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REVIEW

# Clinical perspectives in congenital adrenal hyperplasia due to 11β-hydroxylase deficiency

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**Abstract** Congenital adrenal hyperplasia due to 11 beta-hydroxylase deficiency is a rare autosomal recessive genetic disorder. It is caused by reduced or absent activity of 11β-hydroxylase (CYP11B1) enzyme and the resultant defects in adrenal steroidogenesis. The most common clinical features of 11 beta-hydroxylase deficiency are ambiguous genitalia, accelerated skeletal maturation and resultant short stature, peripheral precocious puberty and hyporeninemic hypokalemic hypertension. The biochemical diagnosis is based on raised serum 11-deoxycortisol and 11-deoxycorticosterone levels together with increased adrenal androgens. More than 100 mutations in *CYP11B1* gene have been reported to date. The level of in-vivo activity of CYP11B1 relates to the degree of severity of 11 beta-hydroxylase deficiency. Clinical management of 11 beta-hydroxylase deficiency can pose a challenge to maintain adequate glucocorticoid dosing to suppress adrenal androgen excess while avoiding glucocorticoid-induced side effects. The long-term outcomes of clinical and surgical management are not well studied. This review article aims to collate the current available data about 11 beta-hydroxylase deficiency and its management.

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## Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by defects in various enzymes responsible for the biosynthesis of cortisol and aldosterone in the adrenal glands [1, 2]. The condition was first described in 1865 by De Crecchio on autopsy of a 46XX male who died of an adrenal crisis [3], and several case reports followed later**.** In 1950, Wilkins *et al*. described use of intramuscular cortisone for treatment of CAH and adrenal androgen suppression [4]. A year later in 1951, Shepherd et al. and Wilkins et al. described three cases of CAH with hypertension who responded to cortisone therapy [5, 6]. Eberlein and Bongiovanni in 1956 were the first to propose a deficiency of 11β-hydroxylase enzyme based on plasma and urinary corticosteroid profile in a case of CAH with hypertension [7].

Patients with CAH have a wide spectrum of clinical presentation depending on the underlying enzymatic deficiency including 21-hydroxylase, 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase, and 17α-hydroxylase. 21-hydroxylase deficiency (21OHD) is the most common variant of CAH accounting for 90–99% of CAH cases, followed by 11β-hydroxylase deficiency (11βOHD) accounting for 0.2–8% and then the rest [8–13]. CAH can present as classic or non-classic phenotype depending on clinical and biochemical features. 21OHD may present as salt-wasting (SW) and simple virilizing (SV) forms (mainly depending on the degree of mineralocorticoid deficiency) of classic CAH or non-classic (NC) CAH. 11βOHD may similarly present as classic or non-classic phenotype

depending on the degree of clinical severity and percentage loss of enzyme activity. NCCAH do not need glucocorticoid supplementation for survival [14]. Classic 11βOHD and 21OHD present with features of androgen excess, such as virilization of external genitalia in females and peripheral precocious puberty in males. Hypertension is present in two-third of the cases with 11βOHD at time of diagnosis [15]. SW is not commonly seen with 11βOHD due to mineralocorticoid receptor simulation [10, 16]. NC 11βOHD has similar clinical features as of NC 21OHD with no abnormalities at birth [17]. Patients may come to medical attention due to mild virilization, peripheral precocious puberty, hirsutism or menstrual irregularities [16]. Hypertension is not found with NC 11βOHD [10].

The aim of this review is to provide a summary of currently available knowledge of CAH due to 11βOHD.

## Physiology

The adrenal cortex is the primary site for steroid hormone biosynthesis. In the adrenal cortex, *zona glomerulosa* and *zona fasciculata* behave as two separate glands with distinct biological functions [11, 18]. Cortisol is synthesized from cholesterol precursor in *zona fasciculata* by series of enzymatic reactions as depicted in Fig. 1. CYP11B1 is responsible for the conversion of 11-deoxycortisol to cortisol, which is the final step in cortisol synthesis.

CYP11B1 has been shown to 11β-hydroxylate 11-deoxycorticosterone (DOC) to corticosterone in in-vitro studies [11, 19, 20]. However, it is unable to convert corticosterone to aldosterone [16]. Aldosterone is produced by the action of aldosterone synthase (CYP11B2), which is exclusively expressed in *zona glomerulosa*. CYP11B2 catalyzes 11β-hydroxylation of DOC to corticosterone as well as acts as 18-hydroxylase and 18-oxidase in the final steps of aldosterone synthesis in *zona glomerulosa* [11].

## Pathophysiology

Mutations in the *CYP11B1* gene result in a defective 11β-hydroxylase enzyme. There is resultant decreased conversion of 11-deoxycortisol and DOC to cortisol and

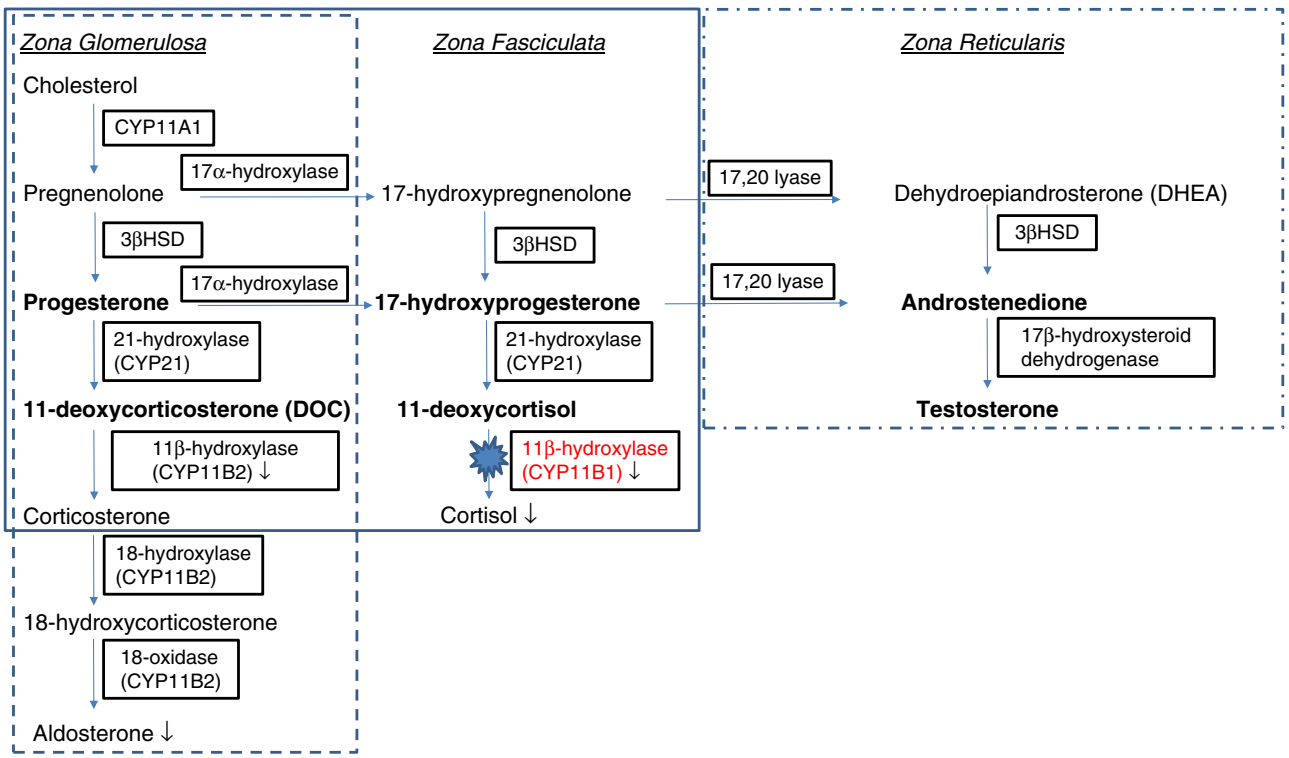


**Fig. 1** Adrenal steroidogenesis. The classic pathways of aldosterone, cortisol, and androgen synthesis and the enzymatic steps from the precursor cholesterol are shown. Deficiency of 11β hydroxylase enzyme results in accumulation of 11-deoxycortisol, 11-deoxycorticosterone, 17-hydroxyprogesterone and progesterone in addition to androgens (all highlighted). The arrows demonstrate decreased synthesis of CYP11B1 and CYP11B2 in *zona fasciculata and zona glomerulosa,* respectively. The low aldosterone levels result from an excess of DOC, which is accumulated due to a blocked glucocorticoid pathway. As this metabolite possesses mineralocorticoid features, the renin angiotensin system is not activated as evidenced by the low renin concentration. This leads to a decreased synthesis of CYP11B2 and thus, to a decreased aldosterone production. 3βHSD, 3 beta hydroxysteroid dehydrogenase

corticosterone, respectively in *zona fasciculata* [11, 16, 19] while in *zona glomerulosa,* CYP11B2 will convert DOC to corticosterone. The low cortisol level activates the negative feedback mechanism of pituitary-adrenal axis leading to increased ACTH production with consequential adrenal cortex hyperplasia [8], and in some cases adrenal tumor formation [21–23]. The increased steroid precursors are then shunted into the androgen pathway (Fig. 1). Elevated mineralocorticoid precursors and androgens including androstenedione and testosterone lead to development of hyporeninemic hypertension and symptoms of hyperandrogenism, respectively. Since adequate cortisol levels are needed for adrenomedullary organogenesis, the epinephrine production has been shown to be impaired and a correlation with the severity of 21OHD has been reported [24–26]. Similar results have been shown in 11βOHD [27].

## Clinical presentation

### Classic 11βOHD

#### *Androgen excess*

Features of hyperandrogenism may be detected at any age from infancy to early adulthood, and in some cases even later, in patients with 11βOHD [10, 15, 16, 28–32].

Female karyotypes present with varying degrees of virilization of external genitalia with intact functional gonads and internal genitalia derived from Mullerian structures. Surgical reconstruction is required in most virilized girls. However, there are no clear guidelines for appropriate age of surgical intervention. Most data is extrapolated from the management of 21OHD, which strongly advocates that the surgical treatment should be performed at specialized centers where medical, surgical, and psychological expertise in CAH care is present and where these procedures are done regularly [1, 33].

Untreated males usually present with enlarged penis and age appropriate testicular size. Left untreated, they can develop pubertal gynecomastia, Leydig cell hyperplasia [15], or testicular adrenal rest tumors (TARTs) [34]. Other signs of androgen excess in both boys and girls include accelerated somatic growth with premature epiphyseal closure and resultant short adult stature. Some children are diagnosed at a later age with premature adrenarche, acne and hyperpigmentation of skin and nipples [35]. A case of infantile acne as presenting symptom of 11βOHD has been described [36]. Hyperandrogenism can also present with peripheral precocious puberty and delayed menarche in females or poor spermatogenesis in males [35].

In a retrospective study in Jewish individuals of Moroccan and Iranian origin, 24 patients (15 girls, 9 boys) with 11βOHD were followed up for 15 years [37]. Before the age of 1 year 42% were diagnosed (2 males, 8 females), 42% (5 males, 5 females) between ages 1 and 4 years, 13% (2 males, 1 female) after 4 years, and 1 patient at age of 8 years. The height, weight, and bone age followed normal growth pattern for first 4 months of life but were accelerated by 11 months of life. By 2 to 5 years of age, height remained at a mean of 4 SDs above the mean for age but the pubertal growth velocity was slower than normal. There was a difference in male and female growth possibly linked to delayed diagnosis in males. Moreover, the onset of puberty was earlier in boys compared to normal.

#### *Hypertension*

Mild to moderate hypertension is observed in two-thirds of the cases of 11βOHD at the time of diagnosis [15, 30]. The mechanism has been assumed to be due to the excess of DOC but it is not as straightforward; please see below Complications—Blood Pressure. Hypertension is one of the differentiating clinical features from 21OHD. However, patients with NC 11βOHD are more often normotensive or have high-normal blood pressure at the time of diagnosis [16, 32, 38]. Although hypertension is usually noted at a later age, the earliest age of onset of hypertension in a case of 11βOHD was at birth [39].

#### *Electrolyte regulation*

Hypokalemia as a result of excess mineralocorticoid activity is found in a minority of patients and is not correlated to blood pressure [28]. Hypokalemic paralysis has been reported in known cases of 11βOHD [40, 41]. 11βOHD is one of the differential diagnoses in hypokalemic paralysis or hypokalemia presenting in combination with hypertension [42].

Salt-wasting in the early neonatal period has been reported before the treatment with glucocorticoids in patients with high basal DOC and renin levels [10, 29]. The pathophysiology is not well-understood and to a certain extent, it has been attributed to the natriuretic activity of 16-hydroxylated steroids, progesterone, and pregnenolone from fetal adrenal tissue. Hence, it spontaneously disappears later in life. None of the cases had clinically significant salt-wasting [10]. Rarely salt-wasting can be precipitated by glucocorticoid treatment. This is explained by suppression of DOC and resultant low mineralocorticoid activity secondary to glucocorticoid therapy [43, 44]. Moreover, occasional patients develop signs of mineralocorticoid deficiency with hyperkalemia, hyponatremia and hypovolemia during acute illness [44, 45]. One case series demonstrated salt-loss with hyponatremia in eight episodes of gastroenteritis amongst patients with 11βOHD treated with glucocorticoid therapy [44]. Hence, during acute illness with electrolyte imbalance, adequate dietary sodium

intake and mineralocorticoid treatment may be required [44, 45]. Few cases with mineralocorticoid deficiency have been described in untreated patients with classic 11βOHD and patients on glucocorticoid replacement with one case of documented homozygous deletion hybrid (*CYP11B2-CYP11B1*) [10, 43, 46].

### NC 11βOHD

The milder NC form is characterized by normal external genitalia at birth but peripheral precocious puberty during childhood or other signs of mild hyperandrogenism in adolescence/adulthood such as acne, hirsutism, and/or oligo-amenorrhea similar to NC 21OHD [14]. The clinical picture can be similar to polycystic ovarian syndrome (PCOS) and the patient may receive a diagnosis of PCOS instead of 11βOHD. This is a well-known phenomenon in 21OHD [14, 47, 48]. Hence, it is a prerequisite that NC 21OHD has been excluded [49]. If the same applies to 11βOHD is unclear. Since in these milder forms, hypertension does not occur, the diagnosis is based on either high basal or ACTH-stimulated levels of serum 11-deoxycortisol. Although NC 11βOHD is rare, it is an important differential diagnosis in cases of premature adrenarche, hirsutism, and menstrual irregularities, especially in the pediatric/adolescent population.

## Diagnosis

Deficient 11β-hydroxylase activity results in impaired production of cortisol and accumulation of steroid precursors (Fig. 1). Steroid precursors including 11-deoxycortisol and DOC are elevated (Table 1). Elevation in 11-deoxycortisol level results in increased 17-hydroxyprogesterone (17OHP), which is shunted to androgen pathway leading to excess androstenedione and testosterone. However, the lack of clear diagnostic nomogram for 11βOHD compared to 21OHD should be noted [50]. Elevated 17OHP levels can sometimes mislead to the diagnosis of 21OHD when used in neonatal screening programs. Hence, on-going assessment of clinical picture and follow-up is important [51–53]. Urinary tetrahydro-metabolites of steroid precursors such as tetrahydro-11-deoxycortisol (THS), tetrahydro-deoxycorticosterone are unequivocally elevated and can be used to diagnose 11βOHD. 24 h urine collection can also be used in monitoring efficacy of treatment [30]. Elevated levels of mineralocorticoid precursors such as DOC result in suppression of renin-angiotensin system and decreased synthesis of CYP11B2. Hence, the plasma renin and aldosterone levels are suppressed (Table 1).

In cases of suspected NC 11βOHD, measurements of basal and ACTH stimulated 11-deoxycortisol and DOC levels are measured. Levels three times above the 95th percentile for normal population have been used as a diagnostic criterion in some clinical studies; however, it is not a specific marker [54–56]. Hormonal profile is important for diagnosis; however genetic profile and functional characterization of mutations is of particular interest to confirm diagnosis, as well as commence appropriate therapy and genetic counseling [32].

In heterozygous carriers of 11β-hydroxylase mutations, there has been documentation of variable degree of 11β-hydroxylase activity with increased plasma levels of ACTH stimulated 11-deoxycortisol and to a lesser extent DOC [57]. However, two other studies did not find any significant changes in hormonal profile of family members who were heterozygous carriers [58, 59].

**Table 1** Comparison between 11β-hydroxylase deficiency and the most common variant of congenital adrenal hyperplasia, 21OHD

| | 11βOHD | 21OHD |
|---|---|---|
| Affected gene | *CYP11B1* | *CYP21A2* |
| Prevalence (classic) | 1 in 100,00 to 1 in 9,000,000[a] | 1 in 15,000 |
| Salt-wasting | Rare | Common |
| Hypertension | Common | Rare |
| Degree of virilization | Mild-severe | Mild-severe |
| 11-deoxycortisol | Elevated | Low |
| Deoxycorticosterone | Elevated | Low |
| 17-hydroxyprogesterone | Elevated | Elevated |
| Progesterone | Elevated | Elevated |
| Renin | Low | Elevated |
| Aldosterone | Low | Low |
| Androstenedione | Elevated | Elevated |
| Testosterone | Elevated | Elevated |
| Treatment | Glucocorticoids | Glucocorticoids and often mineralocorticoids |

[a] Incidence of 11βOHD in Caucasian population

## Molecular genetics

In humans, there are two 11β-hydroxylase isoenzymes. *CYP11B1* gene encoding 11β-hydroxylase (P450c11) is located on chromosome 8q24.3, 40kb upstream from highly identical *CYP11B2* gene, which codes for aldosterone synthase (P450c11Aldo). *CYP11B1* and *CYP11B2* show 95% homology in coding regions and 90% in non-coding regions [16, 60]. The *CYP11B1* gene (OMIM #202010) has 9 exons, which encodes for 503 amino acids and spans over approximately 7kb. Approximately 100 mutations including missense/nonsense, splicing, small/ gross deletions, insertions and complex rearrangements have been described in

various ethnic populations and recorded on Human Gene Mutation Database (www.hgmd.cf.ac.uk). Majority of mutations are clustered in exons 2, 6, 7, and 8 [11, 61].

It is difficult to predict the actual disruptive effects of mutations that affect enzyme activity and the clinical phenotype. This variability in patient genotypes is related to the wide range of clinical presentation among patients with 11βOHD [62]. In 21OHD on the other hand, the genotype-phenotype correlation is generally considered good [63–65], particularly for the genotypes corresponding to SW and NC CAH, while it is more unpredictable in the SV phenotype [66, 67]. However, the *CYP11B1* mutations can distinguish between classic and NC 11βOHD. More important though is that genetic analysis of *CYP11B1* mutations confirms the diagnosis and is essential in genetic counseling similar to 21OHD [1, 65]. In 21OHD, there have recently been speculations that the clinical course may be predicted and serious consequences may be prevented even in adult life by knowing the genotype [65], based on several studies from the same group [25, 68–80]. These aspects of different genotypes have not yet been explored in 11βOHD.

## Classic 11βOHD

In a study of 11βOHD in Jews of Moroccan origin, a point mutation, R448H, was identified in 11 out of 12 patients (92%) [81]. In contrast, in a Turkish cohort, the c.954G>A splice site mutation was the most frequent, with an allele frequency of 14.6%, followed by p.Arg141*, with a frequency of 12.5% and p.Leu299Pro, p.Gln189Hisfs*70, and IVS8+5G>C, each with an allele frequency of 8.3% [62]. Uniparental disomy is a recognized phenomenon causing disease when one parent is non-carrier and other parent is a carrier of disease mutation and was recently reported in a neonate diagnosed with classic 11βOHD with only a mutation identified in the father [82]. A list of commonly known mutations causing classic 11βOHD CAH are listed in Table 2.

**Table 2** Mutations causing classic and NC 11βOHD

| Classic 11βOHD | | | |
|---|---|---|---|
| Mutation | Clinical presentation or comments | Percentage of mutant enzyme activity c.f WT | Reference |
| c.954G > A;p.Thr318Thr | Hypertension Severe virilization | | [62] |
| p.Arg141* | Hypertension Severe virilization | | [62, 207, 208] |
| p.Leu299Pro | Severe virilization | | [62] |
| p.His125Thrfs*8 | Macrogenitalia No hypertension | | [85] |
| p.Leu463_Leu464dup | Testicular adrenal rest tumor | | [85] |
| p.G379V, p.Q356X | Found in Tunisian population | | [209] |
| IVS7+1G>A | Uniparental disomy | | [82] |
| R448H | Moroccan Jews | | [81] |
| Non-classic 11βOHD | | | |
| p.(Arg143Trp) | Premature pubarche, accelerated growth | 8% | [84] |
| p.(Arg332Gln) | Acne, accelerated growth | 6% | [84] |
| p.(Ser150Leu) | Premature pubarche, absent virilization | 19.2% | [85] |
| p.(Gly446Ser) | Premature pubarche | N/A | [62] |
| p.F79I; p.R138C | Premature pubarche, high-normal blood pressure | 9–10% | [38] |
| p.R143W | Hirsutism, primary amenorrhea | 9–10% | [38] |
| p.P159L | Premature pubarche, accelerated growth | 25% | [32] |
| p.M88I; p.R383Q | Peripheral precocious puberty | 40% | [32] |
| p.R366C | Hirsutism | 23% | [32] |
| p.T401A | Accelerated growth | 37.5% | [32] |
| p.P42S | Acne, precocious adrenarche | 15% | [83] |
| p.N133H | Precocious adrenarche | 17% | [83] |
| p.T319M | Acne, precocious adrenarche | 37% | [83] |

### NC 11βOHD

There are up to 13 mutations associated with NC 11βOHD in the literature (Table 2) [32, 38, 62, 83–85]. The degree of enzyme activity compromise associated with NC 11βOHD is similar to that seen in NC 21OHD (20–50%) [14].

#### Heterozygotes/carriers

Contrary to 21OHD, the heterozygotes from families of patients of classic or NC 11βOHD have no significant differences in HLA genotyping or hormonal profile compared to control population [58, 59, 86, 87]. However, there are two mutations in heterozygous carriers (p.R366C, p.T401A) with evidence of reduced CYP11B1 activity by 23 to 37%, respectively [32]. These patients presented with premature pubarche, accelerated growth and hirsutism. All of them had exaggerated response of 11-deoxycortisol to ACTH stimulation with normal or slightly elevated androstenedione levels.

## Prevalence

There is limited data available regarding prevalence in general population. It has generally been stated that 11βOHD comprises 5–8% of patients with CAH [8–10]. A national cohort from United Kingdom found that only three of 203 CAH patients were affected by 11βOHD (1.5%) [12], but it was estimated that overall capture rates were only between 3–5% for classic CAH. However, in another national cohort with a capture rate of more than 90%, only one of 612 Swedish CAH patients had 11βOHD (0.2%) [13, 76]. Some of these differences may be due to selection bias, as well as the ethnic diversity of the study population. The prevalence has been claimed to be 1 in 100,000 in general Caucasian population [10], but this is a very uncertain figure. Calculating from the previously mentioned Swedish national CAH cohort, only one case of 11βOHD in 9 million was diagnosed in a population where most were of Swedish Caucasian origin [13]. However, in a Brazilian study of 133 patients with alleged classic 21OHD, one had been misdiagnosed and was found to have 11βOHD when proper biochemical and genetic evaluation was done [88]. The authors concluded that this may indicate an underestimation of 11βOHD by at least 20%.

In contrast, the frequency is much higher in certain ethnic populations and geographical locations such as Jews from Morocco and Israel, Saudi Arabia, and Turkey [15, 29, 89]. Of 78 Saudi children with CAH, 20 children (from 11 families) had 11βOHD (26%) [29]. The estimated incidence in Israel was 1 in 30,000–40,000 but in the offspring of Moroccan Jews the estimated incidence was 1 in 5000–7000 with a carrier frequency of 1 in 35 to 1 in 42 [15]. Similarly, a study of 273 patients with CAH in Turkey identified 13.5% patients with 11βOHD over 25 year period [89]. One explanation for this exceptionally high frequency compared to other populations could be common occurrence of consanguineous marriages within the ethnic subpopulation. Moreover, none of these studies have confirmed the diagnosis using *CYP11B1* gene mutation analysis.

In women with hirsutism and hyperandrogenism, NC 11βOHD was diagnosed on the basis of high basal or post-ACTH stimulation 11-deoxycortisol levels (no genetic confirmation was sought in any of these studies). In these studies, prevalence varies from 0.8% to 8% depending on the geographic location and ethnicity of study population [54–56, 90, 91].

## Complications

### Cardiovascular and metabolic complications

#### *Blood pressure*

Hypertension is one of the major clinical features with classic 11βOHD. DOC, which has mineralocorticoid activity and is elevated in untreated 11βOHD, has been assumed to be the cause of hypertension. However, DOC has only weak mineralocorticoid activity when administered to humans or animals [16, 92, 93]. Moreover, there is no correlation between plasma levels of DOC and severity of hypertension [10, 35]. This raises the question of mechanism of hypertension in this group. In addition, degree of virilization and features of mineralocorticoid excess are not well correlated [15, 28]. DOC is a less potent mineralocorticoid in-vivo compared to 18-hydroxylated compounds and it could be speculated that these are the cause of hypertension in 11βOHD. There was significant correlation between chronological age at diagnosis and systolic blood pressure in a small case series [10]. Both poorly controlled hypertension and over-replacement with glucocorticoids can adversely affect cardio metabolic profile. There are reports of end-organ damage secondary to severe hypertension. These include left ventricular hypertrophy, hypertensive retinopathy, hypertensive nephropathy, ischemic heart disease, cerebrovascular accidents, encephalopathy and deaths in patients with 11βOHD [15, 28, 40, 94–97].

In contrast, in 21OHD blood pressure is usually low at diagnosis but long-term hypertension is often found in treated patients, presumed due to overtreatment of glucocorticoids and/or mineralocorticoids, even in children [12, 80, 98, 99]. However, others have not found any increased risk of hypertension in 21OHD [25, 100–102].

*Obesity*

Obesity is a well-recognized risk factor for adverse cardiovascular outcomes. There is significant variability in BMI in patients with classic and NC 11βOHD [32, 38, 84, 85, 103]. Similarly, in 21OHD increased BMI has been reported in some [12, 104–114], but not all studies [25, 98, 115, 116].

*Diabetes*

The prevalence of type 2 diabetes in 11βOHD is unknown. There is one report with two cases of type 2 diabetes and NC 11βOHD [103]. In contrast, in 21OHD increased rate of gestational and type 2 diabetes has been noted [2, 69, 80, 100].

## Mortality

Mortality has not been studied in detail in 11βOHD. In contrast, in a recent study of all patients diagnosed with 21OHD in Sweden, the mortality was increased with a hazard ratio of about three compared to controls [117]. However, the cohort had a low median age of only 26 years as most patients probably died undiagnosed before the introduction of glucocorticoids in the 1950s and the increased awareness of CAH in recent years [13]. The cause of death in this young cohort was adrenal crisis (42%), cardiovascular disease (32%) (predominantly cerebrovascular), cancer (16%) and suicide (10%). However, in many of the cardiovascular deaths a severe infection was also reported on the death certificate so these cases may be related to adrenal crises. Thus, possibly up to 58% were associated with or a result of adrenal crisis. Another epidemiological study of CAH, but this time all variants of CAH and only in admitted children, demonstrated high admission rate of adrenal crisis (42%) but decreasing with age and no in-hospital mortality [118]. It could be assumed that the mortality rate in 11βOHD is increased compared to 21OHD due to higher cardiovascular risk. However, since the risk of adrenal crisis has been claimed to be lower in 11βOHD than 21OHD, the mortality rate may in fact be decreased compared to 21OHD but still probably higher than the general population [30].

## Height and bone health

Little is known regarding height and bone health in patients with 11βOHD.

*Final height*

Impaired final height in 11βOHD has been noted irrespective of the age at diagnosis, as well as clinical and biochemical control [37]. The mean final height in 11 females was 10 cm shorter compared to general population and almost 18 cm shorter in six males who reached age of 18 years. There was marked difference in pubertal growth spurt and velocities between males and females with males being more severely affected. This was attributed to a delay in diagnosis and possible over-replacement with glucocorticoids. Hydrocortisone was found to be superior in terms of height velocity compared to cortisone acetate and prednisolone. Similarly the final height is compromised in 21OHD [2, 25, 100, 119]. Good compliance has been observed to have positive effect on final height [2, 120]. Inconsistent evidence exists regarding effects of early diagnosis and treatment in 21OHD on final height outcomes [120–125].

*Bone health*

There are no clinical studies looking at bone mineral density (BMD) in patients with 11βOHD. However, it can be extrapolated from the available data for 21OHD that BMD can be negatively affected with long-term glucocorticoid exposure in an unphysiological manner [68, 74, 106, 126, 127]. Higher fracture prevalence and osteoporosis/osteopenia was noted in adult females with 21OHD compared to controls [68]. Moreover, more fractures occurred in adults patients with classic compared to NC 21OHD [68, 128].

## Testicular adrenal rest tumors

TARTs are benign testicular masses, mostly affecting bilateral testes and present in the rete testes [2, 73, 129]. Based on histological studies, TARTs have close resemblance to adrenocortical tissue [130, 131]. Functional studies in patients with 21OHD have identified ACTH and angiotensin II (AII) receptors and expression of *CYP11B1* and *CYP11B2* adrenal specific enzymes [132–136]. Presence of ACTH and AII receptors in the TART tissue indicates hormone responsive tissue which can undergo hypertrophy and/or hyperplasia due to elevated ACTH (and/or AII) levels [132, 137, 138]. Studies in patients with 21OHD failed to demonstrate any relationship between tumor growth and level of ACTH suppression. Tumor size increase was noted in both under-treated and adequately treated patients [139, 140]. Moreover, no association was found between total TART volume or functional testicular volume and age or present glucocorticoid dose, plasma renin, and ACTH concentrations [73].

Prevalence of TART is variable and up to 86–94%, but most studies have looked at frequency rates only in patients with 21OHD [73, 141–143]. Two case series and one case report describe patients with 11βOHD and TARTs [144–146]. One of these series was a follow-up study of 60 boys

and adolescent males with CAH of which five had 11βOHD. Three of five boys (60%) were identified to have TART based on ultrasonography [145]. All three cases had poor biochemical control and were diagnosed with TARTs at ages 14, 16 and 17 years. Semen analysis was only available in one case who was noted to be azoospermic. Similarly, another case report of 11βOHD and bilateral TART diagnosed at the age of 16 years wherein semen analysis revealed oligoasthenoteratoazoospermia [146]. In two cases reported of TARTs and 11βOHD, one had oligospermia [144]. Due to the central location of TART, it has been shown to cause compression of seminiferous tubules with peritubular fibrosis and tubular hyalinization resulting in obstructive azoospermia. TARTs are a major contributor to male infertility with CAH, specifically studied with 21OHD [2, 129, 131]. However, TARTs may be present in CAH males at the time of conception [2].

The few case reports/series in 11βOHD patients looking at glucocorticoid treatment and TART size showed responses from complete disappearance to no response at all on high dose glucocorticoid therapy [34, 144, 145, 147–149]. In cases of 21OHD with minimal response to increased dose of glucocorticoids or with persistent azoospermia, testis sparing surgery has been shown to improve fertility [150, 151]. However, this is not a consistent finding and hence surgery should be performed only if testicular biopsy confirms viable testicular tissue [2, 136]. It is not unusual that patients with CAH have undergone previous testicular surgery for suspected testicular malignancy [12, 73]. Hence, it is very important that a TART has been considered before doing testicular surgery for suspected malignancy in a patient with CAH [2].

Early diagnosis and adequate treatment of TART in childhood may prevent future complications especially related to infertility. Hence, scrotal ultrasound screening beginning from early childhood followed by annual screening in peripubertal period has been suggested [145]. Current guidelines do not specify frequency of screening in adults but we recommend scrotal ultrasound every 2–5 years or earlier if clinically indicated. Screening with testicular palpation is not adequate since most TARTs are <2 cm and even examination by experienced clinicians could detect only 10% of adult CAH males with TARTs on palpation but 86% were found to have TARTs on ultrasound [73].

## Adrenal tumors

Adrenocortical tumors have been described in patients with 21OHD secondary to chronic stimulation from elevated ACTH levels causing adrenal hyperplasia [22, 23, 152, 153]. Moreover, it has been suggested that patients with undiagnosed CAH may present with an adrenal incidentaloma and screening for CAH, especially 21OHD may be worth considering [154–157]. A recent systematic review and meta-analysis found that in adrenal incidentaloma, the occurrence of biochemically diagnosed CAH was 5.9% ($n = 990$), but only 0.8% ($n = 662$) in those with genetically confirmed diagnosis [153]. However, this meta-analysis only included studies with 21OHD. Impaired 11β-hydroxylation activity has been demonstrated in functional adrenocortical tumors and non-functional adrenal incidentalomas based on in-vitro enzymatic analyses or ACTH stimulation test [158–161]. Bilateral giant adrenal incidentalomas have been reported in a 22-year-old man who after investigations turned out to have 11βOHD and the karyotype was 46XX [162]. A 61-year-old female presenting with hirsutism and left adrenal tumor who was diagnosed with NC 11βOHD based on elevated ACTH and 11-deoxycortisol levels and persistence of hyperandrogenism post left adrenalectomy [163]. A 23-year-old male patient was referred for evaluation of hypertension with complications and a 10 cm left adrenal mass [40]. He underwent adrenalectomy but represented five years later with a 6.5 cm right adrenal tumor and was then diagnosed with 11βOHD. However, none of these cases have genetic confirmation for diagnosis 11βOHD.

## Fertility

### *Male fertility*

Based on the semen analyses results available in patients with 11βOHD mentioned above, it is evident that azoospermia is common [144–146]. Of note, the semen analyses results are available only in cases diagnosed with TARTs which may give an impression of falsely high levels of subfertility in males with 11βOHD. In males with 21OHD, case control and prospective cohort studies demonstrate reduced fertility and fecundity [12, 73, 76, 129, 141, 164]. In addition to the presence of TART (see above) and effects of glucocorticoid therapy, sexual and psychosocial factors are considered to play an important role in male fertility [2].

### *Female fertility*

There is only one case report of successful pregnancy in a patient with genetically confirmed classic 11βOHD [165]. Another case report of successful pregnancy was in a patient diagnosed with 11βOHD on the basis of raised urinary tetrahydro-11-deoxycortisol levels [166]. Low fertility and pregnancy rates in 21OHD CAH have been reported in comparison to age-matched controls [69, 167–171]. The proposed causes of reduced fertility in 21OHD include delayed psychosexual development, difficulties with sexual orientation, low sexual activity, adrenal androgen excess,

anovulation, polycystic ovaries and genital surgery [167, 168, 172]. It seems reasonable to presume the above outcomes could also be true in 11βOHD but has not been studied yet.

In the case report of successful pregnancy outcome with classic 11βOHD, the patient was diagnosed with polycystic ovarian syndrome secondary to chronic androgen excess in adulthood. She conceived after ovulation induction with clomiphene citrate. During pregnancy, increased clinical and biochemical virilization was noted with worsening acne and hirsutism and rising serum testosterone levels. She was on dexamethasone pre-conception which was continued and up-titrated gradually from 0.75 to 2 mg/day by end of pregnancy to control hyperandrogenism. The baby was delivered with elective cesarean section at 37 weeks due to maternal history of vaginal narrowing. No maternal or fetal complications were observed [165].

Due to limited information in current literature regarding pregnancies in patients with 11βOHD, clinical management is based on previous experiences with 21OHD. Most pregnancies are uneventful in 21OHD CAH [69, 169, 172, 173]. Gestational diabetes is believed to occur at higher frequency in CAH patients compared to controls [69, 100]. Emergency or elective cesarean section was performed in 52–84% with the common reason being previous genital surgery [69, 169, 172, 173]. Dexamethasone should be avoided during pregnancy as it is not metabolized by placental 11 beta hydroxysteroid dehydrogenase type II [1].

*Prenatal diagnosis*

Molecular genetic analysis to identify mutations in *CYP11B1* gene in the extracted fetal DNA obtained by chorionic villus sampling has been used to detect fetal status for 11βOHD [61, 174–176]. As with 21OHD, prenatal treatment in case of a female fetus identified to carry homozygous mutation for 11βOHD should only be considered in research settings [1].

### Gynecomastia

There are a few case reports of pre-pubertal male gynecomastia in patients with 11βOHD down to the age of 1 year [10, 15, 177–181]. A literature review of 41 patients with pre-pubertal gynecomastia noted that 11βOHD was present in 4 cases (10%) [182]. Gynecomastia seems to occur in patients with more severe forms of 11βOHD as evidenced by higher 11-deoxycortisol and DOC levels [10, 183]. The pathophysiology of gynecomastia in 11βOHD remains unclear. High levels of adrenal androgens results in peripheral aromatization to estradiol in both 11βOHD and 21OHD. However, gynecomastia has not been reported with 21OHD. This suggests that there is an alternative mechanism for gynecomastia in addition to increased estradiol levels. In a retrospective study, development of gynecomastia was demonstrated in five patients with 11βOHD after commencing fludrocortisone therapy. Hence, they propose that the close structural similarities between the mineralocorticoids, DOC and fludrocortisone, can explain the anti-androgenic effect at the level of tissue androgen receptors leading to gynecomastia [180]. All reports have documented reversal of gynecomastia with adequate glucocorticoid therapy [10, 15, 177–180].

### Skeletal abnormalities

There are four case reports of short fourth metatarsal bone in cases with 11βOHD. There was no familial aggregation and given the rarity of 11βOHD and identification of similar skeletal abnormality in four cases, it was considered to be more than a co-incidence [181]. One case report of Schmid type metaphyseal chondrodysplasia has been reported in a patient with 11βOHD, however, whether this is a co-incidence or association is unclear [184].

## Treatment

The goals of therapy are to replace deficient cortisol secretion and thereby, reduce levels of excess androgens and mineralocorticoid precursors. This is achieved by glucocorticoid administration, mostly in the form of hydrocortisone. Doses of hydrocortisone of 10–20 mg/m$^2$/day in 2–3 divided doses have been used effectively in this group of patients which is similar to those used in 21OHD [11, 30, 185]. Hydrocortisone is the preferred choice in children due to the potential growth suppression of longer-acting preparations [1, 37]. In 21OHD, intermediate-acting glucocorticoids, e.g., prednisolone (2.5–7.5 mg/day divided into two doses) and long-acting glucocorticoids, e.g., dexamethasone (0.25–0.50 mg at bedtime or divided into two doses), may be preferred in adulthood as they only need to be taken once or twice daily [1, 2, 9, 14]. Some clinicians use reverse circadian dosing to improve androgen control [186], while others prefer to avoid this since it may give poor sleep quality and worse cardiovascular and metabolic long-term outcomes [14]. Six children with classic 21OHD and a hydrocortisone regimen with the highest dose first in the morning and then in the evening demonstrated increased 24 h blood pressure levels if highest dose was in the evening and this did not improve their biochemical control [187]. Some clinicians occasionally recommend short-term use of the largest dose of the glucocorticoid at bedtime to suppress night-time ACTH secretion to enhance fertility [14]. The use of cortisone acetate should be discouraged since it needs to be converted via 11β-hydroxysteroid dehydrogenase to cortisol and this conversion can be reduced in some

individuals [2, 188]. Modified-release hydrocortisone has recently been studied in a small number of patients with 21OHD with potential benefits [189], but has not yet been studied in 11βOHD.

The efficacy of treatment is monitored by regular clinical assessment with documentation of degree of virilization, growth velocity, and control of hypertension [28]. The aims of therapy are to prevent virilization, improve blood pressure control, optimize growth, and preserve potential fertility [11]. Biochemical monitoring with plasma 11-deoxycortisol, DOC, and plasma renin activity is helpful [11, 28]. With suboptimal treatment, the DOC levels are elevated and renin will be suppressed. Once adequate glucocorticoid treatment is initiated, the DOC and renin should normalize. Urinary 17-ketosteroids and THS have been used to monitor dose efficacy in the past [37]. The glucocorticoid doses have to be adjusted to minimize the risk of iatrogenic Cushing's syndrome but stress doses of glucocorticoids are required with acute illness in all patients with classic 11βOHD even though the risk of adrenal crisis is lower than 21OHD [11, 30, 185].

If the blood pressure remains elevated despite optimal glucocorticoid treatment, an anti-hypertensive medication should be added. Spironolactone or amiloride can be used as single agent or in combination with a calcium channel blocker [16]. Since the renin-angiotensin system is suppressed, angiotensin-converting enzyme inhibitors and angiotensin receptor II blockers should be avoided. Thiazide diuretics should also be avoided or used together with a potassium-sparing diuretic as it may aggravate or precipitate hypokalemia [16].

### Mineralocorticoid therapy

One study suggested addition of mineralocorticoid therapy in patients with 11βOHD and elevated renin despite adequate glucocorticoid doses with careful monitoring of blood pressure, urinary electrolytes and renin measurements [183]. This approach may allow reduction in glucocorticoid dose and achieve better growth. Patients with electrolyte imbalance during acute illness may require mineralocorticoid replacement on certain occasions as mentioned above [43–45].

### Growth augmenting therapies

Careful monitoring of growth velocity and bone maturation is important in the management of children with CAH [1]. As mentioned earlier, final height has been reported to be significantly compromised in children with 11βOHD irrespective of age at diagnosis and biochemical control [37]. Three case reports with 11βOHD describe the use of growth hormone (GH), gonadotropin releasing hormone analog and glucocorticoid as combination treatment in young children with resultant improvement in final height and no reported adverse effects [190–192]. Another case report documented the use of the aromatase inhibitor letrozole in combination with GH in a 7-year-old 46XX male with significant improvement in final height [193].

Growth augmentation therapy in 21OHD is better studied [1, 194]. Two different randomized studies which compared four drug combination therapy including antiandrogen (flutamide), aromatase inhibitor (testolactone/letrozole), reduced dose hydrocortisone (8 mg/m$^2$ per day) and fludrocortisone with conventional treatment in 12 and 28 children with classic 21OHD, respectively, showed normal linear growth and skeletal maturation in the combination therapy arm [195, 196]. Another non-randomized case control study in children with 21OHD reported significant improvement in final height in the treatment group with GH and luteinizing hormone releasing hormone analog compared to age-matched control group on conventional glucocorticoid treatment at the end of 4 years [197].

Due to the lack of randomized trials and unknown long-term outcomes of above treatment regimens, such treatment for enhancing growth in children with 21OHD has been recommended to be used only in experimental settings for children with predicted final height of less than −2.25 S.D [1]. As with 21OHD, in 11βOHD a cautious stance should be emphasized with the primary use of above therapy in research settings only.

### Adrenalectomy

Bilateral adrenalectomy has been proposed as a potentially effective long-term management strategy in patients with suboptimal control and complications of classic 21OHD [198–204]. To date, five case reports of 11βOHD are known where bilateral adrenalectomy has been described as a successful surgical management option in patients with poorly controlled hypertension, end-organ damage secondary to hypertension, hypokalemia and extreme features of hyperandrogenism requiring high doses of glucocorticoid replacement [40, 96, 205, 206]. The long-term follow-up after bilateral adrenalectomy has been reported in one case that was followed until 72 months. There was rapid resolution of hypertension 15 days post operatively. The 11-deoxycortisol levels were high later on during follow-up with normal blood pressure and no clear focus of adrenal rest tissue [206]. Another case similarly reports persistent elevation in 11-deoxycortisol and DOC after bilateral adrenalectomy with normalization of blood pressure within 1 year postoperatively [96]. Due to scarcity of evidence, bilateral adrenalectomy should be offered only in selected cases with careful consideration of risks and benefits.

## Conclusion

CAH due to 11βOHD is a rare disorder with significant challenges in diagnosis and management. Significant phenotypic variability and relatively low prevalence are largely responsible for the delay in diagnosis of 11βOHD. High index of clinical suspicion is required to identify this disorder with clinical clues being features of androgen excess and hypertension at young age. Currently available literature suggests significant adverse cardiovascular events in patients with classic 11βOHD. Though there is little evidence at present, early diagnosis is likely to improve long-term outcomes. Constant clinical surveillance for treatment and disease related complications is of paramount importance. Majority of clinical decisions are currently based on experiences from management of 21OHD (Table 1). Ongoing research is required for better understanding of 11βOHD, its complications and management, preferably in multi-center/multi-national collaborations.

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**Compliance with ethical standards**

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