Received: 7 July 2023 | Revised: 16 August 2023 | Accepted: 24 August 2023

DOI: 10.1111/cen.14967

INVITED REVIEW

WILEY

Long-term health consequences of congenital adrenal hyperplasia

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Funding information
NIHR Oxford Biomedical Research Centre

Abstract

Congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency accounts for 95% of all CAH cases and is one of the most common inborn metabolic conditions. The introduction of life-saving glucocorticoid replacement therapy 70 years ago has changed the perception of CAH from a paediatric disorder into a lifelong, chronic condition affecting patients of all age groups. Alongside health problems that can develop during the time of paediatric care, there is an emerging body of evidence suggesting an increased risk of developing co-morbidities during adult life in patients with CAH. The mechanisms that drive the negative long-term outcomes associated with CAH are complex and involve supraphysiological replacement therapies (glucocorticoids and mineralocorticoids), excess adrenal androgens both in the intrauterine and postnatal life, elevated steroid precursors and adrenocorticotropic hormone levels. Alongside a review of mortality outcome, we discuss issues that need to be addressed when caring for the CAH patient including female and male fertility, cardio-metabolic morbidity, bone health and other important long-term outcomes of CAH.

KEYWORDS
congenital adrenal hyperplasia, glucocorticoid, long-term, mineralocorticoid, outcome

1 | INTRODUCTION

Congenital adrenal hyperplasia (CAH) comprises a group of rare genetic conditions that impair adrenal steroid synthesis. The commonest form is caused by 21-hydroxylase deficiency (21-OHD), an autosomal-recessive disorder of adrenal steroidogenesis that results from *CYP21A2* mutations. There are two clinical forms of 21-OHD CAH. Classic CAH is a severe life-threatening condition due to deficiencies of both cortisol and aldosterone. Lack of negative feedback on the hypothalamic–pituitary–adrenal axis leads to increased adrenal androgen production as elevated steroid precursors that are shifted towards androgen synthesis[1] (Figure 1).

Classic CAH is commonly divided into two forms on the basis of disease severity: salt-wasting CAH (SW-CAH), with severely reduced or absent 21-OH enzyme activity, and simple virilizing CAH (SV-CAH), retaining <5% of 21-OH enzyme activity and some ability to make aldosterone. In the absence of early diagnosis and treatment which is now possible with new-born screening programmes, SW-CAH patients experience life-threatening adrenal crises in the first 2-weeks of life. SV-CAH patients can present with ambiguous genitalia at birth, as well as with signs and symptoms of hyperandrogenism as a consequence of premature adrenarche and precocious pseudopuberty (a gonadotropin-independent hyperandrogenism occurring due to excess production of adrenal sex

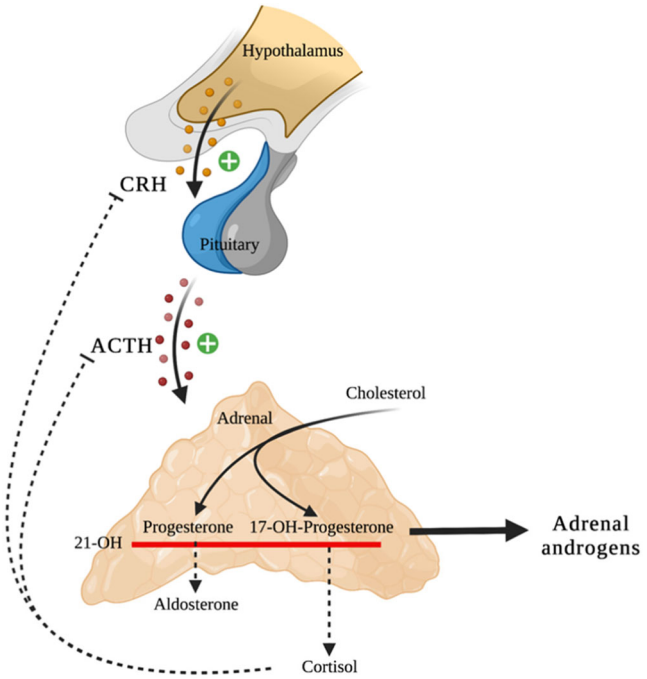

FIGURE 1 Hormonal alterations in classic CAH. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; 21-OH, 21 hydroxylase.

hormones) including the early development of pubic hair and growth acceleration.[2,3]

Nonclassic CAH is mild, often asymptomatic (although can present with symptoms of androgen excess in females presenting in a similar fashion to polycystic ovarian syndrome), more common than the classic form and results from CYP21A2 mutations that retain 20%–50% of enzyme activity.[4]

Glucocorticoid (GC) and mineralocorticoid (MC) replacement are the mainstay of treatment for the classic forms of CAH. While these treatments are critical to prolonging life, normalizing the growth and development of children, and limiting the occurrence of treatment-related iatrogenic Cushing syndrome or disease-related hyperandrogenism in adults are also fundamentally important. The overarching treatment goals are to prevent life-threatening adrenal crises across all ages, prevent virilization, optimize linear growth and development in affected children, and prevent long-term adverse clinical and patient-reported outcomes from GC under- or overtreatment.[2,5,6]

Standard biomarkers used for treatment monitoring include clinical and biochemical variables (see also *Monitoring of CAH* below). For the management of MC therapy, electrolyte monitoring, blood pressure measurements, plasma renin and symptoms suggestive of salt loss (salt craving, postural hypotension and, in infants, poor weight gain and failure to thrive) are helpful. The role of plasma renin activity or plasma concentrations of renin in MC does monitoring and titration has recently been questioned.[7,8] With respect to GC therapy titration, electrolytes and adrenal androgen precursors such as 17-OHP and androstenedione are most frequently used. Target concentrations for 17-hydroxyprogesterone (17-OHP) are often above the normal range as normal or suppressed 17-OHP concentrations in patients with CAH indicate overreplacement and are associated with the undesired effects of prescribed GC excess.[2] Treatment aims to keep androstenedione concentrations within the normal range.[5] As a result of the high variability of traditional biomarkers (17-OHP and androstenedione) in different situations (stress, fluctuations related to the GC dose assumption, secretion by other organs) there are data to suggest that new biomarkers may be helpful in CAH monitoring. These include the 11-oxygenated C19 adrenal steroids that are bioactive, dominant steroids in CAH,[9–11] derived primarily from the adrenals and correlate well with poor long-term disease control and disease-specific comorbidities.[12,13] While these biomarkers do show promise, they are not used routinely in the management of patients with CAH. Several short-acting, intermediate-acting and long-acting oral GC formulations are available for use in the management of patients with CAH.[5] Hydrocortisone (HC) is the preferred GC in children with CAH owing to its short half-life and the lowest growth suppressing effects.[14] The recommended body surface area-HC dose for infants and children is 10–15 mg/m^2 per day, often administered three/four doses per day.[1,5] There is high variability of GC regimens used in adults with CAH.[15,16] Approximately one-third of adults receive HC and the remaining receive long-acting GCs (prednisolone, prednisone, dexamethasone or combinations).

However, currently available GC preparations fail to replicate the physiological cortisol circadian rhythm.[17,18] To control androgen excess, supraphysiological doses have been given and in the past, this was frequently in a reverse circadian fashion, but due to concerns over the long-term impact of high nocturnal GC exposure, this approach is used much less commonly in recent years.[1] Inadequate hormonal control is common and up to two-thirds of patients display hormonal concentrations compatible with under- or overtreatment.[19,20] This is concerning considering that both conditions result in increased risk of adverse long-term health consequences. Very recently, an analysis using the I-CAH registry, aimed to understand the current practice for assessing cardiometabolic and bone outcomes in adults with CAH at expert centres. However, there is still no consensus as to what should be considered a core set of long-term clinical outcome measures that should be performed routinely.[21] This review aims to summarise the current evidence on long-term clinical outcomes in patients with CAH (Figure 2).

2 | GONADAL FUNCTION IN ADULT PATIENTS WITH CAH

Gonadal dysfunction is one of the most important long-term complications in both sexes in patients with CAH including hypogonadism and infertility.[22,23] In addition to hormonal imbalances, female patients with CAH can also suffer with anatomical and psychological issues alongside a reduced interest in pursuing parenthood.[24]

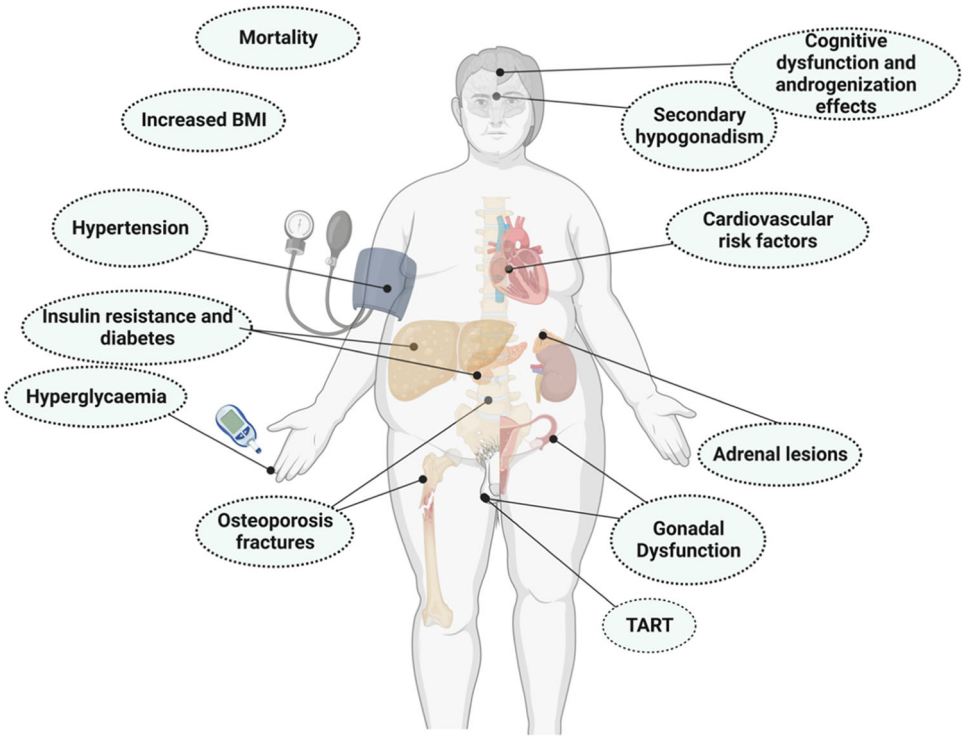

FIGURE 2 Long-term health consequence of classic CAH. CAH, congenital adrenal hyperplasia; TART, testicular adrenal rest tumour. [Color figure can be viewed at wileyonlinelibrary.com]

2.1 | Primary gonadal failure in adult male with CAH

Males with CAH can present with primary gonadal failure caused by the presence of testicular adrenal rest tumours (TART) which can impair reproductive function.[22,25–27] The reported prevalence is approximately 30%–50% of adult males with CAH mainly in the classic forms[28] although in some cases they have been reported in nonclassic forms.[25,27,29] The prevalence increases during puberty and into adulthood,[20,30–34] and clinical evaluation of testes in patients with classic CAH in adolescence and into adulthood should be performed in all patients. TARTs are benign testicular lesions[19,22,25,27,35,36] histologically resembling adrenocortical cells with features of a steroid producing tissue. Clinically, TARTs typically present as bilateral (>80% of the cases), painless lesions.[25] The aetiology of TART has still not been completely understood; in addition to expressing adrenal specific genes,[29,37] Leydig cell-specific features of TART tissue have been described, suggesting that TARTs might derive from a more totipotent cell type.[38] Larger lesions can associate with pain or discomfort and may be palpable. However, the majority of TARTs measure <2 cm and generally are not detectable on clinical examination due to their typical central location adjacent to the mediastinum testes.[35,39] Therefore, ultrasound is the preferred method to detect the small tumours; it is as sensitive as MRI and more accessible in most clinics.[40–44]

TARTs are most often described in patients with poor hormonal control[28,45] with some evidence showing positive correlations between lesion size and ACTH concentrations.[46–48] However, TARTs can also occur in patients with well-controlled disease[49,50] suggesting that undertreatment is not the only cause for their development in these patients. Therefore, a definitive correlation between hormonal concentrations and either prevalence or tumour size remains elusive. A mainstay of management remains the intensification of GC treatment to suppress ACTH. Due to its strong corticotrophin-suppressive effect, dexamethasone is preferred in the treatment of TART in the context of trying to achieve fertility and where the presence of TARTs are thought to be significantly compromising testicular function. The rationale of using supraphysiological doses and/or change to synthetic long-acting dexamethasone is to decrease ACTH concentrations thereby reducing tumour size.[25] This approach results in TART shrinkage in some, but not all cases[51–57] and exposes the patient to the side effects related to high-dose GC treatment.[58–61]

Currently, there are no definitive guidelines for treating or preventing TARTs.[5,62] As mentioned, scrotal ultrasound (US) is the preferred method for diagnosis and follow-up of TARTs.[63] The frequency of monitoring varies based on the presence, size, and progression of TARTs.[40,64] In the absence of specific guidelines, a decision on US frequency is often based on clinical judgement. The differential diagnosis between TARTs and Leydig cell tumours (LCTs) relies on clinical, radiological[65–67] and histological features,[52] and it is of utmost importance, since the management approaches are fundamentally different (surgery or active surveillance in LCTs and medical treatment in TARTs).[68] When first detected, while potentially

all testicular lesion are benign in CAH patients, close observation (perhaps every 3–6 months) might be reasonable to evaluate lesion volume stability, and therefore confirming the benign nature of the lesion. The same timing can apply to patients starting dexamethasone treatment for fertility issues, to assess potential treatment effects. Once the tumour is stable over time, clinicians might choose for a longer follow-up (6–12 months).

Testicular dysfunction as a result of TARTs can comprise both hypogonadism and altered sperm production.[69] Due to the location of TARTs, often adjacent to the mediastinum testes, they may lead to mechanical obstruction of the seminiferous tubules with consequent obstructive azoospermia. Many studies in males with CAH have shown decreased sperm concentrations ranging from 48% to 66%.[22,27,34,35,51,57] It has been hypothesized that chronic obstruction of the efferent flow in the seminiferous tubules reduces spermatogenesis and induces peritubular fibrosis, leading to irreversible damage of the surrounding tissue.[70] An additional paracrine effect of the steroids locally produced by TARTs on the surrounding tissue, potentially damaging the Sertoli or germ cells[25,52] cannot be excluded. Therefore, when this is appropriate for age, a semen analysis should be performed before and after treatment to assess the functional impact of TARTs and the effect of treatment.[34,71] However, the frequency of semen analysis again varies based on clinical judgement.[71] If there is concern about fertility, a semen analysis (perhaps on a 6-month basis) and cryopreservation of sperm could be considered, especially if TARTs are large or increasing in size despite treatment with dexamethasone. In this particular case, surgical treatment might be an option. Testis sparing surgery as opposed to orchiectomy,[72] has been advocated as a potential treatment option for TARTs,[73,74] and testicular sperm extraction simultaneously with TART resection can be offered.[75] However, postsurgical gonadal function has not shown significant improvement in the published studies, and fertility prognosis is yet uncertain. Moreover, there is also concern that surgery might contribute to irreversible testicular damage as a consequence of additional scarring.[70,75] Therefore, when clinical and sonographic findings strongly suggest benign behaviour, a "watchful-waiting" approach, avoiding unnecessary surgery, might be the best strategy.[76] Patients should be carefully informed by a multidisciplinary team about the consequences of TARTs.

2.2 | Secondary gonadal failure in adult male with CAH

In males with poorly controlled CAH, high concentrations of adrenal androgens are aromatised to oestrogens which in turn suppress the hypothalamic–pituitary–gonadal (HPG) axis, leading to hypogonadotropic hypogonadism with a reduction in testicular size.[22] Moreover, any attempt to suppress androgens with higher dose of GC therapy may cause further HPG-axis suppression. There are also data suggesting that even steroids produced by TART may contribute to the suppression of gonadotropins.[34,35,77,78] Clinically, it is very difficult to distinguish these two conditions. Given the synergistic hypogonadotropic effect of progestogens and testosterone in males, it is likely that excessive and combined secretion of androgens together with progesterone and 17OHP, will contribute to the gonadotropic inhibition in men with classic CAH.

As opposed to other forms of secondary hypogonadism, most males with CAH do not complain of symptomatic testosterone deficiency due to significant adrenal androgen generation. Recently, it has been shown that 11-oxygenated C19 steroids, namely 11-ketotestosterone (11KT) and 11KT-dihydrotestosterone amongst others,[12] can bind and activate the androgen receptor with equal potency to testosterone and dihydrotestosterone.[79,80] Interestingly, TARTs have also been reported to be able to produce 11-oxygenated C19 steroids.[81] However, the inverse relationship between testosterone and 11ketoT and the evidence that CYP11B1, a key enzyme in the synthesis of all 11oxC19 steroids, is only expressed in trivial amounts in the gonads compared with the adrenal cortex, suggest that adrenal gland production is the main driver for the 11-oxoandrogen imbalance in CAH.[12]

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.[82–85] A typical biochemical profile is therefore suppressed or normal gonadotropins with testosterone levels within the lower normal range, but low inhibin B levels,[22,35] which can serve as an additional marker for Sertoli cell function alongside FSH.[27,35] In the attempt to distinguish testosterone of adrenal or testicular origin, the serum androstenedione to testosterone ratio (A/T ratio) has been suggested as useful tool.[12,62] A low A/T ratio (<0.5) suggests well-controlled disease and higher contribute of testicular testosterone. In contrast, increased androstenedione levels in poorly controlled males and an A/T > 1 indicates that a significant fraction of testosterone is of adrenal origin.[62] In the absence of TART, most reports show reversible hypogonadism and improved fertility after initiating or increasing GC therapy.[86,87]

Reported fertility and fecundity in men with CAH on routine steroid replacement therapy range from normal to severely impaired. Historically, studies had shown male patients with classic CAH to be less likely to father children, however, with early diagnosis of classic CAH, fertility may be normalised.[36] Importantly, fertility and fecundity rates in CAH are also impacted by psychosexual factors.[27] Data on fertility outcome in men with CAH are scarce.[35] Populations studies have found lower birth rates in patients with classic CAH compared with an age-matched population.[27,51,71,88] A large French study including 219 males with classic CAH demonstrated a 24% chance to become a father in CAH male patients[22] which was significantly lower than national reference population; 11% needed assisted reproductive techniques. Interestingly, in a Swedish epidemiological study including 221 male patients with CAH, only patients born before the introduction of neonatal screening had reduced rates of fatherhood; rates matched the normal reference population for those born after the introduction of screening.[36] Finally, males with NC-CAH have normal rates of fatherhood. Of those CAH males who

succeed in becoming fathers, the number of children was reported the same as controls.[36]

2.3 | Gonadal dysfunction in adult female with CAH

Gonadal dysfunction with elevated adrenal steroids in females with CAH can result in amenorrhoea, infertility and irregular menses. Regular monthly menses generally indicate appropriate hormone replacement therapy although menstrual disturbances in CAH might be as common as in the general female population.[23] Several factors contribute to gonadal dysfunction in female patients with CAH: overproduction of adrenal androgens (including 11-oxygenated C19 steroids), elevated adrenal precursor steroid (17-OHP and progesterone), polycystic ovaries, hypogonadotropic hypogonadism and, vary rarely, ovarian adrenal rest tumours (OART).

Poor hormonal control with increased adrenal C-19 steroids production can affect ovarian function and cause menstrual disturbances.[5] As in male patients, increasing GC doses can suppress adrenal androgen secretion and restore ovulation as well as normalising the menstrual cycle.[89] The potential contribution of the alternative (backdoor) steroid and the 11-oxo-steroid pathways to androgen excess have also been suggested as significant contributors,[12,90,91] further highlighting their possible role as biomarkers of CAH control.[12]

Adequate suppression of adrenal androgen concentrations is not always sufficient to correct menstrual abnormalities. Elevated levels of other steroid precursors (such as progesterone and 17-OHP) have also direct and indirect effects on the pituitary production of gonadotropins and can interfere with the normal menstrual cycle.[89,92,93] Adequate suppression of adrenal progestins (<2 nmol/L in the follicular phase[93]), as well as androgens, has been suggested to be crucial in achieving regular menstrual cycle and improving fertility in females with CAH. However, this can often only be achieved with supraphysiological GC doses and finding the balance between over- and undertreatment can be difficult.[94]

In contrast to the high prevalence of TART in male patients with CAH, OART appear to be very rare. Only a few case reports have been published,[95–99] but the low prevalence may be explained (at least in part) by the challenges presented in detecting these tumours by ultrasound scanning. When routine ultrasound imaging techniques fail to detect these lesions, ultrasound or MRI,[100] ^{18}F-FDG PET/CT,[95,96] ^{131}I-noriodocholesterol imaging, selective and pelvic venous sampling[101] can help in identifying occult OART or localise virilising ovarian tumours.[97] Routine imaging to detect ovarian adrenal rests is, however, not routinely recommended.

It is important to distinguish between pregnancy (fecundity) and fertility rates in female patients with CAH. Pregnancy rates, as opposed to fertility rates, have been demonstrated to be normal.[93] However, a recent Swedish study in 272 female patients with CAH found that live birth rates were half that observed in matched controls.[102] Mothers with CAH were older at first pregnancy and had fewer children in total. Women with SW-CAH were less likely to be mothers compared with those with SV or nonclassic CAH.

The reduced live birth rate compared with the general population may have multiple explanations including hormonal, anatomical, psychological and psychosexual reasons.[103] A more detailed description of fertility in females with CAH is described elsewhere.[104–106]

Several studies have reported mostly uneventful pregnancies in this context.[103] As dexamethasone crosses the placenta, it is essential that only HC and prednisolone are used for hormone replacement during pregnancy to avoid adverse effects on the foetus. As advised in primary adrenal insufficiency, an increase of GC dose of 20%–40% in the second- and third-trimester may be considered, The management of pregnancy in women with CAH have been reviewed elsewhere.[107]

2.4 | Surgical intervention in females with classic CAH

Females with classic CAH can exhibit virilized genitalia at birth due to adrenal androgen exposure around the 9th week of gestation, a critical period for genital organogenesis. This results in changes like clitoral enlargement and scrotalization of the labial folds, despite the normal development of internal female reproductive organs (which ensures that fertility potential is preserved).[108] All adolescent females with CAH should undergo a thorough gynaecological evaluation to ensure a functional female reproductive anatomy and to check for potential issues including vaginal stenosis or menstrual irregularities. Those presenting with virilizing effects of CAH should be referred to a specialized gynaecologist and/or a paediatric surgeon/urologist. Conducting a comprehensive genitourinary examination under sedation or anaesthesia, when deemed suitable, is recommended.[5] In severely virilized females, especially those at Prader stage III or higher, surgical interventions such as vaginoplasty and clitoroplasty may be considered.[109] While traditionally, the choice of surgery depended on genital appearance and fertility potential, recent advocacy leans towards delayed procedures to allow patient participation in decision-making.[110] Most importantly, the patient's family should always be educated on the advantages and disadvantages of having and not having surgery. An interdisciplinary team of specialists is often required to navigate the decision-making process.[111] Education is pivotal, ensuring families understand the implications of both surgical and nonsurgical routes. The timing for surgery varies, with options including a one-stage approach in infancy (simultaneous neurovascular-sparing clitoroplasty, labioplasty, and vaginoplasty, the standard option in many countries including the USA and UK[112–114]) or a delayed or a multistep approach, with certain procedures deferred until puberty.[113,114] Notably, many patients with CAH caused by 21-OHD opt for early surgery.[115] Surgical challenges concern potential functional and cosmetic complications including urinary incontinence, vaginal stenosis, and clitoral pain, impacting overall well-being.[113] Recent surgical advances may promise better results, but their outcomes still remain

unverified.[116–118] Urogenital mobilization with or without neurovascular sparing clitoroplasty has been advocated as the technique preferred by many surgeons.[5] Patients should ideally consult specialized and experienced surgeons as genital reconstruction is both complex and challenging.[1,119]

3 | BONE HEALTH IN ADULTS WITH CAH

Bone health is a major clinical concern in patients with CAH chronically exposed to GC therapy. The impact of both CAH and its management on bone health are complex; with underreplacement there is the risk of androgen excess, adrenal insufficiency, and irregular menstruation in females, on the other hand androgen excess itself may counteract some of the detrimental GCs effects on bone.[120] It is well-established that GCs have direct and indirect effects on bone leading initially to increased resorption and later a decrease in bone formation ultimately leading to microarchitectural distortion and increased fracture risk.[121–124] While the long-term use of GCs in patients with CAH may have a negative impact on bone health, the evidence published to-date shows inconsistent findings, some studies reporting no differences,[20,125–132] reduced[133–140] or even high[141] bone mineral density (BMD) in patients with CAH compared with controls. This is likely related to the heterogeneity of the cohorts enroled, notably with respect to age, GC replacement regimes, and methods of evaluation for BMD. However, a recent meta-analysis on 598 young (median age 31 years) adults with CAH showed decreased BMD at all sites and reduced bone turnover markers (osteocalcin and NTX) compared with age and sex matched controls.[142]

There is a clear association between GC dose and osteoporosis.[28,143,144] Previous studies in patients with CAH showed that GC actual and cumulative dose,[134,144–146] long-acting GC formulations[146,147] and reverse circadian regimens all negatively impact BMD.[15] Importantly, a 2-year prospective, single-centre study in patients with primary adrenal insufficiency (including 33 patients with CAH) demonstrated a positive effect on BMD after cautious reduction in the daily GC dose.[148]

It is important to note that fragility fractures, as opposed to BMD per se are the clinically most relevant end-point. The association between BMD and fracture risk, particularly in GC-induced osteoporosis, is poor.[124] Relatively small studies have reported fracture rates ranging from 0% to 53% in patients with CAH.[125,130,139,146,147,149–152] However, there is a high degree of heterogeneity with respect to fracture identification, the populations included, sex differences, and rate of fractures within the controls groups.[147] A recent Swedish national cohort study found an increased risk of fractures in patients with CAH (both male and female) compared with controls, but only in those patients born before the introduction of neonatal screening. Patients with SW and SV CAH had an increased prevalence of fractures compared with those with a nonclassic phenotype, but a subgroup analysis focussing on GC dose or regimen was not performed.[153] It remains controversial as to whether BMD differs between SW and SV-CAH. Early studies showed no BMD relationship with genotype,[134,139] while others found lower BMD in women with SV-CAH[146] possibly related to higher daily GC doses. Recently, a retrospective study on 92 women with SW- or SV-CAH showed that BMD did not differ according to subtype and that BMD was more related to androgen excess rather than the effect of GC dose or regimen: women with irregular menstrual cycles (and therefore higher 17-OHP, DHEAS and testosterone concentrations) exhibited higher BMD at spine than those with regular cycles.[154] These data endorses previous studies that have demonstrated a direct relationship between DHEAS concentrations[139,147,150] and androstenedione-to-testosterone ratio[146] with BMD in adults with CAH.

While there is no specific guidance, bone densitometry should be considered for young adults who are treated with long-acting GCs, or with supraphysiological doses, showing cushingoid stigmata, or having chronically suppressed 17OHP and androgens. If osteopenia or osteoporosis are detected, periodic bone densitometry must be repeated every 2–3 years[62] and dedicated treatment should be considered.[61]

4 | METABOLIC DISORDERS AND CARDIOMETABOLIC MORBIDITY IN PATIENTS WITH CAH

Published data has shown a variable prevalence of cardiovascular disease (CVD) risk factors and metabolic morbidity in patients with CAH.[89,155–157] An epidemiological study from Korea on 2840 patients with CAH identified a 50% increased risk of CVD and stroke in patients compared with controls[158] but there was no increased risk for thromboembolic disease. A population-based Sweden registry study on 588 patients with classic CAH demonstrated an increased prevalence of hypertension, dyslipidaemia and venous thromboembolism compared with matched controls.[159] Abnormal glucose homoeostasis has been previously reported in patients with CAH.[20] A meta-analysis of 20 studies in patients with CAH confirmed these results and demonstrated a high prevalence of insulin resistance (IR) and carotid intima thickness although the quality of evidence was relatively low.[157] A prospective cross-sectional study from the UK in 203 patients with CAH found metabolic abnormalities including obesity, hypercholesterolaemia, and IR to be common.[19] Two large registry-based studies have demonstrated a higher prevalence of diabetes[158,159] and gestational diabetes in patients with CAH.[102]

Increased BMI and unfavourable body composition have been described in several cohorts of patients with classic CAH, with prevalence rates ranging from 20% to 45%, regardless of type of GC used.[19,20,28,160,161] Age and disease control (as assessed by renin, androstenedione, 17-OHP) have both been suggested as being possible contributory risk factors.[8,28] Importantly, a recent single-centre analysis on 60 patients with classic CAH demonstrated the detrimental effects of night-time dexamethasone administration on IR.[160]

A 5-year longitudinal study performed in the United States found higher prevalence rates of obesity, hypertension, fasting hyperglycaemia and IR in 57 patients with classic CAH due to 21-OHD compared with the general population. Obesity per se was associated with hypertension, IR, and hypertriglyceridemia independently from sex and adrenal biomarkers of disease control. Interestingly, where the mothers of patients with CAH were obese during the patient's childhood, obesity during adulthood was more common, suggesting dietary and lifestyle choices of the family or genetic causes of obesity.[162] The increased prevalence of hypertension in this study endorsed previously published data.[156,157] As expected, higher MC doses and lower renin concentrations/activity were both associated with increased hypertension risk. Multivariate analysis showed that both obesity and suppressed androstenedione were independent risk factors. Confirming previous reports,[157,163] increased prevalence of IR was also reported in this study. Multivariate analysis showed obesity and suppressed testosterone to be related to the diagnosis of IR. Notably, none of the results were related to GC dose or formulation but many of their findings are perhaps suggestive of treatment-related metabolic risk, possibly related to the inability of current formulations to mimic the circadian and ultradian rhythm of endogenous cortisol secretion.[163,164] Left ventricular hypertrophy, systolic and diastolic myocardial subclinical alterations have all been described in patients with CAH and seem to be related to GC dose.[165] In addition, the impact of MC exposure on metabolic outcomes has rarely been assessed: a positive correlation between MC daily dose and BMI,[8] as well as with and LDL[162] levels has been reported suggesting that both replacement therapies might play a role in the development of cardiometabolic morbidity.

In addition to GC type, dose and regimen, genetic factors modulating GC metabolism and peripheral sensitivity might also be involved.[166] CAH patients carrying the BclI variant of the GC receptor gene, (with enhanced receptor transactivation activity) have been reported to have higher BMI, waist circumference and blood pressure, compared with the patients carrying the wild-type allele.[167]

5 | OTHER LONG TERMS HEALTH OUTCOMES IN ADULT PATIENTS WITH CAH

5.1 | Adrenal masses

The trophic effects of chronic ACTH elevation predispose to adrenal tumour formation.[156,168,169] Adrenal nodules are common and seen in approximately 29% of patients with CAH. In patients with nonfunctional adrenal incidentalomas, (especially bilateral lesions or large adrenal myelolipomas), undiagnosed CAH should be considered.[170–173] Myelolipomas are relatively common accounting for 37% of adrenal tumours in those patients with genetically confirmed 21-OHD.[169] In a meta-analysis of patients with CAH undergoing to bilateral adrenalectomy, 10% were diagnosed with a myelolipoma on histological assessment.[169] The presence of myelolipomas was associated with poor CAH control. Increased adrenal volume is correlated with suboptimal disease control, defined as by elevated adrenal androgens, and other comorbidities, including adverse cardiovascular profile, hypogonadism and oligomenorrhoea.[12,168,169]

5.2 | Mortality and adrenal crisis

Patients with CAH have shortened life expectancy compared with controls, with mortality rates ranging from 1.6 to 5.17.[158,174,175] In the UK Clinical Practice Research Datalink, mortality rates of the 270 patients with CAH were at a five-fold higher than controls, with a mean age of death 18 years younger than controls.[174] In the Sweden national population-based registry on 588 patients with CAH, the risk of death was 2.3- and 3.5-fold higher in men and women with CAH, respectively.[175] Adrenal crises were responsible for 42% of deaths and those with the SW form were especially at risk.[175]

Adrenal crisis is often triggered by infectious illness[176–178] and increased rates of infections have been reported in patients with CAH in population-based retrospective cohort study from the UK.[76] Fortunately, the frequency of adrenal crises has decreased over time, perhaps reflecting a greater awareness of "Sick day rules" that should be followed during intercurrent illness.[179,180] However, protocols for the prevention and treatment of adrenal crisis are mainly based on expert opinions and clinical experience,[181–184] with differences in the treatment protocols between centres that could potentially impact outcome.[185]

5.3 | Short stature

Patients with classic CAH typically have a shorter final height than predicted. This may be associated with their exposure to elevated androgen levels or inappropriate GC therapy during childhood.[186] Those with nonclassic CAH can also face growth implications, though usually less pronounced than in classic CAH.[20] Enzyme deficiencies in the steroid synthesis pathway in untreated 21-OHD CAH individuals result in blocked steroid production. This triggers an overproduction of adrenal androgens, which are then metabolized to oestrogens via aromatase. The ensuing increase in oestrogen secretion[187,188] can lead to rapid skeletal maturation, early epiphyseal growth plate closure, and ultimately, reduced adult height.[187]

Oestrogen promotes BMD by enhancing osteoblast secretion, regulating osteoclast formation, inhibiting osteoclast differentiation, and preventing osteoblast apoptosis.[189,190] While puberty onset often initiates an acceleration in height, individuals with CAH usually have a final adult height one to two standard deviations below their peers.[16] Growth disturbances can be attributed to two primary causes. First, if GC replacement therapy does not sufficiently suppress adrenal androgen secretion, high levels of androgens will stimulate linear growth and premature skeletal maturation, leading to early epiphyseal fusion and shorter adult height. The second reason relates to growth suppression due to excessive GC treatment, particularly in the first

years of life. Infants are relatively insensitive to androgen excess[191] but are highly susceptible to growth inhibition from GC treatment. Therefore, only minimal doses of GC are advisable during infancy, as larger doses risk inhibiting growth with lasting implications for height throughout childhood and adulthood.[192] While adjusting the GC dose might facilitate some height recovery, complete normalization is seldom achieved, typically resulting in long-term short stature.[193] Thus, it's vital to optimize adult height through balanced GC dosing.[194,195] Although long-acting GCs efficiently suppress adrenal androgens, they have a higher potential to impede growth velocity compared with short-acting HC.[16,145] A meta-analysis found that adults treated for CAH have an average height about −1.4 SD (10 cm) below the general population's average.[196] The UK's CaHASE study showed a correlation between delayed CAH diagnosis and reduced final height.[186] As mentioned, the growth-suppressing effects of GCs are most pronounced during infancy and adolescence; daily doses over 15–20 mg/m^2 of body surface area can notably reduce adult height.[197] Consequently, in these patients, chronic use of supraphysiological doses of long-acting agents is discouraged due to their potential impact on growth dynamics.[198,199]

In paediatric patients, height status influences bone mineral content (BMC) and BMD measurements acquired through dual-energy X-ray absorptiometry (DXA). There is currently no established consensus as to how to adjust BMC or BMD measurements for deviations in height. While many methods for adjusting BMC/BMD *Z*-scores based on height are influenced by age or height-for-age *Z*-scores (HAZ), adjustments utilizing HAZ show the least bias in relation to age and height and therefore these can be employed to assess the impact of stature deviations on BMC/BMD *Z*-scores.[200]

5.4 | Quality of life (QoL)

Studies on the QoL of patients with CAH have yielded varied results, likely due to differences in clinical practice, treatment regimens, and disease severity. Some findings indicate a QoL for CAH patients similar to, or slightly impaired compared with the general population,[201–203] while others suggest a poorer QoL.[115,204,205] The CaHASE study underscored significant impairments in the QoL SF-36 health survey, especially in domains such as general health, vitality, and emotional well-being.[19] Variables including adiposity, IR, and certain GC treatments were also linked to a reduced QoL.[206]

A subsequent analysis of the same CaHASE cohort emphasized substantial QoL and psychological concerns among CAH-affected children.[207] It revealed that 16% of the cohort might benefit from psychiatric evaluation. Parents and children displayed differing perceptions of the disease impact, highlighting the importance of actively engaging patients and parents in the dialogue involving multidisciplinary teams. School functioning emerged as a significant concern, linked to cognitive and mental health challenges.[5,60,208] Importantly, however, an early diagnosis can enhance cognitive outcomes.[209]

There is some evidence suggesting sexual differences in QoL,[210] these are not uniformly observed.[205,206,211,212] Participants often cite disease chronicity, medication reliance, sexual health concerns, potential child inheritance fears, frequent hospitalizations, and complications such as reduced growth as psychological burdens.[211,213–216] Other studies have found increased psychiatric symptoms and morbidity rates in children, adolescents, and adult patients with CAH,[216,217] as well as increased anxiety and suicidal thoughts.[215]

5.5 | Monitoring of CAH

Treatment for classic CAH replaces GC and, when needed, MC hormones aiming to prevent adrenal crises, and limit excess adrenal androgen secretion.[5] The goals of treatment include ensuring normal growth, puberty, and avoiding complications.[5,218,219]

GC replacement in CAH has challenges as it should replicate the natural cortisol circadian rhythm, which peaks in the early morning.[17,220] Moreover, it should adapt to stress[221] and regulate ACTH to control adrenal androgen excess.[119] To do that, clinicians often need to use higher GC doses than in other causes of adrenal insufficiency. Balancing treatment (avoiding over- or underreplacement) is crucial to prevent adverse side effects that can impact on growth, metabolism, cardiovascular risk and bone health. While detailing specific treatment options falls beyond the remit of this review, essential insights can be sourced from dedicated guidelines.[1,5]

Regular assessments should include height, weight, blood pressure, and physical examinations. In children, it is crucial to assess changes in height progression, weight gain, hyperpigmentation, virilization, early puberty indicators, salt cravings or unusual daytime fatigue that might indicate a need for treatment adjustment.[5] Routine bone age X-rays are recommended for children over 2 to monitor potential early bone age progression due to excess adrenal androgens.[1]

Typically, biochemical monitoring focuses on serum 17OHP, androstenedione, and plasma renin, with ACTH often deemed nonessential. The aim should be to keep serum androstenedione and testosterone in within normal references ranges for sex and age, with 17-OHP around ULN (normal values indicating overtreatment).[1] For MC dosage adjustments, plasma renin activity and direct renin levels are extremely variable and should be used along with blood pressure, electrolytes and, importantly, patient's treatment adherence.[5,8,222,223] Newer adrenal androgen monitoring methods are emerging, including 21-deoxycortisol[224] and 11-oxygenated androgens,[225] although currently they are not part of routine practice. In addition to blood-based measurements urine,[226,227] saliva,[228] and dried blood samples on filter paper[229] have all been used to monitor therapy.

6 | CONCLUSIONS

Despite increased awareness of the long-term complications of CAH and its treatment, there is still no universal consensus as to the core set of long-term clinical outcome evaluations. In everyday practice,

achieving optimal disease control is difficult and compliance with treatment remains a major clinical challenge.[174] The difficulty in the management of CAH remains obtaining the correct balance between disease control, without the adverse consequence of overexposure to GC (and potentially MC) treatment. As an additional complexity, there is a significant degree of patient heterogeneity in their sensitivity to treatment meaning that adopting a precise and personal approach to patient management to limit long-term adverse outcomes is crucial. Newer GC preparations and regimens that combine better control of CAH alongside minimising GC exposure are undoubtedly the way forward, but there is a fundamental need to assess long-term outcomes with these approaches as they develop.

ACKNOWLEDGEMENTS

Dr. Xiaochen Ji is the recipient of a scholarship from the Chinese Scholarship Council (CSC File NO. 202108210275). This work has been funded by the NIHR Oxford Biomedical Research Centre.

CONFLICT OF INTEREST STATEMENT

Jeremy W. Tomlinson is a member of the scientific advisory board for Diurnal. The remaining authors declare no conflict of interest.

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How to cite this article: Pofi R, Ji X, Krone NP, Tomlinson JW. Long-term health consequences of congenital adrenal hyperplasia. *Clin Endocrinol*. 2023;1-15. doi:10.1111/cen.14967