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ORIGINAL ARTICLE

Experience in optimizing fertility outcomes in men with congenital adrenal hyperplasia due to 21 hydroxylase deficiency

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Summary

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

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 luteinizing 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 ($P = 0{\cdot}01$). Severe oligospermia was present in 11 of 23 (48%), and this was associated with an elevated FSH ($P = 0{\cdot}02$), suppressed LH ($P < 0{\cdot}01$) and TART ($P = 0{\cdot}03$) when compared to those with a sperm count $>5 \times 10^6$ per ml. Of those that desired fertility, 10 of 17 (59%) required treatment intensification and four underwent *in vitro* fertilization. Intensification resulted in a rise in median LH (0·6–4·3 IU/l; $P = 0{\cdot}01$). Live birth rate was 15 of 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 with TART formation. If TART are detected, sperm cryopreservation should be offered given the risk of progression to irreversible testicular failure. Male fertility in CAH can be improved by intensified treatment and assisted reproductive technology.

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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 luteinizing 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 hypogonadotrophic hypogonadism, testicular adrenal rest tumours (TART) and testicular failure.

Hypogonadotrophic 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 recognized 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 to 94% and that of low sperm count from 32 to 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 characterized and may relate to local steroid production that has a toxic paracrine effect on Leydig and/or germ cells.[5,12]

Poor compliance and nonattendance 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 of 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 was 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 luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, androstenedione and 17-hydroxyprogesterone (17-OHP).

The hospital laboratory reference range was used for testosterone (7·6–31·4 nmol/l), androstenedione (2·1–12·9 nmol/l) and 17-OHP (0–5 nmol/l). 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 gonadotrophin 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 intracytosplasmic 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.

If fertility was desired, treatment was intensified and subjects were seen every 3–6 months until conception. When subfertility was identified, or a delay in conception reported, glucocorticoid treatment was intensified in a stepwise manner. Dose regimens and adjustment intervals were individualized depending on compliance, biochemical parameters and side effects of glucocorticoid excess. In general, hydrocortisone 5–20 mg was used 6–8 hourly, followed by prednisolone 2–5 mg 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 h to reduce the drive to TART, and to reduce adrenal testosterone production and resulting suppression of pituitary LH secretion.

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 UCLH 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. Fisher's exact test was applied to calculate the probability for differences between subgroups. Mann–Whitney *U*-test was used to test continuous variables. The influence of predictive factors for fertility outcomes was compared using the Phi coefficient.

Results

There were 64 men with CAH in total, nine 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). Four subjects had been characterized as NSW on presentation, but borderline mineralocorticoid deficiency had been questioned during the course of their follow-up and they had been commenced on fludrocortisone.

Forty-six subjects were taking regular glucocorticoid therapy at their last clinic visit, with two taking stress doses only and

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)

two not taking any medication. Median PredEq dose was 6·7 mg per day, and 24 subjects were receiving prednisolone, 19 hydrocortisone, two dexamethasone and one betamethasone. Thirty-nine subjects were receiving mineralocorticoid replacement with fludrocortisone dose ranging from 25 to 300 micrograms per day. The median number of gonadotrophin measurements was 6 (range 1–27). During the course of monitoring, serum LH was suppressed at least once in 26 of 50 (52%), and FSH was elevated at least once in 13 of 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. There was no difference in the presence of TART or abnormal gonadotrophin levels in those who had or had not performed semen analysis. Semen analysis groups are shown in Table 2. The laboratory upper limit of normal (12·9 nmol/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 ($P = 0{\cdot}03$) and a suppressed LH ($P < 0{\cdot}01$) and elevated FSH ($P = 0{\cdot}02$) during the course of monitoring. Of these three parameters, suppressed LH had the strongest correlation with severe oligospermia (Table 2). When comparing variables between the semen analysis groups, there were no statistically significant differences in salt-wasting status, 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, $P < 0{\cdot}01$. 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. Fig. 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.

Table 2. Semen analysis groups: subjects with severe oligospermia (sperm count <5 m/ml) compared to those with a sperm count >5 m/ml

	Sperm count >5 m/ml (*n* = 12) (%)	Sperm count <5 m/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

Elevated FSH and suppressed LH were defined as ever having had an FSH > 8 IU/l or an LH < 1·6 IU/l during the course of monitoring. The last recorded androstenedione and 17-OHP levels were used for analysis. Elevated androstenedione was >12·9 nmol/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 one case.
†Data not available for three cases.

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

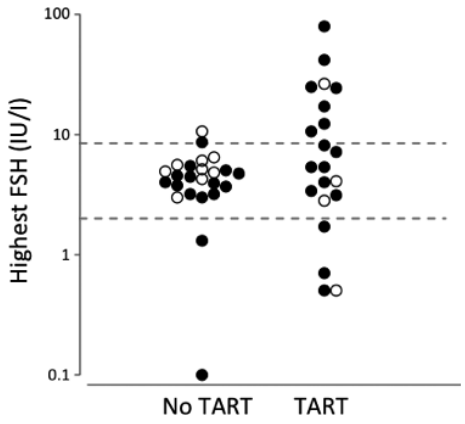

Fig. 1 The distribution of the highest recorded FSH levels (log IU/l) in subjects with TART *vs* no TART. Open circles represent NSW, and closed circles represent SW forms. Horizontal lines indicate upper and lower reference range.

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

Of the 10 subjects that required intensification of treatment, five required a higher dose of steroid or a change to a more potent formulation, and five required recommencement of treatment. These five 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 two, prednisolone in four and dexamethasone in four subjects. Median (range) pre-intensification and peak intensification PredEq doses were 5 mg (0–12·5) and 7·5 mg (3·3–12·5), respectively. Intensification resulted in a rise in median LH (0·6–4·3 IU/l; $P = 0{\cdot}01$) and FSH (2·3–4·8 IU/l; $P = 0{\cdot}01$), but no significant change in testosterone or 17-OHP. Raised FSH appeared during intensification of treatment in two subjects, Fig. 2. Because of intermittent testing, there were too few results for a useful analysis of semen parameter response to intensified treatment.

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 intracytoplasmic 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 fertilization (IVF) and ICSI was 3 of 4 (75%).

The time taken to achieve paternity is shown as cumulative fertility rate (Fig. 3) with 50% succeeding in 8 months and the maximum time taken was 38 months. Fertility was achieved in four of the five 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 gonadotrophins, 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 of 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 the 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 (Fig. 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 gonadotrophin treatment. Exposure of an elevated FSH during intensification was observed in two subjects, Fig. 2. This

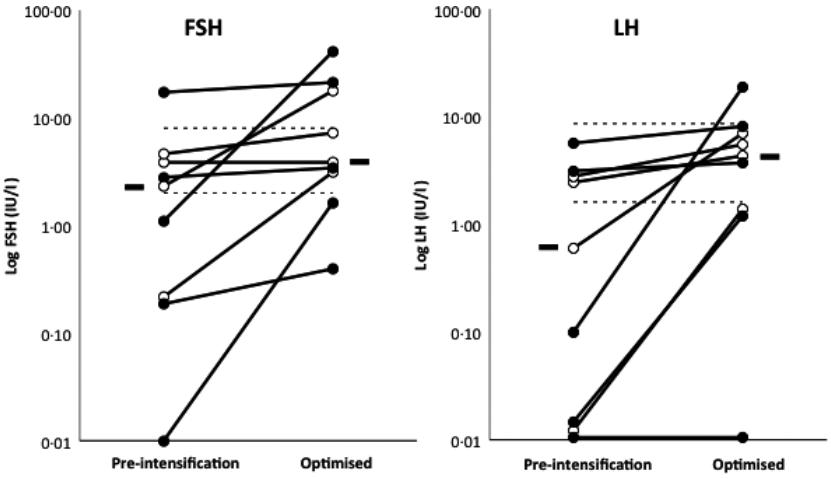

Fig. 2 Gonadotrophin response to intensification of treatment. Intensification resulted in a rise in median LH (0·6–4·3 IU/l; $P = 0{\cdot}01$) and FSH (2·3–4·8 IU/l; $P = 0{\cdot}01$). Bars represent median gonadotrophin level pre-intensification and at optimization. Open circles represent NSW, and closed circles represent SW forms. Long dashed line represents normal range for gonadotrophin.

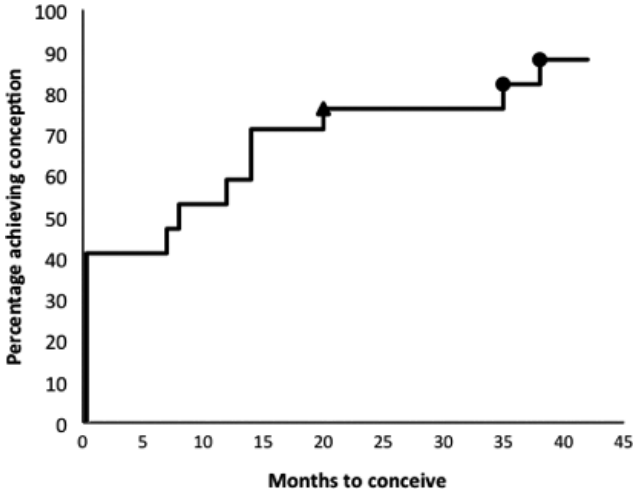

Fig. 3 Fertility timeline demonstrating the cumulative percentage of 17 subjects who sought fertility achieving conception over time. Three subjects required assisted reproductive technology; one with testicular sperm extraction followed by intracytoplasmic sperm injection (ICSI) (triangle) and two with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

is consistent with previous reports of testicular failure unmasked by optimization of glucocorticoid treatment.[14] We found 17-OHP to be an imprecise marker of response to intensified treatment, and the lack of significant change may also reflect ongoing poor adherence.

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 the 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, optimization 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 three of eight 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, six 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 two subjects with raised FSH in whom optimization of glucocorticoids alone was not successful in retrieving azoospermia.

After exclusion of female factors, we found an overall 88% success rate in men who desired fertility. While 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.

We found no differences in height, BMI or Predeq doses between those with and without severe oligospermia. As height may be viewed as a surrogate measure of childhood disease control,[29] this suggests that disease control was similar in the two groups in early life and any loss of control in may have occurred in adult life. This highlights the importance of the transition process from paediatric to adult services and lifelong specialist follow-up.

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, semen analysis was performed in less than half of all men so the prevalence of severe oligospermia cannot be extrapolated from this study to the wider CAH population. Thirdly, 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,[30] 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 gonadotrophin 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.

Disclosure statement

The Authors have nothing to disclose.

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