REVIEW

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Treatment and Follow-up of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency in Childhood and Adolescence

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Abstract

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease caused by the deficiency of one of the enzymes involved in cortisol synthesis. More than 95% of the cases occur as a result of defects in the gene encoding 21-hydroxylase (*CYP21A2*). 21-hydroxylase deficiency has been divided into classical and non-classical forms. In the treatment of classical CAH, it is necessary to replace both glucocorticoid (GC) and mineralocorticoid hormones to prevent salt wasting crisis and reduce excessive corticotropin. In addition to biochemical measurements to evaluate the adequacy of GC and mineralocorticoid treatment; growth rate, body weight, blood pressure and physical examination should be evaluated regularly. There is insufficient data regarding the use of continuous slow-release or modified-release hydrocortisone (HC) preparations and continuous subcutaneous HC infusion, additional/alternative treatment approaches, and cell-based therapies and gene editing technology in children with CAH. GC therapy is recommended in children with inappropriately early onset and rapidly progressing pubarche or accelerated bone age progression, and in adolescents with non-classical CAH (NCCAH) who have overt virilization. In patients with NCCAH, stress doses of HC is recommended for major surgery, trauma, or childbirth but only if the patient has a suboptimal cortisol response to the adrenocorticotropic hormone test. Here, members of the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes' present an evidence-based review with good practice points and recommendations for optimize treatment, and follow-up of children with CAH due to 21-hydroxylase deficiency in the light of the most recent evidence.

Keywords: Congenital adrenal hyperplasia, children, adolescent, 21-hydroxylase deficiency, non-classic congenital adrenal hyperplasia, glucocorticoid replacement treatment

Introduction

21-hydroxylase deficiency has been divided into classical and non-classical forms. The classical form is characterized by absence or severe deficiency in enzyme activity. The most serious form is the classical form of CAH with salt loss and is characterized by adrenal insufficiency with cortisol and aldosterone deficiency and excessive androgen production (1,2). If the disease is not recognized, salt wasting crises (hyponatremia, hyperkalemia, acidosis, hypovolemia and shock) develop in 75% of classic CAH cases in the first three weeks of life. In the simple virilizing form, enzyme activity is at the level of 1-5%, and cortisol deficiency and androgen excess are prominent. Milder forms of the disease are defined as 'late-onset' or 'non-classical' CAH (NCCAH), and partial enzyme deficiencies are compensated by elevations in adrenocorticotropic hormone (ACTH) (1). In non-classic

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CAH, mild subclinical impairment in cortisol synthesis does not usually lead to adrenal crises.

This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for 'Treatment and follow-up of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency in Childhood and Adolescence'. The overall purpose of this evidence-based review is to provide good practice points, with focus on recommendations for daily management.

Treatment of Classical Congenital Adrenal Hyperplasia

Clinical goals are to ensure normal growth, development, and pubertal maturation from birth to adolescence and to prevent adrenal crisis, virilization, and other long-term complications (3).

Glucocorticoid (GC) therapy forms the basis of the treatment for CAH. The aim of treatment is to eliminate the symptoms of deficiency by replacing steroids that cannot be synthesized by the adrenal gland, and to prevent excessive production of adrenal androgens by normalizing ACTH secretion (3). The GC dose required to suppress ACTH secretion in CAH is generally above the physiological dose. However, in primary adrenal insufficiency other than CAH, physiological dose is sufficient. While inadequate treatment causes adrenal crisis, increased virilization, advanced bone age and short adult height; excessive treatment results in inadequate growth, Cushing syndrome, osteoporosis, increased cardiovascular diseases and impaired metabolic control (2,4).

The aim of treatment with GC is to prevent adrenal crisis, prevent hyperandrogenemia, and ensure normal age-appropriate growth and puberty (3,4,5). GC replacement therapy has many challenges. The first is the difficulty of current treatment strategies to mimic the physiological cortisol rhythm, which is high in the morning and low at midnight (6). The second is the difficulty of imitating adaptation to stress (7). A continuous infusion pump that best mimics the physiological rhythm can be used, but the cost of the pump, the difficulty of constantly carrying the pump, the need for training, technical problems and local irritation make its use difficult (2,8,9). The third challenge is the difficulty of suppressing ACTH and controlling high androgen levels with negative feedback. Both overtreatment and undertreatment adversely affect fertility in both sexes (2,3,10).

A good knowledge of the pharmacokinetic and pharmacodynamic properties of GCs is important in evaluating the treatment of individual CAH patients. The first choice GC in growing children is hydrocortisone (HC), a synthetic form of cortisol. Among GCs, HC has a shorter half-life and fewer side effects, such as growth suppression (2,3). Cortisone must be converted to cortisol for its bioactivity, and its use is not recommended because differences in these conversion rates may change drug effectiveness (2,3,11,12,13). Interestingly, HC clearance is 26% lower in the evening than in the morning. Since the absorption and clearance of GCs show individual differences, individuals' GC treatment should be evaluated and titrated at regular intervals. In children, it is recommended to divide the tablets and give them with water or food (14,15). Oral GCs are recommended to be given after a meal to prevent damage to the gastric mucosa.

Suspensions for young children were withdrawn from the market 20 years ago because the active components were not distributed homogeneously throughout the preparation (16). In recent years, 0.5, 1, 2 and 5 mg rapid-release granule formulation preparations of HC (Infacort®/Alkindi®, Diurnal Ltd.) have been approved for use in the European Union and the United States (17,18).

More potent, synthetic, long-acting GCs, such as prednisolone and dexamethasone are not preferred in children due to the severity of side effects (2,3). Long-acting and more powerful GCs are preferred to increase treatment compliance in adolescents who have reached adult height and adults. However, due to their pharmacokinetic properties, the risk of iatrogenic Cushing syndrome is higher in these forms. It has been reported that adult height decreased in adolescents using prednisone (19). HC has mineralocorticoid properties (20 mg HC ~0.1 mg fludrocortisone) and fludrocortisone has GC properties (0.1 mg fludrocortisone ~1-1.5 mg HC) (20).

1) Treatment in Newborn and Early Infancy

There is no single objective parameter for determining the optimal dose of GCs. HC should be given in 3 or 4 divided doses at a supraphysiological dose of 10-15 mg/m^2/day for adequate control of adrenal androgen production in most patients (2,3). There is insufficient data regarding the administration of HC doses predominantly in the morning or evening hours (21,22). Total dosage should be individualized based on adequate monitoring and may need to be increased for short periods in certain situations. Therefore, all children with CAH should be under the follow-up of a pediatric endocrinologist (23). Some clinicians exceed the recommended dose of GCs during the neonatal period to reduce high androgen levels as quickly as possible. If this treatment strategy is implemented, the dose should be rapidly reduced once the target metabolic regulation is

achieved to avoid the adverse effects of high doses of GCs (24). After a few months, maintenance daily totals of about 3 to 4 mg HC divided into three doses (ie, 1-2 mg 3 times daily) are usually sufficient. Infants have low sensitivity to androgens, and completely suppressed adrenal androgens should not be the main target in the first year of life (2,3,14,24)

Mineralocorticoid replacement is provided by fludrocortisone. Subclinical or overt aldosterone deficiency is present in all forms of classical CAH (25). Fludrocortisone is started in all newborns with classical CAH detected in neonatal screening programs before hyponatremia develops (2). There is relative mineralocorticoid resistance in newborns and young infants and antimineralocorticoid effects of 17-hydroxyprogesterone (17-OHP), which increases in this period. Due to these effects, fludrocortisone may be required at doses of 100-200 µg/day, and sometimes higher. However, to avoid iatrogenic hypertension, serum electrolytes, plasma renin, and blood pressure need to be closely monitored and the fludrocortisone dose titrated. Due to lower glomerular filtration rate, immature renal tubules, breast milk intake, and low sodium concentration in infant formula, infants often require supplemental sodium chloride (NaCl) to maintain sodium balance. The recommended daily amount of sodium is 2-4 mmol/kg/day. Salt solution or NaCl tablets containing approximately 1-2 g/day of NaCl (17-34 mmol/day, up to 10 mmol/day of Na) should be given in divided doses (26). NaCl supplementation may not be necessary in patients receiving high doses of fludrocortisone (27). In addition, 0.1 mg of fludrocortisone has the GC potency of approximately 1-1.5 mg of HC, so high fludrocortisone doses may allow for a reduction of the HC dose in young children. Unlike GC therapy, fludrocortisone does not need to be increased in stress situations (2).

2) Treatment During Childhood

Children younger than 18 months should be monitored at least every three months, and older children should be monitored every 4 to 6 months or more frequently after a dose change. The recommended target 17-OHP range should be 100-1200 ng/dL (3-36 nmol/L) when measured in the early morning hours before the drug dose is given, and age-appropriate androstenedione levels should be targeted (13,28). Attempts to normalize 17-OHP levels should be avoided due to the risk of HC overdose causing iatrogenic Cushing syndrome. As prepubertal children normally have low circulating sex steroid levels, adequate androgen suppression is important to achieve normal growth and puberty. To ensure hormonal control in growing children, long-acting GCs should be avoided, except for short periods when HC is not available (2,3). If long-acting GCs are used, care should be taken not to overdose and the dose should be reduced as quickly as possible after hormonal control is achieved (19,29).

After infancy, the need for fludrocortisone in classical CAH is generally 50-200 µg/day. Fludrocortisone half-life is approximately 3.5 hours, biological half-life is 18-36 hours and it is sufficient to give it once a day. However, doses above 0.1 mg can be divided to be given twice daily. In hot and humid weather conditions, some endocrinologists recommend a seasonal increase in fludrocortisone, although increased salt intake may be sufficient. Suspension forms are not recommended. Since daily salt intake through breast milk is insufficient until the first 6-8 months, salt should also be added to the treatment (2). Salt supplementation is generally not required beyond infancy.

3) Treatment During Puberty and Adolescence

During adolescence, hormonal control is often difficult even if the maintenance dose is adequate and treatment compliance is good. During this period, the clearance of HC increases due to the decrease in 11β-hydroxysteroid dehydrogenase type 1 activity (2). Therefore, higher GC doses are required during adolescence (30). Due to the negative effects of high doses on growth during puberty, HC doses above 17 mg/m^2/day are not recommended (28). To achieve treatment goals, treatment should be continued with the lowest effective dose and height should be allowed to increase. In case of completion of growth, long-acting GCs may be considered but are not preferred (31). However, long-acting GCs may be preferable, especially in patients with poor compliance with HC treatment.

Management of CAH during adolescence and the transition from pediatric care to adult healthcare are challenging. Continuous GC and mineralocorticoid administration during the transition from adolescence to adulthood is necessary to prevent morbidity and mortality, especially from adrenal crises (2). Multidisciplinary transition clinics that include pediatric and adult endocrinologists, gynecologists, urologists, and psychologists can promote good medical adherence among adults with CAH (2,3). Changing mineralocorticoid requirements from birth to adolescence should be re-evaluated during adolescence/young adulthood to prevent mineralocorticoid over- and under-intake. Gynecological evaluation should be recommended to all adolescents with CAH during the transition period, especially in cases of menstrual irregularity, planned sexual intercourse or desired pregnancy (2,3,32). After the completion of puberty, boys should undergo scrotal ultrasonography and regular testicular adrenal rest tumor (TART) examination

(33). All patients should be aware of the risk of reduced fertility with poor medical compliance (2,3). Psychosexual and genetic counseling is recommended for the adolescent patient during the transition to adulthood (34).

Good practice points:

1. In classical CAH treatment, it is necessary to replace both GC and mineralocorticoid hormones to prevent salt wasting crisis and reduce excessive corticotropin, which triggers adrenal androgen release (1⊕⊕⊕O).

2. In affected but stable cases in the neonatal period, HC is started at an average dose of 20-30 mg/m^2/day (15-20 mg/m^2/day in those without clinical symptoms). In early infancy, it should be continued at 10-15 mg/m^2/day (in 3 or 4 doses). Fludrocortisone should be given at 100-200 µg/day in 1 or 2 doses. Approximately 1-2 g/day NaCl can be given in divided doses as saline solution or NaCl tablets (1⊕⊕⊕O).

3. In childhood, instead of long-acting GCs, treatment should be continued at a maintenance dose with HC, which has the least negative effects and side effects on growth, and fludrocortisone should be added to the treatment regimen in those with mineralocorticoid deficiency. HC should be given in 3 or 4 divided doses at 10-15 mg/m^2/day for adequate control of adrenal androgen production in most patients. Fludrocortisone 50-200 µg/day should be given in 1 or 2 doses (1⊕⊕⊕O).

4. During puberty, instead of long-acting GCs, maintenance treatment should be performed with HC, which has the least negative effects and side effects on growth. To achieve treatment goals, treatment should be continued with the lowest effective dose and height should be allowed to increase. Fludrocortisone should be added to the treatment regimen in those with mineralocorticoid deficiency. At puberty, HC should be given at 10-15 mg/m^2/day in 3 or 4 divided doses for adequate control of adrenal androgen production in most patients. Long-acting GCs can be given to patients who have completed their growth. Fludrocortisone 50-200 µg/day should be given in 1 or 2 doses (1⊕⊕⊕O).

4) Monitoring

Patients should be monitored regularly with physical examinations that include measurements of height, body weight, and blood pressure. In addition to the symptoms of decrease or increase in growth rate, rapid weight gain, skin and mucosal hyperpigmentation, and virilization in children, particular attention should be paid to signs of central precocious puberty, such as pubic hair growth, apocrine odor development, and breast/testicular enlargement. The presence of salt cravings, unusual fatigue during the day, irregular menstrual cycles in girls, and hyperpigmentation on the skin indicate the necessity of drug titration (2).

Plasma renin activity and renin levels are highly variable, and therefore serum electrolytes should be measured along with ambulatory blood pressure to titrate the mineralocorticoid dose (2,3,35). Although not routine, adrenal-specific metabolites, such as 21-deoxycortisol and 11-oxyandrogens, can also be used in follow-up to evaluate adrenal androgen production in CAH (36,37). Steroids can be measured in blood, urine, saliva, and dried filter paper blood samples and may vary depending on both the circadian rhythm and the time of GC intake (2,3,38,39,40).

Bone age is evaluated by left-hand and wrist roentgenogram in children over two years of age to determine whether rapid progression is occurring as a result of exposure to excessive adrenal androgens. Since increased adrenal androgens may activate the hypothalamic-pituitary-gonadal axis, signs of early puberty should be monitored (testicular enlargement in boys, breast enlargement in girls). Clinical features are also important in adjusting HC and fludrocortisone doses and should not be based solely on laboratory data. Patients should be monitored for reproductive complications, especially decreased fertility in women and TART in men (2).

Good practice points:

1. In patients with CAH, close monitoring should be performed in the first 3 months of life, evaluation should be made every 3 months between 3-18 months, and every 4 months after 18 months. In addition to biochemical measurements to evaluate the adequacy of GC and mineralocorticoid treatment, growth rate, body weight, blood pressure and physical examination should be evaluated regularly, and cases should be monitored for central precocious puberty that may develop (1⊕⊕OO).

2. In patients with CAH over two years of age, bone age should be assessed annually until adult height is reached (ungraded good practice statement).

3. Evaluation of bone age is especially important in patients with inadequate growth rate or suspected puberty precocity (ungraded good practice statement).

5) Modified Glucocorticoid Preparations

Sustained slow-release HC preparations have been developed as an alternative to longer-acting synthetic GCs, such as prednisone/prednisolone or dexamethasone.

Plenadren (Shire Services BVBA, Belgium), a modified HC formulation, is approved in Europe for the treatment of adrenal insufficiency in adults. Plenadren is a modified HC formulation characterized by a dual-release mechanism, wherein the core of the formulation provides a delayed release of HC, while the peripheral components allow for rapid release. It has been shown that when given once a day to patients with primary adrenal insufficiency, it significantly improves metabolic variables such as body weight, body mass index and HbA1c compared to conventional HC replacement (41,42). However, data on its use in patients with CAH are lacking. Clinical experience shows that once-daily HC treatment cannot achieve a sufficient increase in morning cortisol value and adequate suppression of ACTH and androgens, thus requiring an additional dose of GC in the evening (43,44). Plenadren is a treatment that has not yet been approved for use in the treatment of CAH in children. Another modified-release preparation (Chronocort, brand name Efmody, Diurnal, UK) continues to be studied for the treatment of CAH. This preparation has a delayed effect, beginning four hours after intake, and a continuous effect (45). When administered at 23:00 at night, the cortisol level, which rises throughout the night due to delayed release, peaks in the morning, and when a second dose is administered in the morning (07:00), the cortisol need during the day is met (45,46). Chronocort received marketing authorisation in the UK and Europe in 2021 for CAH patients aged 12 years and older. The long-term safety extension phase of Chronocort is ongoing and additional studies are planned in the USA (2,47).

Continuous subcutaneous administration of HC mimics physiological cortisol release. It is especially useful in patients with rapid cortisol metabolism or impaired intestinal absorption, but this approach is not as practical as oral medications. A better cortisol release is achieved with continuous subcutaneous HC infusion via pump and has been reported to be superior in reducing serum androgen levels in CAH (48). Pump HC treatment is seen as a limited treatment option in patients with complete GC deficiency due to the complexity of device use, cost, need for family-patient education, local sensitivity problem, necessity of constantly carrying the device and risk of malfunction. However, in the long term, it is hoped that extended-release formulae or pumps will improve the quality of life compared to standard treatment (2,3,8,9,49).

6) Alternative Treatment Approaches

Treatment goals for classical CAH include both hormonal replacement and reducing adrenal androgen production. Drugs that reduce androgen production and/or effects can be added to physiological GC therapy. Adjuvant treatments for the control of hyperandrogenism in CAH are under investiagtion. The combination of testolactone (aromatase inhibitor) and flutamide (androgen receptor antagonist) with 8 mg/m^2/day HC normalized growth and bone maturation in a 2-year randomized study of 28 children (50). In various studies, it has been reported that letrozole and anastrozole treatment, which are selective aromatase inhibitors, are effective in correcting adult height calculated according to bone age in CAH (51,52).

Abiraterone acetate is a potent CYP17A1 inhibitor used in the treatment of prostate cancer and is considered a promising alternative treatment by reducing the need for exogenous GCs at supraphysiological doses (53). Abiraterone acetate therapy may cause 11-deoxycorticosterone (DOC) accumulation via CYP21A2-mediated 21-hydroxylation of intra-adrenal progesterone, resulting in hypertension and/or hypokalemia in patients with prostate cancer. However, this transformation does not occur in patients with classic CAH. Abiraterone acetate is likely to be useful in prepubertal children with classical CAH to suppress androgens and estrogens until normal pubertal age, and a phase 1 trial testing this approach is ongoing (NCT02574910). Abiraterone acetate monotherapy, unless combined with GC therapy or a mineralocorticoid receptor antagonist, may cause DOC accumulation in patients with NCCAH. Furthermore, its use in teenage girls will require estrogen therapy with oral contraceptives (OCs) (2,54). Since it does not reduce ACTH levels and inhibits gonadal sex steroid production, its use is restricted in men with TARTs and in cases with fertility desire (55,56). Third-generation antiandrogens, such as enzalutamide, apalutamide, and darolutamide have not been tested in CAH patients (2,54).

One of the possible treatment approaches is the suppression of ACTH-mediated androgen production. Binding of corticotropin releasing hormone (CRH) to the type 1 receptor (CRHR1) stimulates ACTH secretion by increasing intracellular cAMP in corticotrophs. This is one of the new treatment options. In a study involving eight women with CAH who were given a single dose of 300 or 600 mg of CRHR1 antagonist, significant decreases in ACTH and 17-OHP were demonstrated compared to a control period with GC therapy (57). Theoretically, an anti-ACTH antibody or melanocortin type 2 receptor antagonist could also reduce adrenal androgen synthesis in patients with classical CAH, but these approaches have only been tested in preclinical models and their long-term effects are unknown. It should be kept in mind that most of these approaches do not eliminate the need for treatment and monitoring with GC replacement, even at lower doses (2,58,59,60).

Unilateral or bilateral adrenalectomy has been suggested as an approach in the long-term treatment of classical CAH to limit adrenal androgens (2,61). In a recent meta-analysis of 48 cases of CAH, 34 (71%) described symptomatic improvement after bilateral adrenalectomy. However, short-term adverse outcomes were reported in five cases (10%) and long-term adverse outcomes in thirteen cases (27%), including an increased risk of adrenal crisis (62). The development of adrenal rest tumors due to high ACTH levels has been reported, even in women (63). This adrenalectomy approach has currently fallen out of favor (3). Adrenolytic therapy with mitotane has been reported as an approach to restoring fertility in men with TARTs, but long-term results have not been published (2,3,64). Therefore, current data do not recommend the "medical adrenalectomy" approach.

7) Gonadotropin-releasing Hormone Analogue and Growth Hormone Therapy in CAH

In a meta-analysis that included 35 observational studies with methodological limitations and very low-quality evidence, it was reported that the adult height of patients with CAH was -1.05 standard deviation score (SDS) behind the target height (65). Similarly, individuals with NCCAH may be at risk of short adult height, but short stature is less severe than in classical CAH. In a non-randomized study, it was reported that growth rate and height z score increased with the use of growth hormone alone (n = 12) or in combination with gonadotropin-releasing hormone analogue (GnRHa) in children with CAH (66). In another study, fourteen patients treated with growth hormone and GnRHa for 4 years showed improvement in adult height (+1.1 SDS) compared to historical controls with CAH treated with conventional therapy alone (67). Individuals with CAH can reach normal adult height with the use of standard GC and mineralocorticoid treatments at appropriate doses, and height-enhancing drugs can only be considered for individuals whose height is, or is expected to be, significantly shorter than that of their peers (2,68).

8) Cell and Gene-based Treatments in Classic Congenital Adrenal Hyperplasia

Potential cell-based therapies have been studied in recent years. Somatic cells can be induced to differentiate into an embryonic stem cell-like phenotype by forcing the expression of specific transcription factors. Adrenocortical-like cells have been generated from skin, blood, and urine cells in humans using steroidogenic factor-1 expression, protein kinase A, and activation of the GnRH pathway (65). These reprogrammed cells exhibited ultrastructural properties similar to steroid-secreting cells and secreted steroid hormones in response to physiological (such as ACTH) and pharmacological stimuli, as well as expressing *de novo* steroidogenic enzymes. In the future, gene editing may be applied to reprogrammed cells obtained from patients to achieve normal steroidogenesis (2,69). Gene therapy using adeno-associated viruses has been used in an animal model of 21-hydroxylase deficiency. Intra-adrenal injection of viruses carrying the human *CYP21A2* gene reversed the CAH-like phenotype for 40 days (70,71).

Good practice points:

1. There is not enough data regarding the use of continuous slow-release or modified-release HC preparations and continuous subcutaneous HC infusion in children with CAH (2⊕⊕OO).

2. Although it is recommended not to use experimental treatment approaches in CAH patients, additional/alternative treatment approaches may be considered in those whose adrenal androgen production is not sufficiently suppressed (ungraded good practice statement).

3. In CAH, GnRHa should be considered in selected cases (those with advanced bone maturation or early puberty problems). It is not recommended to give additional growth hormone therapy (2⊕OOO).

4. Cell-based therapies and gene editing technology in CAH may offer new options for disease cure or treatment, but future data on their use are expected to become clearer (ungraded good practice statement).

Treatment of Non-classical Congenital Adrenal Hyperplasia

It has been shown that patients who are diagnosed with NCCAH and left untreated, may enter puberty earlier than the population average age, and this may negatively affect final height, resulting in short stature. Therefore, it has been stated that early diagnosis and treatment initiation may improve final height (72,73,74). In a previous study, it was reported that puberty and growth spurt occurred an average of 2.3 years earlier in the group of patients with untreated NCCAH (75). In another study, it was reported that patients with advanced bone age at diagnosis were significantly shorter than others. In the same study, individuals who were compound heterozygous for both the mild and severe alleles were shown to have significantly shorter final heights (76).

In individuals with asymptomatic NCCAH, treatment is not recommended (77,78). In cases of inappropriately early onset of body hair growth and body odor in children, treatment is recommended only if bone maturation has accelerated enough (two or more years advanced) to negatively affect final height. In the presence of premature

pubarche without advanced bone age, clinicians may opt for careful monitoring without treatment. In adolescents with menstrual irregularities and acne, symptoms usually improve within three months after GC therapy, whereas resolution of hirsutism is more difficult to achieve with GC monotherapy. As in other androgenic disorders, the use of OCs alone or in combination with anti-androgens appears to be the best approach to treating hirsutism in women with NCCAH (79,80,81,82). In patients with NCCAH, in whom treatment has already been initiated, discontinuation of GC therapy should be planned once they have reached final adult height or other symptoms have resolved (3).

In adolescent girls and adult women presenting with signs of hyperandrogenism, such as acne or hirsutism, therapy with estrogen and progesterone-containing OCs is the treatment of choice. Women who will receive OC therapy should be informed that hirsutism will begin to improve only after 6-12 months and that hair removal methods such as epilation or electrolysis may be used during this period (80). If OCs alone are not successful, anti-androgenic agents may be added. However, this treatment should never be used in women of reproductive age who are not receiving safe contraceptive treatment as it has negative effects on the development of the external genitalia of the male fetus during the intra-uterine period. Spironolactone is a mineralocorticoid antagonist that also has anti-androgenic effects (83). Other treatments for hirsutism include finasteride, a progesterone derivative that competes with DHT to bind to the androgen receptor, the 5α-reductase inhibitors, or cyproterone acetate. Flutamide, a nonsteroidal androgen receptor antagonist, is not recommended due to hepatotoxicity. Both spironolactone and finasteride have similar efficacy in improving hirsutism (72). GCs form the basis of androgen deprivation therapy only in classical CAH. Although GCs have been shown to be more effective than OCs or anti-androgens in suppressing serum adrenal androgen concentrations in women with NCCAH, they have been found to be less effective in improving hirsutism and have a greater risk of toxicity (81,84). Therefore, GCs are only used to manage hirsutism in female patients with NCCAH, when intolerance to OCs and/or anti-androgens develops (72).

Monitoring the Treatment of NCCAH

Due to the lack of reliable tests, monitoring the treatment of patients with NCCAH relies mostly on clinical assessment. Elevated testosterone and androstenedione levels need to be normalized, while 17-OHP levels may be allowed to increase as normalization of 17-OHP typically indicates GC overtreatment (72).

The first treatment option in women with NCCAH who have irregular or anovulatory cycles and want to get pregnant is the use of GCs. When pregnancy cannot be achieved with GC therapy, ovulation induction with clomiphene citrate and other reproductive endocrinological methods are recommended (85,86). If a woman with NCCAH conceives while not receiving GC therapy, she does not need to be treated during pregnancy. There are limited data on whether GC therapy reduces the risk of miscarriages in women with NCCAH (86). Therefore, women with subfertility may benefit from GC therapy to conceive and maintain pregnancy. HC, prednisone and prednisolone are safe to use in women who are planning pregnancy. However, the use of dexamethasone, which is not inactivated by the placenta, is not recommended during pregnancy, as it suppresses the fetal hypothalamic-pituitary-adrenal axis and growth. Maternal 17-OHP and androstenedione levels are elevated during pregnancy and should not be used as biomarkers of CAH control. Therefore, pregnant women should be monitored clinically. Guidelines are insufficient in terms of the optimal management of patients with NCCAH during pregnancy. In some practices, low-dose GC therapy is continued during pregnancy if the patient has been receiving GC therapy before conception, while in other practices, GC therapy is discontinued once pregnancy is confirmed or after the first trimester (3).

Available data show that TARTs are extremely rare in men with NCCAH (87). Therefore, GC prophylaxis therapy is not recommended in men.

There is no evidence of clinically significant cortisol deficiency or adrenal crisis in NCCAH. Some individuals with NCCAH (60 % in a small study) have shown inadequate response to the ACTH stimulation test (stimulated cortisol level less than 500 nmol/L), but overt episodes of adrenal insufficiency have not been observed (82,88,89). GC therapy may be recommended for severe illness in individuals with previously untreated NCCAH, who have a subnormal cortisol response to the diagnostic ACTH test. However, it should be taken into consideration that when daily GC therapy is initiated, the hypothalamic-pituitary-adrenal axis will be suppressed and the risk of adrenal crisis will increase in cases of severe stress. Therefore, it is extremely important to inform the patients and their families about treatment and stress dosing (74).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (90).

Good practice points:

1. GC therapy is recommended in children with inappropriately early onset and rapidly progressive pubarche or accelerated bone age progression, and in adolescents with NCCAH who have overt virilization (2⊕⊕OO). However, the family of the patient should be adequately informed considering the risks and benefits of GC therapy.

2. In patients with NCCAH, in whom treatment has already been initiated, discontinuation of GC therapy should be planned once they have reached final adult height or other symptoms have resolved (2⊕⊕⊕O).

3. GC therapy is not recommended in most adult men with NCCAH (2⊕OOO).

4. In non-pregnant women with NCCAH, who are asymptomatic, therapyi is not necessary (1⊕⊕⊕O).

5. Treatment of women with NCCAH, who show signs of hyperandrogenism and are not planning pregnancy, is similar to treatment of those with polycystic ovary syndrome and includes OCs and/or anti-androgen therapy. However, infertility treatment in women with NCCAH is initiated with GCs. In infertile women with NCCAH low-dose GCs can induce ovulation and lead to pregnancy (1⊕⊕⊕O).

6. In patients with NCCAH, stress doses of HC are given for major surgery, trauma, or childbirth only if the patient has a suboptimal (14-18 mg/dL, 400-500 nmol/L) cortisol response to the ACTH test (2⊕OOO).

Footnotes

Authorship Contributions

Surgical and Medical Practices: Havva Nur Peltek Kendirci, Zeynep Şıklar, Concept: Havva Nur Peltek Kendirci, Zeynep Şıklar, Design: Havva Nur Peltek Kendirci, Zeynep Şıklar, Data Collection or Processing: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar, Analysis or Interpretation: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar, Literature Search: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar, Writing: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar.

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