

# Review of Health Problems in Adult Patients with Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

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## ABSTRACT

The introduction of newborn screening programmes in most Western countries for classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) enables timely introduction of life-saving glucocorticoid replacement in affected babies. Early diagnosis and optimised pediatric care not only successfully led to survival but also allow that almost all patients reach adulthood. Cohort studies in adults, however, provided evidence for significant health problems and co-morbidities of adult patients such as life-threatening adrenal crises, cardiovascular and metabolic health problems, fertility problems, benign endocrine tumours, and osteopenia and osteoporosis. This review summarises the current state of knowledge aiming to emphasize the necessity of primary and secondary prevention of additional long-term health issues as a major task of health professionals in the care of CAH.

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting in glucocorticoid insufficiency [1]. The vast majority of cases is caused by 21-hydroxylase deficiency (21-OHD). Steroid 11 $\beta$ -hydroxylase deficiency accounts for only 5–8% of CAH cases, other enzymatic defects causing CAH as 17 $\alpha$ -hydroxylase deficiency, 3 $\beta$ -hydroxysteroid dehydrogenase type 2, steroidogenic acute regulator protein, P450 cholesterol side-chain cleavage enzyme or P450 oxidoreductase deficiency are extremely rare. The impaired cortisol synthesis in classic 21-OHD leads to a loss of negative feedback on the hypothalamic and pituitary level, thereby increasing ACTH driving adrenal androgen excess and adrenal hyperplasia. In most Western countries newborn screening programmes aim to detect the severe form, the so called classic 21-hydroxylase deficiency and therefore incidences are known to be 1:10,000 to 1:15,000 [2–4]. Classic 21-OHD is defined by clinically glucocorticoid deficiency and is subclassified in the simple –virilising or salt-wasting form in case of additional mineralocorticoid deficiency. The mild, non-classic form, is more frequent found affecting about 1:2000 [5]. The latter is characterised

by adrenal androgen excess, however, usually without clinically relevant cortisol deficiency. (► **Table 1**)

Since the 1950ies life-saving glucocorticoid replacement therapy has become available enabling longterm survival of classic CAH patients. Thus, the oldest patients with this condition are in their late sixties. However, timely correct diagnosis has been difficult and before the introduction of Newborn Screening programmes often overlooked. As a consequence many patients presumably died from salt wasting crises in their first few weeks of life. Therefore most patients are still at a young age, most adult patient cohorts are on average in their thirties.

We therefore have become aware of the long-term consequences and outcome of classic CAH patients only recently.

Despite optimised diagnosis, life-saving glucocorticoid and mineralocorticoid replacement therapy, the patients struggle with a variety of comorbidities affecting their health-related quality of life. Current glucocorticoid replacement therapies cannot mimic circadian cortisol rhythmicity nor stress-related glucocorticoid increase. It is a real therapeutic challenge to strike the right balance of gluco-

► **Table 1** Checklist for surveillance of long-term health problems in adult patients with classic 21-OHD. Adapted from Reisch N, Arlt W., Congenital Adrenal Hyperplasia. In: Oxford Desk Reference Endocrinology Oxford: Oxford University Press, 2018: 221-224.

To do:	Interval
<b>Biochemistry/Endocrine laboratory:</b> 17-hydroxyprogesterone, androstenedione, testosterone (SHBG), progesterone, estradiol, LH, FSH, Sodium, Potassium, Renin	Annually
<b>Physical examination:</b> Body mass index, blood pressure, acne, hirsutism, striae, hyperpigmentation, Cushingoid features	Annually
<b>Stress dosing:</b> Adrenal crisis since last review? Stress dosing of hydrocortisone for illness since last review? Steroid emergency card? Knowledge of sick day rules? Glucocorticoid injection kit for emergency use available? Are the patient and/or parent/partner/guardian educated on parenteral self-administration of emergency glucocorticoids?	At least annually
<b>Genetic assessment and counselling</b>	Once at transition and when fertility is planned
<b>Female fertility:</b> Gynaecological assessment	Once at transition and then as required, as recommended in the general female population
<b>Male fertility:</b> Testicular ultrasound (check for presence of testicular adrenal rest tumours)	Once at transition, thereafter according to findings
<b>Cardiovascular health:</b> Fasting lipid profile, HOMA IR, 24 h ambulatory blood pressure, refer to counseling with regard to healthy lifestyle	If clinically justified
<b>Bone health:</b> BMD	In patients with non-traumatic fractures and with higher glucocorticoid dosing and/or long-acting glucocorticoids
<b>Mental health:</b> Consider referral to psychological or psychiatric treatment for behavioral/mental health consultation and evaluation to address any concerns related to 21-OHD	
<b>Adrenal nodules:</b> No routine adrenal imaging, only in patients with poor disease control, with lack of response to intensified therapy, with history of periods without treatment	

corticoid dosing. Both, under- as well as overtreatment cause side effects and complications. In order to control adrenal androgens, however, often supraphysiological glucocorticoid doses need to be given. Impaired fertility is of importance for the patients. Several groups showed impaired health status in 21-OHD [6], as well as impaired survival [7]. The main causes of death have found to be adrenal crises and cardiovascular comorbidities highlighting these aspects of the disease [7].

## Adrenal Crises

All patients with the classic form of 21-OHD suffer from glucocorticoid deficiency and thus are at risk for life-threatening adrenal crises life-long. There is no generally agreed definition of adrenal crisis, which is defined as a situation when the increased demand in circulating cortisol cannot be met. Based on the current knowledge and experience and previous definitions of adrenal crisis Rushworth et al.[8] have suggested the following definition: “an acute deterioration in health that is associated with an absolute (systolic blood pressure (BP) < 100 mmHg) or relative (systolic BP < 20 mmHg lower than usual) hypotension, the features of which resolve following parenteral glucocorticoid administration (marked resolution of hypotension within 1 h and improvement of clinical symptoms over 2 h)”. Other typical clinical findings comprise dehydration, salt-wasting (hyponatremia and hyperkalemia), hypoglycaemia or altered mental status. Patients present with weakness, vomiting, abdominal pain of confusion. If left untreated it is life-threatening leading to shock, coma and ultimately death. Severe symptomatic hypoglycemic events mainly seem to be a problem in the pediatric population not any longer in adulthood [9]. They may be caused by a lack of cortisol at night. In addition hypoglycaemia may be caused by adrenomedullary dysfunction [10].

Infections or injuries are the most common precipitating factors of adrenal crisis. As children are more prone for infectious diseases, the incidence of adrenal crises is highest in childhood [11]. In a pediatric study based on data extracted from a population-based prospective long-term follow-up study of children detected in neonatal screening in Southern Germany the incidence of adrenal crises in childhood was 6.5 per 100 patient years [9]. This correlates well with our own data showing an incidence of adrenal crisis over lifetime of 5.8 per 100 patients years, with the highest incidence during childhood and substantially lower incidence of adrenal crises in adulthood [11]. Transition has been shown to be the second vulnerable period predisposing 21-OHD patients for adrenal crises [11]. The main triggers of adrenal crises in this study in CAH patients were respiratory and gastrointestinal infections [11]. So far it is not clear which patients are predisposed for experiencing multiple adrenal crises. Bancos et al. [12] have shown that primary adrenal insufficiency is associated with impaired natural killer cell function potentially causing a weakened immune defence contributing to an increased rate of infections and adrenal crises. Another study also found a pro-inflammatory state in patients with primary adrenal insufficiency on conventional glucocorticoid replacement therapy [13]. Switching from conventional glucocorticoid replacement twice or thrice daily to a once daily modified-release hydrocortisone preparation normalised the immune cell profile and reduced intercurrent infections [13]. At this stage, however, it is not entirely clear if the observed effects are due to the more physiologic circadian glucocorticoid rhythm by the modified release formulation or simply due to an overall dose reduction of glucocorticoid replacement by modified-release formulations and might as well be observed on a reduced dose of conventional glucocorticoids. Further research on the interactions among glucocorticoid deficiency, adrenomedullary dysfunction, and immune cells is necessary for a better understanding of the pathophysiology and the prevention of adrenal crises.

Prevention of adrenal crises remains a permanent challenge. Expert care, education in stress dosing and emergency recommendations as well as equipment is essential and considered the best approach to prevent adrenal crises. However, adrenal crises may even occur in well educated patients with excellent knowledge of preventive strategies [14–16]. Despite intensive education, patients may still hesitate to implement stress dosing, in particular if parenteral use is necessary and thus is not sufficiently effective. In Germany a standardized patient education programme for patients with adrenal insufficiency and a special part for patients with CAH has been developed. However, so far the education relies entirely on the commitment of the physicians as it is not reimbursed by health care insurances. Patient support groups are extremely helpful in providing educational material and organising educational programmes.

Swedish data revealed that adrenal crises also are the most frequent cause of death in patients with 21-OHD, not only before the introduction of newborn screening [7]. This study was designed as a matched case-control study with 588 patients with 21-OHD from the national CAH or patient registry compared 58800 controls from national population-based registers. It is also the first study to show an increased mortality in 21-OHD. Thus, management of adrenal crisis remains a major challenge in the care of CAH patients and more research is needed to fully understand causes and develop better prevention strategies.

## Cardiovascular Morbidities

The Swedish population-based study [7] identified cardiovascular events as the second most important cause of death in CAH patients. This is the first study to show increased morbidity and mortality and not only increased risk factors, thus emphasizing the importance of cardiovascular prevention in CAH. Several studies have shown increased cardiovascular risk factors in 21-OHD [17–24]. The major cardiovascular risk factor in CAH seems to be overweight and obesity [20]. Obesity was identified already a major problem in pediatric cohorts [25, 26]. In adult cohorts even more than half of the female patients were found to be obese [20]. However, there is also data from France showing that body weight is not substantially different in CAH from the general population [23, 27], also an American cohort study showed a similar obesity rate (one third) in CAH compared to the general population [24]. Investigation of body composition in CAH shows that overall and abdominal body fat is increased [28]. Few studies also showed a high prevalence of the metabolic syndrome in CAH [24, 29]. Studies investigating blood pressure show conflicting results with either normal [18, 21, 30, 31] or elevated blood pressure [32]. There are several studies in young cohorts with a trend towards high blood pressure (diurnal or nocturnal) indicating that blood pressure needs to be monitored and may become a more prevalent problem at a higher age [20, 32–37]. Interestingly, a French cohort of male CAH patients showed rather low blood pressure compared with healthy controls [27]. Fludrocortisone and glucocorticoid overexposure contributes to elevated blood pressure and needs to be avoided. In adrenal insufficiency recent studies show an improved metabolic risk profile in patients on modified release hydrocortisone compared to conventional glucocorticoid replacement regimens [13, 38–41].

Blood glucose and body weight seem to improve with a more physiologic circadian cortisol day profile reducing the glucocorticoid exposure in particular in the afternoon by about 20% [41]. Over-treatment by glucocorticoids and mineralocorticoids on the one hand have detrimental effects on the cardiovascular risk profile in CAH [42, 43], undertreatment with the consequence of adrenal hyperandrogenism on the other hand induces impaired insulin sensitivity [44, 45].

The Swedish population based study also showed an increased prevalence of hyperlipidemia, diabetes, venous thromboembolism and atrial fibrillation [46]. Morphology of the left ventricle has been reported as normal [21, 30]. In CAH women QT interval duration was shorter than in controls [47]. In summary, many studies indicate that CAH is associated with higher cardiovascular and metabolic risk factors and morbidity. However, patients included in these cohorts are young, thus cardiovascular events and morbidity only is beginning to be characterized. Clearly, these data implicate the responsibility of monitoring cardiovascular and metabolic risk factors and keeping a close eye on the glucocorticoid and mineralocorticoid dosis with regular re-evaluation also in adulthood.

## Bone Health

Bone health is impaired in both males and females in CAH [1]. The prevalence of osteopenia and osteoporosis even in young adults from an age of 40 onwards is increased compared to controls. Some studies even reported an increased fracture risk [48]. The main risk for low bone mass density is chronic glucocorticoid excess [49]. Current replacement regimens all cannot mimic circadian glucocorticoid rhythm irrespective of the formula used, e. g. hydrocortisone, prednisolone or dexamethasone, and all lead to several phases of overtreatment during the day. Even in an attempt to best mimic circadian rhythms with thrice of four times daily hydrocortisone dosing with the highest dose in the early morning and lower doses at midday and in the afternoon, overdosing of about 20% compared to physiological cortisol day profiles occurs in the afternoon [41]. Due to its higher glucocorticoid potency prednisolone is associated with lower bone mineral density in patients with adrenal insufficiency [50, 51]. Most cohort studies could not show a direct link of the glucocorticoid dose equivalent to the degree of reduced bone mineral density. This most likely is rather a methodological problem as retrospective data on glucocorticoid doses are often not exact and there is no prospective longterm study on glucocorticoid dose and bone health. Recent studies show normal bone mineral density, when not using glucocorticoids in excessive doses [49, 51]. A particular problem in males is hypogonadotropic hypogonadisms that can be caused by both over- and undertreatment [52]. On the one hand an excess of adrenal androgens being converted to estrogens can suppress the pituitary-gonadal axis, on the other hand excess glucocorticoids may cause hypogonadotropic hypogonadism with detrimental effects on bone mineral density [53]. Therefore it seems that males are even more affected by osteopenia or osteoporosis than women, in whom undertreatment with androgen excess rather protects them from loss of bone mineral density.

## Mental Health

Population-based studies from Sweden showed that the incidence of psychiatric disorders in females and males with 21-OHD is increased [6, 54]. In females in particular the risk of alcohol abuse was increased with the highest risk in the most severe null genotype. On the contrast, in males, psychiatric morbidity seems not to be raised in the more severe genotypes. A Swedish study also investigated criminal behaviour in CAH but did not find any increased risk for crime [55]. Interestingly, 21-OHD carriers had a lower risk of developing psychiatric disorders, affective disorders or substance misuse [56]. In this study having a child with 21-OHD was assessed as a psychological stressor and the incidence of psychiatric diagnoses before and after the birth of the child were investigated and compared to the general population and parents with a child with hypospadias or diabetes mellitus type 1.

## Female Fertility and Pregnancy Rate

The number of pregnancies is significantly reduced in women with CAH, however, pregnancies themselves are commonly normal and uneventful [57–59]. Reduced female fertility is the result of multiple factors including, anovulation, the effects of genital surgery, reduced heterosexual partnership and progesterone hypersecretion. The expression of these factors is related to the severity of the steroid 21-hydroxylase mutation so that child rate is particularly poor in the salt-wasting group [60, 61]. In the simple virilising form, additional mineralocorticoid replacement therapy may be beneficial for conception [62]. In the CAHase study 20% of patients had primary and 21% secondary amenorrhea [20]. Menstrual cycle disturbances have been shown to be more frequent in patients with altered LH pulsatility [63], emphasising the importance of optimal hormonal control, in particular suppression of serum progesterone. Fertility is only mildly reduced in non-classic CAH although two studies found that an increased miscarriage rate in non-classical CAH normalises with glucocorticoid treatment [64, 65].

The endocrine aspects of fertility can be normalised resulting in a normal pregnancy rate [66]. A study from the UK reported that 91.3% of patients with classic CAH who tried to become pregnant were successful, however, most patients never tried to conceive (only 23 out of 106 women in the study). Thus, this study showed the same pregnancy rate in CAH patients as in the normal population and no difference between the salt-wasting and the simple virilising form [66]. Suppression of testosterone hypersecretion and resulting anovulation is relatively simple to achieve. In addition, hypersecretion of progesterone of adrenal origin despite suppressed 17- $\alpha$ -hydroxyprogesterone is present in a subgroup of patients, which has to be specifically addressed in order to achieve normal endometrial responsiveness [67]. A normal pregnancy rate can be achieved only with the suppression of follicular phase progesterone to  $<2$  nmol/L as a result of increased glucocorticoid doses [66]. In exceptional cases, where progesterone concentrations were impossible to normalise, adrenalectomy has been shown to successfully result in spontaneous conception [68].

Other underlying causes for poor fertility in females with classic CAH include unsatisfactory intercourse due to inadequate vaginal introitus and a higher rate of homosexuality [69]. Vaginoplasty is performed in about 90% of infants with CAH, the timing of surgery

remains a matter of debate [70–72]. The outcome of genital surgery certainly is a key factor for fertility outcome as vaginal function and sexual activity are closely related. Surgical techniques have changed over time, outcome of sexual function will take time to emerge [73, 74]. Cosmetic outcomes of genitoplasty have been rated good to excellent in 151 patients in a recent review [70], other data report unsatisfactory results [20, 75]. In contrast to testicular adrenal rest tumours in males, ovarian adrenal rest tumours as underlying cause for infertility in females seem to be rare [76–79]. For fertility and pregnancy monitoring all females with CAH should see an endocrinologist and a gynaecologist.

## Male Fertility

Several studies found significantly impaired fecundity in males with classic CAH [27, 52, 80, 81]. The CaHase study showed that 37% (24/65) of males had sought fertility and 67% (16/24) had been successful [20]. Three main factors contribute to male infertility in CAH, adrenal androgen excess driving gonadotrophin suppression, excessive ACTH drive resulting testicular adrenal rest tumours (TART) and testicular failure which can follow on from TART formation.

TART formation results in secondary gonadal dysfunction due to obstruction of the seminiferous tubules. These tumours can be observed in prepubertal children and tumour number and size increase with age [82, 83]. Their prevalence has been reported between 0–94% [52, 81]. The tumours have been shown to be responsive to ACTH-suppressive glucocorticoid therapy with dexamethasone resulting in tumour shrinkage and restoration of sperm counts and fertility [84, 85]. Effective treatment of TART generally requires therapeutic doses of 0.75 mg dexamethasone per day. This dose typically leads to substantial side effects and therefore it is only recommended as short-term treatment in order to achieve fertility. Whilst the glucocorticoid responsiveness of the tumours suggests an association with disease control, so far no study could show this. Moreover, TART even have been observed in overtreated patients as indicated by suppressed ACTH levels [52, 81, 83, 86], showing that undertreatment is not the only cause of TART. Molecular characterization of TART has shown not only the expression of adrenal cortex markers but also Leydig cell markers, potentially explaining why most TART evolve after puberty [87]. Surgical treatment of TART is no longer advised as it offers no benefit and probably results in additional testicular damage [88]. Treatment options are therefore limited to optimising hormonal control. A recent study also showed that mitotane, used in adrenal cortex cancer, can restore fertility in CAH patients with TART [89]. Inhibin B may serve as an additional marker to FSH and LH in monitoring and optimising fecundity. Inhibin B differs significantly in patients with and without TART and correlate with sperm concentrations [27].

Importantly, glucocorticoid overdosing can also result in reduced fecundity due secondary hypogonadism [52]. Furthermore, suppression of gonadotrophins by adrenal androgen excess (aromatized to estrogens) because of poor disease control may lead to infertility. In such a case replacement of gonadotrophins may restore fertility [90]. Fertility issues therefore openly need to be discussed with the patients and cryoconservation of sperm offered [91].

## Adrenal Tumors

It could be shown that adrenal volume correlates well with disease control markers and in poor disease control large adrenal tumors can be found [86, 92]. Also myelolipomas are associated with 21-OHD and can be of huge size, requiring removal for mass effect [93]. However, there is no study showing increased malignant potential of these adrenal nodules.

## Summary

Patients with CAH face multiple health risks and problems during adult life which become increasingly evident. Many of these problems most likely are associated with suboptimal glucocorticoid therapy. It seems obvious that current glucocorticoid regimen cannot mimic circadian cortisol secretion and research into more physiologic glucocorticoid replacement and novel therapeutic options is necessary. Monitoring of cardiovascular risk factors needs to be part of the regular follow-up visits of these patients. Furthermore, future research should aim at a better understanding of interindividual vulnerability to adrenal crises in order to develop optimised prevention strategies. With regard to TART, fertility and pregnancy, future investigations will help to define optimal management recommendations.

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## Conflict of Interest

No conflict of interest has been declared by the authors.

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