MANAGEMENT OF ENDOCRINE DISEASE

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: update on the management of adult patients and prenatal treatment

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Abstract

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is characterized by cortisol and in some cases aldosterone deficiency associated with androgen excess. Goals of treatment are to replace deficient hormones and control androgen excess, while avoiding the adverse effects of exogenous glucocorticoid. Over the last 5 years, cohorts of adults with CAH due to 21-hydroxylase deficiency from Europe and the United States have been described, allowing us to have a better knowledge of long-term complications of the disease and its treatment. Patients with CAH have increased mortality, morbidity and risk for infertility and metabolic disorders. These comorbidities are due in part to the drawbacks of the currently available glucocorticoid therapy. Consequently, novel therapies are being developed and studied in an attempt to improve patient outcomes. New management strategies in the care of pregnancies at risk for congenital adrenal hyperplasia using fetal sex determination and dexamethasone have also been described, but remain a subject of debate. We focused the present overview on the data published in the last 5 years, concentrating on studies dealing with cardiovascular risk, fertility, treatment and prenatal management in adults with classic CAH to provide the reader with an updated review on this rapidly evolving field of knowledge.

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Introduction

Congenital adrenal hyperplasia (CAH, MIM 201910) corresponds to a group of inherited autosomal recessive disorders that arise from defective steroidogenesis and results from a deficiency in one or several of the enzymes of cortisol biosynthesis.

Deficiency of the 21-hydroxylase enzyme is the most common form of CAH, accounting for more than 95% of the cases and is one of the most commonly known autosomal recessive disorders. CAH due to 21-hydroxylase deficiency (21OHD) is the result of deletions or deleterious mutations in the active gene CYP21A2 (1). There are many mutations of the CYP21A2 gene identified so far, which are the causes of varying degrees of impairment of 21-hydroxylase activity (2). Most patients are compound heterozygotes. The clinical phenotype, related to the less-severe mutated allele, is classified as classic for the severe form, or non-classic (NC). Classic CAH encompasses salt-wasting (SW) or simple virilizing (SV) forms, depending on the degree of aldosterone deficiency. Hormonal treatment is based on cortisol and, when necessary, aldosterone substitution. Its role is to reduce the excessive ACTH production and consequently the increased androgen production by the adrenal gland, to ensure normal fertility, and to avoid the long-term consequences of glucocorticoid (GC) use. The physiological circadian rhythm of cortisol cannot be mimicked with oral GC, and the doses needed to suppress the androgens are usually higher than those needed for substitution (1, 2, 3).

In this review, we decided to focus on the new findings published on CAH over the last 5 years. An exhaustive PubMed research has been performed with the terms ‘congenital adrenal hyperplasia’ and ‘21-hydroxylase deficiency’. For space constraints, we excluded all the data that were dealing with non-classic CAH and childhood outcomes of CAH, to focus on studies dealing with classic CAH in adults or prenatal management. We also chose to go further into four themes: cardiovascular risk, fertility, treatment and prenatal management as most of the recent publications concern those topics.

Cardiovascular (CV) risk

Cohorts of adults with CAH due to 21OHD from Europe (4, 5, 6) and the United States (7) have been described in the recent years. They have shown an increased risk for metabolic disorders in adults (1, 3, 8, 9). Overweight and obesity have been reported in adult patients with CAH. In the prospective cross-sectional study conducted in the United Kingdom (UK) among 199 patients, BMI was found to be higher in CAH patients than that in the general population of the Health Survey for England data (4). In the American cross-sectional study of 244 CAH patients, prevalence of obesity (one-third of patients across phenotypes) was similar to the adult U.S. obesity rate of 36% (7). In two French cohorts of respectively 108 and 219 patients, the prevalence of obesity and overweight in CAH patients was similar to that found in the general population in the latest nationwide survey (5, 10). More recently, repartition of adipose tissue was precisely studied in CAH adolescents and young adults (11). Increased abdominal adiposity, with a higher proportion of proinflammatory visceral adipose tissue compared to subcutaneous adipose tissue was present in CAH patients compared to age-, sex- and BMI-matched controls. Metabolic syndrome was also evaluated in CAH patients and was observed in nearly 20% of adults in the NIH cohort (7). It was associated with older age, whereas no association was found with androgens, GC type or dose (7). In a Brazilian cohort of young CAH patients, there was a higher prevalence of metabolic syndrome, which was associated to family history of metabolic syndrome (12). As these studies were cross-sectional, it would be interesting to follow-up the patients longitudinally to perform an association analysis of glucocorticoid, androgen exposure, BMI and visceral fat.

Blood pressure (BP) control in children and adult CAH patients has been investigated by several independent groups, with some studies reporting normal resting (13, 14, 15, 16) and 24-hour BP profile (17) and others reporting a slight increase of either diurnal or both diurnal and nocturnal SBP, compared to matched controls (4, 18, 19, 20, 21, 22, 23). These differences may be influenced by the methods for recording blood pressure. There are minimal data available on the prevalence of hypertension in adult patients with CAH (24). In a recent epidemiological Swedish registry study, increased frequency of hypertension in individuals with CAH has been shown, but when analyzing the different subgroups, only SV females had increased blood pressure, whereas this was rare or nonexistent in the more severe phenotypes and genotypes (6). This was in accordance with a recent study showing that adult males with classic CAH have a rather low BP compared with healthy men (10). Dyslipidemia in individuals with CAH has been...
reported in some studies. In the epidemiological Swedish registry study, an increased rate of dyslipidemia was found, especially in males with a null genotype (6). In the NIH cohort, approximately 10% of both classic and NC adult patients had decreased HDL. In adults, 6% had elevated total cholesterol, whereas approximately 15% had decreased HDL (7).

In this intricate scenario, it is reasonable to expect a high CV risk profile in CAH patients. However, the impact of these risk factors on the vascular system has never been systematically ascertainment. Cardiovascular morbidity and mortality are not easy to bring out in this population, as very few of the studied patients are aged older than 50 years. Carotid intima-media thickness (cIMT) is a well-established marker of early, subclinical atherosclerotic change, that is correlated to the risk for coronary artery disease and stroke (25). However, cIMT results vary in existing studies of individuals with CAH (12, 26, 27, 28, 29). Adults with CAH have been found to have increased cIMT in one study (15). There was no correlation between cIMT and cumulative GC doses or androgen levels. Further studies in children or adolescent CAH patients showed normal cIMT compared to a BMI-matched cohort (12, 26) or increased cIMT compared to controls, but found it linked to higher BMI and unfavorable metabolic parameters (27, 28, 29). These variations between studies may be due to differences in measures and in study design. Other surrogate markers of endothelial or cardiac dysfunction have been studied. Children with CAH have been shown to have significant vascular endothelial and smooth muscle dysfunctions, at a level comparable to the subjects with mild-to-moderate obesity (12). In adolescent and adult CAH patients, normal left ventricular morphology has been reported (13, 16), but mild diastolic dysfunction and impaired exercise performance were shown. Recently, we reported the complex interactions between gonadotropins and steroid hormones on the duration of ventricular repolarization. We found that CAH QT interval duration was shorter in women with CAH than that in control women (30). These findings and their clinical impact have to be further examined. The association between endothelial dysfunction, cIMT progression, hormonal imbalance, treatment of CAH and CV events, will be important to figure out in this at-risk cohort.

The rate of CV events among adults with CAH is beginning to be characterized (6). The long-term outcomes in CAH patients were studied using the Swedish national CAH registry. Five hundred eighty-eight patients (335 females and 253 males) were compared with 100 controls per patient, matched for sex, year and place of birth (31). Information on mortality, cause of death, morbidity and mortality was derived through linkage of national population-based registers. The mean age of death was lower in CAH patients (41.2 ± 26.9 vs 47.7 ± 27.7 years (P<0.001)). The hazard ratio of death was 2.3 (1.2–4.3) in males and 3.5 (2.0–6.0) in females. The causes of death were adrenal crisis (42%), cardiovascular diseases (32%), cancer (16%) and suicide (10%).

Interestingly, the same team analyzed CV and metabolic morbidity in CAH patients (6). This study showed an increase in both CV and metabolic disorders (OR (odds ratio): 3.9; 95% CI (confidence interval): 3.1–5.0) and CV disease (OR: 2.7; 95% CI: 1.9–3.9), with some subgroups being more affected than others (females, specifically I172N and NC and males in the null genotype group). Separate analyses of the individual diseases showed higher frequencies of hypertension, dyslipidemia and atrial fibrillation in CAH patients (6). Obesity was consistently increased in all subgroups. However, the non-obese patients with CAH were similarly affected as the entire CAH cohort. There was also an increased frequency of obstructive sleep apnea in this CAH cohort. Similarly, the frequency of diabetes was increased, especially in females with SV (I172N genotype) or NC phenotype. Increased frequency of venous thromboembolic events was also reported. This should be further studied to determine if, as reported in both Cushing’s syndrome and GC use, there is a higher risk of venous thromboembolism due to a state of hypercoagulability that should lead to more frequent use of thrombosis prophylaxis in this population.

CAH is therefore associated with higher CV risk factors and probably with excess CV and metabolic morbidity. Some subgroups of patients seem to be more affected. Regular follow-up is needed, along with lifestyle interventions, to limit the onset of weight gain and obesity, to screen for diabetes, other metabolic disorders and CV risk factors. Close monitoring of GC doses is important. Further studies on larger cohorts are necessary to better clarify the mechanisms leading to metabolic and CV abnormalities and to precise the respective roles of androgen and lifelong GC treatment, as well as the impact of new findings, such as GC receptor gene polymorphisms, which have recently been shown to be associated with an adverse metabolic profile (32).
Female fertility

Fertility in women with classic CAH is reduced, especially for the patients with the SW form, as a result of several issues such as biological (poor hormonal balance), mechanical (related to surgeries), psychological and sexual factors (33, 34).

Menstrual irregularities and anovulation are frequent in CAH women, affecting from 30% to 68% of women with the SW form and 30–75% of those with the SV form (4). Menstrual cycle control represents therefore an important therapeutic target in these patients. Several factors (androgen and progesterone overproduction and prenatal exposure to sexual steroid) are suspected to disturb the reproductive axis in CAH females. A recent study has described LH pulsatility in women with classic CAH (35). No differences have been observed between patients and controls in terms of mean LH levels, LH pulse amplitude or LH frequency. In CAH patients, 2 different profiles of LH pulsatility were recorded. One group of patients had LH pulsatility patterns similar to the controls. The other one had lower LH pulses amplitude and frequency and presented more frequently with menstrual cycle disturbances, higher 17OHP progesterone (17OHP), testosterone, progesterone and androstenedione levels and lower FSH levels. This study has suggested the absence of a neonatal programming of a disrupted gonadotropic axis and has shown that CAH adult women may have a normal LH pulsatility and secretion and that hormonal control is a key factor. Optimized GC and mineralocorticoid (MC) regimens during fertility monitoring should thus be an important concern in CAH women, and in particular, suppression of serum progesterone concentrations, that are probably responsible for reduced LH pulsatility during the follicular phase of the menstrual cycle.

The consequences of the genital surgery are another factor implicated in the reduced fertility of CAH women. Surgery can include clitoroplasty, vaginoplasty and labiaplasty (36). Thanks to a detailed assessment of current surgery practice, during a limited period of 4-years, a recent American study has shown that the feminizing genitoplasty in infants with CAH continues to be performed and that approximately in 90% of the case it includes a vaginoplasty as a portion of the procedure (37). It was also found that combined vaginoplasty and clitoroplasty is the most common procedure performed in infancy and early childhood and appears to be primarily restricted to this age range despite controversy regarding the optimal timing of vaginoplasty. Second and third procedures were performed later in childhood or adolescence and about 2/3 were performed by experimented surgeons. Urinary incontinence, vaginal stenosis and inadequate introitus, poor cosmetics, anorgasmia and painful intercourse have been reported and currently remain relevant issues (36, 38). It is well established that there is a relationship between sexual activity and vaginal function; thus, genital surgery may result in sexual dissatisfaction. Surgical techniques for genital feminization in female CAH patients have evolved significantly over time. There are nowadays new surgical procedures that, for instance, preserve innervation and clitoral sensation to conserve erotic sensitivity and orgasmic capacity secondary to the clitoroplasty (39) and improved vaginoplasty techniques (40). Moreover, to date, the choice of the timing of the surgery (early or late surgery) remains therefore a matter of debate (41). Unfortunately, there are few data in the literature about the outcomes of this surgery in terms of sexual function, and the outcomes of the current techniques will take time to emerge. In a cohort study of 138 CAH patients, Arlt et al. have shown that 92 women had undergone genital reconstruction, 43% of whom had more than one surgery and 23% during adulthood (4). Among these patients, 46% have stated being unhappy about their sexual life. In a more recent review including 151 patients with genitoplasty, assessments of cosmetic results have shown that the majority of patients (between 60 and 94%) reported good or excellent outcomes (36). When the physician was the person who assessed the cosmetic outcomes, 59–94% reported satisfactory results (36). Fertility rate, i.e. live births per woman, is significantly lower in CAH women than in the general female population (42). On the other hand, pregnancy estimates are more encouraging when examined only in the patients actively trying to conceive (43). In a UK cohort of 103 CAH women among whom 25% wanted to conceive, the pregnancy estimate was 54% (4). Pregnancies were most often spontaneous, obtained after a good hormonal control with optimized GC and MC regimens. Recently, a large population-based epidemiological study on psychosocial outcomes in CAH patients was conducted in Sweden. Five hundred and eighty-eight CAH patients including 253 women were compared to the general population (44). Women with the SW form were less often married (OR: 0.5 (0.2–1.1)) and had fewer partnerships compared with controls. CAH patients were less likely to have biological children than controls (OR: 0.3 (0.2–0.3)) and when assessing women with the SW and SV forms,
it was still significantly decreased (SW OR: 0.05 (0.0–0.1); SV OR: 0.4 (0.2–0.7)). Better fertility and fecundity in CAH women will be largely dependent on surgical advances in genital reconstruction, earlier treatment, optimized compliance to therapy, availability of psychological support, organization of transition from pediatric to adult specialist care, procurement of menstrual cycle control and sexual well-being.

**Male fertility**

Male patients with CAH may present impaired gonadic function and infertility. It appears that adult males with CAH face a dual problem. Adrenal steroid overproduction, especially androgen and progesterone, might interfere with FSH and LH production, resulting in gonadotropic deficiency. In addition, testicular adrenal rest tumors (TARTs) may become hypertrophic under chronic ACTH stimulation and influence both endocrine and exocrine testicular functions (45). TARTs have been identified with a prevalence of 30–95% depending on age and modality of diagnosis, i.e. palpation or ultrasound (10, 46). The prevalence of TARTs increases with age, after onset of puberty (47, 48). TARTs volume and prevalence seem higher in patients with SW form compared with those in the SV form (46, 49, 50). Some studies report the development of TARTs despite good hormonal control, suggesting that undertreatment is not the only cause for their growth (51, 52). Indeed, a recent study about molecular characterization of TARTs has shown that these tumors have multiple steroidogenic properties, including the expression of adrenal cortex and typical Leydig cell markers (53).

TARTs are most often responsible for impaired spermatogenesis. In patients with and without TARTs, inhibin B levels differ significantly and there are higher total sperm counts and concentration in patients without TARTs (10). In a large cohort of 164 male CAH patients who underwent testicular assessment with ultrasound, 71 had a sperm analysis. Seventy percent of the patients had severe oligospermia or azoospermia when TARTs were found versus only 3.6% when they were not (10). Because of their central localization near the rete testis, TARTs can lead to compression of the seminiferous tubules that may finally lead to obstructive azoospermia and irreversible damage of the surrounding testicular tissue (49). They also can destroy and replace healthy testicular tissue. The profile of the gonadotropic-testicular axis in these patients will primarily show testicular failure and eventually reveal endocrine and exocrine testicular dysfunctions (54).

Treatment options for male patients with TARTs are still limited and mainly based on a good hormonal control with GC (50). However, in some patients, treatment is poorly tolerated, and the medical response is disappointing. Surgery can be proposed but there are no data on fertility preservation. Recently, Bry-Gaillard et al. have shown that mitotane could restore fertility in CAH patients with TARTs (54). After 8 months of treatment, gonadotropins levels, inhibin B and sperm counts have improved, and on the other hand, size of TARTs has shrunk. Prevention has a real important place in the management of male CAH fertility. A systematic ultrasound evaluation is recommended at puberty to detect lesions at an early stage. A semen analysis should also be realized as soon as possible, and the question of systematic sperm cryopreservation seems fully justified (55).

Reduced fertility in CAH men can also be secondary to hypogonadotropic hypogonadism due to poor hormonal control with increased adrenal androgens and progesterone, leading to an increase in estrogen levels by aromatization. A recent case report has demonstrated the restoration of fertility by gonadotropin replacement in a CAH man (56). The patient had hypogonadotropic azoospermia and TARTs due to untreated SV form. A treatment with gonadotropin replacement permitted to obtain after 21 months a stable low sperm concentration with good sperm motility, enabling the couple to have a healthy girl.

Besides these somatic causes of impaired fertility in CAH males, there might be aspects of psychosocial adaptation and sexual well-being. Very few data have been reported on sexual satisfaction in CAH males. Two recent studies have shown that fewer CAH patients than controls had an active sexual life and that they had fewer lifetime partners (57, 58). In a Swedish cohort of 30 CAH males, erectile dysfunction was found in about half of these patients (58) as was described in the study from Dudzinska et al. (59). A sexual well-being study of 20 CAH males has revealed impairments in sexual drive, erections and ejaculations (59). Poor control disease was associated with a reduced sexual drive. However, in the recent Swedish follow-up study described previously, although the reason is unknown, men were more often married than controls (OR 1.6 (1.0–2.5)) but, as the CAH women, they had less biological children than controls (OR 0.4 (0.2–0.6)) (44). Further studies are needed to properly assess these psychosocial outcomes, to improve the care given to the patients.
Treatment of classic CAH in adults

Treatment in classic 21OHD is necessary to compensate for GC and MC deficiencies and also to correct adrenal androgen excess. Ideally, the treatment should be monitored to avoid iatrogenic comorbidities and to enable a good quality of life (60). However, this goal is not reached up to now as increased comorbidities and mortality are reported in patients with CAH.

GC substitution is available since the 50s. Although this treatment has notably changed the prognosis of children with CAH, it has remained the only medical solution for the last decades and has failed to meet all the needs for the patient. Indeed, contrarily to primary adrenal insufficiency, the aim of GC treatment is not only to compensate for the deficient hormone but also to blunt the nocturnal ACTH secretion, which is the major driver of adrenal androgen production. As cortisol is secreted mainly in the morning and, reaches a peak between 06:00 and 08:00h, most oral GC regimens are proposed with at least half or 2/3 of the global dose in the morning. Up until now, whatever regimen was used, the dilemma has persisted between using the physiological hydrocortisone (HC), well tolerated but with a poor control of androgen secretion or the long-acting prednisone, prednisolone or dexamethasone (DEX), with a higher risk of side effects. Unfortunately, an adequate androgen secretion is difficult to achieve without a high dose of GC, therefore leading to side effects in relation to hypercorticism. Recently, a new slow-release HC formula (Plenadren) has become available and another one (Chronocort) is currently under investigation. In addition, besides the GC approach, non-GC approaches are under current development, such as the use of molecules interfering with CRH function and non-selective adrenal steroidogenesis blockade (61) (Fig. 1).

New glucocorticoid approaches

Treatment of classic CAH adults

The first molecule is a dual-release HC, which was developed for once-daily morning administration in patients with primary adrenal insufficiency (Plenadren(R), ViroPharma-Shire) (62). It is a modified-release HC with an outer coating layer that provides an immediate release of the drug and an extended-release core. It provides a more extended serum profile of cortisol compared with immediate-release HC. In adults, a single morning dose of Plenadren gives similar cortisol exposure to a thrice-daily regimen of immediate-release HC. Preliminary studies in patients with primary adrenal insufficiency and CAH have demonstrated that this new formula compared with HC regimen, improves body weight, systolic and diastolic blood pressure and glucose metabolism (63, 64). This molecule also provides a more circadian-based serum cortisol profile in patients with primary adrenal insufficiency. Unfortunately, there are no data currently available regarding hormonal control in patients with CAH. However, in the latter case, this molecule is unlikely to control excess androgens as the overnight rise in cortisol is not replicated, and evening administration of Plenadren would expose patients to high levels of cortisol during the night.

The second molecule, Chronocort(R), is under current development by Diurnal (Cardiff, UK) (65). This molecule is a modified-release HC, but it differs from Plenadren by having a delayed and sustained absorption profile rather than an immediate- and sustained-release profile. Chronocort aims at replacing physiological cortisol concentrations by dosing at morning and

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**Figure 1**

Potential therapeutic targets in congenital adrenal hyperplasia. 3βHSD2, 3-hydroxysteroid dehydrogenase type 2; ACTH, adrenocorticotropic hormone; AR, androgen receptor; CRH, corticotropin-releasing hormone; CSHI, continuous subcutaneous hydrocortisone infusion; CYP11A1, cholesterol side chain cleavage enzyme; CYP17A1, 17α hydroxylase/17,20 lyase; GC, glucocorticoids.
night such that the night dose provides release of HC in the early hours of the morning providing a pre-waking rise in cortisol levels. In a first phase II, open-label study, Chronocort has shown its ability to decrease the 08:00h 17OHP level; however, androgen levels rise in the afternoon with once-daily dosing, suggesting that an additional morning dose of GC is needed (66). Another phase 2 study on 16 patients was designed to evaluate the efficiency of a double dose of Chronocort (10mg at 07:00h and 20mg at 23:00h). It showed that after 6 months of treatment, the mean androstenedione and 17OHP levels were diminished compared with those observed under classical GC therapies (67). These preliminary data need to be confirmed also on clinical parameters and in larger populations.

Before the development of these new molecules, the use of parenteral GC had been discussed. The reproduction of cortisol circadian rhythm permitted to bring 17OHP and ACTH levels closer to physiological values compared to conventional therapies (68). More recently, a continuous subcutaneous HC infusion was found to be more efficient than conventional GC in a randomized trial on 33 patients with primary adrenal insufficiency. Doses of HC were adjusted depending on salivary cortisol. In this study, ACTH levels and cortisol profiles were respectively lower and more physiological than those observed under conventional GC therapy. However, the impact of this treatment on quality of life remains a matter of debate (69, 70). Another approach has been proposed to improve the dynamics of HC infusions. In healthy volunteers, intrinsic adrenal function was blocked by DEX, whereas HC was permanently infused subcutaneously (71). Cortisol and ACTH were measured every 10 and 60 min, leading to the replication of the circadian rhythmicity. A recent phase 2 trial on the use of subcutaneous hydrocortisone pump in 8 CAH patients with poor control has been published (72). In this study, subcutaneous hydrocortisone pump approximated physiologic cortisol secretion. Six-month treatment resulted in improved adrenal steroid control and had positive effects on quality of life. All these studies may be considered as interesting or even more promising; however, they also underline the difficulty in managing the patients daily (71). The cost of these pumps, the potential dysfunction and local irritation, may also be considered as limiting factors. The long-term effect, tolerance and acceptation of this treatment will require further studies.

### Non-glucocorticoid approaches

#### Treatment of classic CAH adults

The most radical treatment is the surgical removal of both adrenal glands. This approach must be carefully discussed as it can induce the development of TARTs in men and less frequently retroperitoneal adrenal rest tumors in women (73, 74). Chemical adrenalectomy may be obtained using mitotane, an adrenolytic agent for which the mechanisms of action remain poorly understood. Recent evidence focuses on apoptotic effects at adrenocortical level reducing the activity of the respiratory chain complex and inducing mitochondrial fragmentation, leading to programmed cell death (75, 76). Mitotane also modulates the expression of several genes involved in steroid hormone biosynthesis (76). In addition, the lack of LH increase after the decrease in free testosterone suggests that mitotane may have a toxic effect on the testes and also on the pituitary by reducing the viability of gonadotroph cell lines through activated apoptosis (75).

Two novel approaches are under current investigation: the development of androgen biosynthesis inhibitors and the development of ACTH and CRH receptor antagonists.

The development of androgen biosynthesis inhibitors is based on the necessity of decreasing secretion and action of androgens since, as previously mentioned, most of the GC treatments are unable to induce such blockade. Abiraterone is an inhibitor of CYP17A1, an enzyme necessary for androgen synthesis (Fig. 1). In men treated for prostate cancer, abiraterone acetate has proven its efficiency in decreasing testosterone levels (77). A recent phase I study in CAH women permitted to observe, after 6 days of treatment, a decrease by 2/3 of the androstenedione level when the administered dose was 100mg/day. When the dose was increased up to 250mg/day the androstenedione level was completely normalized after 6 days of treatment. However, this approach does not compensate for the adrenal insufficiency, and therefore, requires the adjunction of a GC, and in some patients, MC treatment (78). This treatment cannot be used in male patients, as it blocks all androgen synthesis.

As ACTH is a key factor in controlling adrenal function, the opportunity of interfering with corticotroph axis has been proposed. ACTH is the only known naturally occurring agonist for its receptor. The high degree of ligand specificity suggests that antagonism of its receptor could provide a useful therapeutic approach and at least an investigational tool. Different experimental models, in
animals, may provide new insights in this potential new approach (79).

Besides ACTH, CRH is at the hypothalamic level, the key factor inducing, after a specific binding to CRH receptor type 1, ACTH secretion. Any antagonism to this receptor could be a potential therapeutic strategy. This approach has been recently explored with a selective CRH receptor type 1 antagonist NBI-77860. In a single-blind, placebo-controlled study, 8 patients with CAH have received a fixed dose of 300 or 600 mg, each period of treatment being separated by a 3 weeks washout time; treatment was prescribed at 22:00 h, and ACTH and 17OHP were measured sequentially during the day after treatment administration. There was a reduction of ACTH by a mean of 43% and 41%, under 300 and 600 mg respectively compared with placebo, whereas 17OHP was reduced by a mean of 0.7% and 27% under the same treatments (80). These promising data provide a rationale for ongoing experimental studies using CRH receptor antagonist, without forgetting that this approach does not compensate for cortisol and aldosterone deficiencies.

**Prenatal management of CAH**

In CAH, 46XX female fetuses are virilized in utero due to their increased exposure to androgens. This results in the development of clitoromegaly, fusion of the labioscrotal folds and formation of a common urogenital sinus in place of a separate urethra and vagina. The aim of prenatal treatment is to avoid the need for surgery in the little girl and to relieve the emotional distress and anxiety of the parents that may be caused by an external genitalia anomaly in their child.

Prenatal treatment was first introduced in the early 80s (81, 82), using DEX, which is a synthetic GC with a long half-life, not deactivated by the placental 11-hydroxysteroid dehydrogenase type 2 and that crosses the placenta and becomes bioavailable to the fetus. In the CAH fetus, DEX leads to ACTH suppression and reduction of androgen excess, which blocks the virilization of the external genitalia in female fetuses. The dose of DEX used is 20 μg/kg maternal body weight (pre-conception)/day, divided in 2 or 3 daily doses, without exceeding 1.5 mg/day (83, 84). This dose corresponds to about 6 times the physiologic GC needs of the mother (85, 86) and 60 times the fetus’ (87, 88). Studies with lower doses have not been performed, but some data show that the DEX dose could probably be reduced when poorly tolerated in the mother (89, 90). DEX must be initiated before the presumed date of gestational sensitivity to androgens, at the latest at the 7th week of gestation (WG) or 9th week of amenorrhea and continued until birth in CAH females to ensure its efficacy (91, 92, 93, 94, 95, 96). The timing of DEX initiation seems to play an essential role in the genital morphology of CAH girls (90, 97).

Early DEX initiation before 7 WG, ideally at the latest at 6 WG, and its maintenance during the whole gestation have resulted in normal feminine genitalia in CAH girls in 80–85% cases, failure being usually observed when treatment was started after 8 WG (84, 90, 92, 93, 94, 95, 98). A recent small study from French surgeons has suggested that prenatal DEX therapy could potentially be limited to the period of the partitioning window, during the time of urogenital cleavage, which would both reduce total fetal exposure to DEX, yet still facilitate easier surgical correction (99). Enlargement of the genital tubercle continues to occur in late pregnancy without ongoing antenatal treatment, but it is generally responsive to postnatal treatment (100, 101).

Prenatal DEX exposure has decreased over the years. Circulating cell-free DNA in maternal serum allows fetal sex determination by detecting the Y chromosome (SRY test). It was first described in the late 90s (102) and used in CAH a few years later to prevent the use of DEX in CAH males and to initiate the treatment at the latest at 6 WG in females (103, 104). It has recently been shown that the sensitivity of the SRY test was guaranteed just after 4 WG in 96% cases (90). Moreover, trophoblast retrieval and isolation from the cervix was recently proven to be an approach that noninvasively and correctly identifies male fetal DNA in fetuses at risk for CAH as early as 5 WG (105). In addition, the development of chorionic villi sampling (CVS) performed earlier than amniocentesis (approximately 14 WG vs 20 WG) and with a shorter response delay has allowed minimizing DEX exposure of non-CAH females. Very interestingly, the first demonstration of non-invasive prenatal diagnosis of CAH using cell-free fetal DNA in maternal plasma, as early as 6 WG, has recently been published (106, 107). Even though large-scale prospective studies are needed, this technique offers the possibility to only treat the affected female fetus.

Prenatal DEX, however, continues to be a subject of debate. Rare adverse events have been reported in treated children, but no harmful effects have been documented that can be clearly attributed to this treatment (84, 108). A large study on 600 CAH-affected pregnancies where infants were treated prenatally with DEX, reported no significant difference in head circumference, birth weight or length, compared to untreated affected siblings (109). A long-term follow-up study in Scandinavia showed...
that 44 children who were variably treated prenatally demonstrated normal prenatal and postnatal growth compared to matched controls. Furthermore, there was no observed increase in fetal abnormalities or fetal death (95). A recent large French retrospective study confirmed the absence of malformations and of growth restriction at birth (90). Maternal side effects of prenatal DEX include weight gain, edema, mood change, sleep disturbance, acne and striae (84, 98, 109). However, there has not been a confirmed association with major pregnancy complications such as hypertension, gestational diabetes, stillbirth or spontaneous abortions (98, 109). It has recently been shown that nanoencapsulation of DEX enhances the permeability of the drug from the maternal to the fetal compartment more than 10-fold, allowing the delivery of the medication to the fetus while minimizing the adverse effects in the mother (110).

Concerns have been raised in regard to the GC effects on the fetal brain, which arise from studies of other conditions rather than direct studies on prenatal treatment of CAH. These include studies where much higher doses were given to the human subjects at the later part of pregnancy or to animals (111, 112, 113, 114), potentially holding little relevance to prenatal DEX in CAH. A small study M. New’s group described children prenatally exposed to DEX compared to untreated children from CAH at-risk pregnancies and showed no significant differences in cognitive abilities but demonstrated an increase in internalizing behaviors, such as being more shy, more emotional and less sociable (115). Another large study from the same group was unable to find any adverse effects of prenatal DEX on motor and cognitive outcome (116). Recently, the same American group published a large study evaluating the long-term effects of prenatal DEX in affected and unaffected CAH patients and found no adverse effects such as increased risk for cognitive defects, disorders of gender identity and behavior or sexual function in adulthood (117). Conversely, in a small-sample Swedish study of 26 children treated with DEX in utero, compared to 35 matched controls, the authors from S. Lajic’s group found no effects on intelligence, handedness, memory encoding or long-term memory. However, they found that, in comparison to controls, CAH-affected children treated prenatally for a short time had significantly poorer performance on a test of verbal working memory. In addition, treated children had lower questionnaire scores than controls in self-perceived social anxiety and scholastic competence (118). On the other hand, parents described their treated children as more sociable than the controls’ parents did, and treated children did not display any significant difference in psychopathology, school performance, adaptive functioning or behavioral fields (119). In the same patients, the authors suggest effects on gender role behavior in boys exposed to short-term prenatal DEX (120). A large neuropsychological American study also found that subjects treated with short-term prenatal DEX actually performed better than controls in most areas of mental processing and memory performance; however, girls treated with DEX in the long-term had slower mental processing (117).

Despite these inconsistencies, a meta-analysis has found no significant difference in neuropsychological outcomes of children treated prenatally with DEX, although only 4 eligible observational studies were identified, which in addition had low methodological quality (98). Moreover, a very recent Scandinavian study concluded that non-CAH children who were treated with DEX during early fetal life seemed to be well adjusted without major behavioral or emotional problems, as assessed by their parents, and even scored lower than the

Table 1  Management of adult patients with classic CAH.

<table>
<thead>
<tr>
<th>Monitoring of the efficacy of glucocorticoid replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-morning serum concentrations of 17-OHP, Δ4-androstenedione, total testosterone, SHBG every six months ± 12 months</td>
</tr>
<tr>
<td>Diurnal 17OHP curve with dried blood spots if available</td>
</tr>
<tr>
<td>Weight gain and clinical signs of cortisol and androgen excess</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitoring of the efficacy of mineralocorticoid replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Plasma electrolytes</td>
</tr>
<tr>
<td>Early-morning plasma renin activity concentration</td>
</tr>
</tbody>
</table>

Periodic measurements and/or monitoring of the following:
- Weight
- Lipid profile
- Blood pressure
- Glycemia
- Bone mineral density
- Assessment of male gonadic function and fertility
  - Testicular adrenal rest by ultrasonography
  - Sperm analysis
  - Fertility preservation
- Hormonal measurements: total testosterone, LH, FSH
- Assessment of female gonadic function and fertility
  - Gynecological, obstetrical and endocrinological care
  - Menstrual cycle
  - Sexuality
  - Clinical and biological hyperandrogenism
- Hormonal measurements: progesterone, estradiol, FSH
- Genetic counseling
- Pregnancy management
- Close monitorage by a gynecologist and an endocrinologist
- Psychological support
control subjects on items assessing anxiety in new, social situations (121).

Since the early 2000, several medical societies have issued opinions concerning prenatal treatment of CAH based on data presented previously and agreed that it is experimental and should only be done in Institutional Review Board-approved prospective research protocols, with written informed consent, and that this treatment is inappropriate for use in community practice (122, 123, 124, 125, 126, 127). The Swedish group has stopped recruiting patients due to concerns regarding abnormal behavioral development in children exposed to prenatal DEX and notified the Regional Ethics Committee in Stockholm (128).

It is certain that DEX safety in children treated in utero remains controversial and needs to be better assessed. However, the review of the literature shows an overall efficacy of prenatal DEX. The actual perspective of only treating affected girls with specific transplacental delivery devices, even though the techniques are not routine yet, is a major improvement in the care of these at-risk pregnancies. It is obvious that treatment should only be proposed in multidisciplinary reference centers, with informed consent of the parents and long-term follow-up of the prenatally treated patients.

**Conclusion**

Recent years have brought new insights in the description of CAH comorbidities especially in the CV and fertility areas (Table 1). In both cases, this description suggests the need for new therapeutic approaches. After decades of relatively stagnant progress, advances are now noted. Besides improved GC delivery systems, oral or parenteral, new GC approaches are under current elevation such as inhibitors of androgen biosynthetic enzymes or CRH receptor antagonists. All these approaches may have pros and cons. In all cases, larger trials to determine the outcomes and safety profiles are needed, in adults as well as in children. The use of DEX during pregnancy remains another matter of debate. Its use to prevent or diminish the risk of virilization of the young girl has to be discussed taking account the potential long-term use of such molecules on brain function or metabolism.

**References**


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