follow up (n)	5 (1-35)
Number of laboratory tests analysed (n)	6 (1-27)
Salt Wasting (n (%))	35 (70)
Height (m)	1.68 (1.55-1.82)
BMI (kg/m^2)	26.3 (18.4-54)
Prednisolone Equivalent dose (mg/day)	6.7 (0-15)
Fludrocortisone dose (mcg/day)	100 (0-300)

Table 2: Semen analysis groups: subjects with severe oligospermia (sperm count <5m/ml) compared to those with a sperm count >5m/ml. Elevated FSH and suppressed LH were defined as ever having had an FSH >8IU/L or an LH <1.6IU/L during the course of monitoring. The last recorded androstenedione and 17-OHP levels were used for analysis. Elevated androstenedione was >12.9nmol/L (laboratory upper limit of normal), and 17-OHP >58 nmol/L (median value for the group). Data are n(%). The associations between categorical variables and the presence of severe oligospermia are expressed as Phi coefficients. *data not available for 1 case. **data not available for 3 cases.

	Sperm count >5m/ml (n=12)	Sperm count <5m/ml (n=11)	Phi coefficient	p value
FSH elevated	1 (8.3%)	6 (54.5%)	0.50	0.02
LH suppressed	3 (25%)	10 (90.9%)	0.66	<0.01
17-OHP elevated	7 (58.3%)	7 (63.6%)	0.05	0.80
Androstenedione elevated	9 (75%)	5 (62.5%)**	0.13	0.55
Presence of TART	3 (27.2%)*	9 (81.8%)	0.55	0.01
Salt Wasting status	8 (66.7%)	9 (81.8%)	0.17	0.41

Figure 1: The distribution of the highest recorded FSH levels (log IU/L) in subjects with TART vs. no TART. Open circles represent NSW and closed circles represent SW forms. Horizontal lines indicate upper and lower reference range.

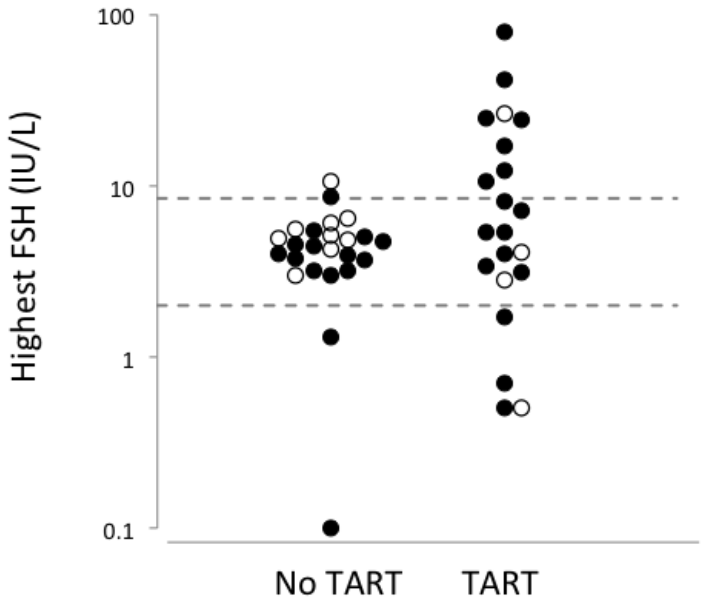

Figure 2. Gonadotropin response to intensification of treatment. Intensification resulted in a rise in median LH (0.6 to 4.3 IU/L; p=0.01) and FSH (2.3 to 4.8 IU/L; p=0.01). Bar and represents median gonadotropin level pre-intensification and at optimisation. Open circles represent NSW and closed circles represent SW forms. Long dashed line represents normal range for gonadotropin.

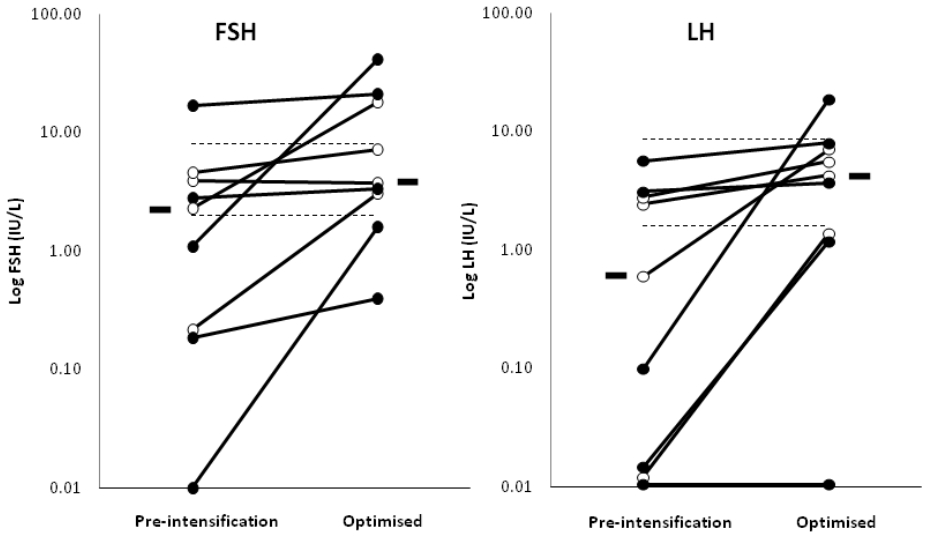

Figure 3: Fertility timeline demonstrating the cumulative percentage of 17 subjects who sought fertility achieving conception over time. Three subjects required assisted reproductive technology; one with testicular sperm extraction followed by intracytoplasmic sperm injection (ICSI) (triangle) and two with ICSI alone (circles).