Congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) due to deficiency of 21-hydroxylase is a disorder of the adrenal cortex characterised by cortisol deficiency, with or without aldosterone deficiency, and androgen excess. Patients with the most severe form also have abnormalities of the adrenal medulla and epinephrine deficiency. The severe classic form occurs in one in 15 000 births worldwide, and the mild non-classic form is a common cause of hyperandrogenism. Neonatal screening for CAH and gene-specific prenatal diagnosis are now possible. Standard hormone replacement fails to achieve normal growth and development for many children with CAH, and adults can experience iatrogenic Cushing's syndrome, hyperandrogenism, infertility, or the development of the metabolic syndrome. This Seminar reviews the epidemiology, genetics, pathophysiology, diagnosis, and management of CAH, and provides an overview of clinical challenges and future therapies.

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Congenital adrenal hyperplasia (CAH) describes a group of autosomal recessive disorders of cortisol biosynthesis. We discuss here 21-hydroxylase deficiency, which is the cause of about 95% of CAH cases. CAH caused by deficiency of 21-hydroxylase is characterised by cortisol deficiency, with or without aldosterone deficiency, and androgen excess.

CAH shows a range of severity. The clinical phenotype is typically classified as classic, the severe form, or non-classic, the mild or late-onset form. Classic CAH is subclassified as salt-losing or non-salt-losing (simple-virilising), reflecting the degree of aldosterone deficiency.

The lives of patients with CAH have improved greatly since the discovery that cortisone was an effective treatment for the disorder in the 1950s.[1] Neonatal screening is being done in several countries. Gene-specific prenatal diagnosis is now feasible. Research on the pathophysiology of CAH has shown endocrinopathies beyond the characteristic abnormalities of the adrenal cortex, including adrenomedullary dysfunction and insulin resistance. Despite these advances, existing treatment has failed to achieve normal growth and development for many children with CAH, and the clinical management of adults is complicated by iatrogenic Cushing's syndrome, hyperandrogenism, or infertility. We review here the epidemiology, genetics, pathophysiology, diagnosis, and management of CAH and provide an overview of the clinical challenges and future therapies that await further investigation.

Epidemiology

Data from several neonatal screening programmes show that CAH due to 21-hydroxylase deficiency is common. Data from roughly 6·5 million newborn infants screened in 13 countries (USA, France, Italy, New Zealand, Japan, UK, Brazil, Switzerland, Sweden, Germany, Portugal, Canada, and Spain) show an overall incidence of one in 15 000 livebirths for the classic form.[2,3] Thus, the carrier frequency of classic CAH is about one in 60 individuals. Salt-losing CAH accounts for 67% of the cases reported and non-salt-losing CAH for 33%.[2]

Incidence varies according to ethnicity and geographical area. The highest rates of classic CAH occur in two geographically isolated populations: the Yupic Eskimos of Alaska (one in 280)[4] and the French island of La Réunion (one in 2100).[5] High rates have also been reported in Brazil (one in 7500)[2] and the Philippines (one in 7000).[3] In the USA, the incidence of CAH is lower in African-Americans than in the white population (one in 42 000 *vs* 15 500).[6]

Neonatal screening does not accurately detect non-classic CAH, so data on the incidence of the milder form of the disorder are lacking. However, non-classic CAH is estimated to be more common than classic

Search strategy and selection criteria

We searched PubMed for articles published in English on congenital adrenal hyperplasia between 1998 and 2004, with MeSH terms "adrenal hyperplasia, congenital" and "steroid 21-hydroxylase" as well as natural-language equivalents "congenital adrenal hyperplasia", "(adrenal OR hyperplas*) AND CAH", "cyp21 OR cyp-21", or "21-hydroxylase AND deficien*". The results of these searches were pooled, and subsearches were run with additional MeSH and natural-language terms as well as floating subheadings for the following: "epidemiology", "diagnosis", "genetics", "therapy", "management", "pathophysiology", "embryology", "quality of life and psychological issues", "classic or nonclassic CAH". The citations not subdivided by any of these terms were examined individually. Web of Science was searched for articles published in English during the same years with search terms "congenital*and adren* and hyperpl*", "OR CYP21 OR CYP 21 OR CAH OR", "steroid and 21 and hydrox*", or "21 and hydroxylase and deficien*"; citations and their cited references were examined individually and selected for relevance. We also reviewed books on congenital adrenal hyperplasia published in the same period. We reviewed selected references from articles retrieved by the initial search. Several earlier, commonly referenced key publications have been cited. Relevant references cited in the original source of references were also reviewed.

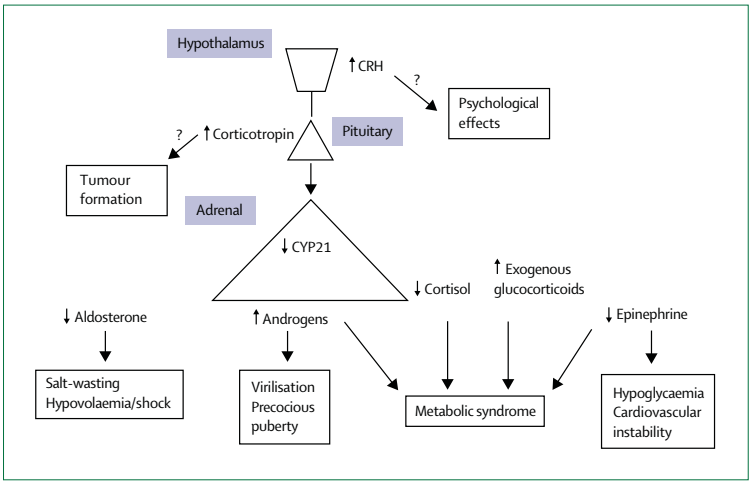

Figure 1: **Endocrine imbalances characteristic of CAH**
Potential clinical manifestations are given in the text boxes.

CAH, with a prevalence of one in 1000 in the white population.[7,8] A study in New York City found that non-classic CAH is more frequent in certain ethnic populations, such as Jews of eastern European origin, Hispanics, and Yugoslavs (1·0–3·7%).[7]

Genetics

The 21-hydroxylase gene is located on chromosome 6p21·3 within the HLA histocompatibility complex.[9] There are two highly homologous 21-hydroxylase genes resulting from ancestral duplication: an active gene, *CYP21A2* (*CYP21B*), and an inactive pseudogene *CYP21A1P* (*CYP21A*, *CYP21P*).[10] CAH is unusual among genetic disorders in that most of the mutant alleles (about 90%) are generated by recombinations between the pseudo and active genes.[11,12] When deleterious sequences normally present in the pseudogene are transferred to the active gene, the latter becomes incapable of encoding a normal enzyme; this process is called gene conversion. In patients, 1–2% of affected alleles are spontaneous mutations.[13] Spontaneous recombinations between *CYP21A2* and *CYP21A1P* are detected in one in 10^3–10^5 sperm cells.[14] The high rate of intergenic recombination that occurs could be indirectly due to the position of the gene within the MHC.

Most patients are compound heterozygotes (ie, they have different mutations on the two alleles), and the clinical phenotype is generally related to the less severely mutated allele and, consequently, to the residual 21-hydroxylase activity.[13,15–17] Several studies have suggested high concordance rates between genotype and phenotype in patients with the most severe and mildest forms of the disease, but less genotype–phenotype relation in moderately affected patients.[13,15–17]

Pathophysiology

The pathophysiology of 21-hydroxylase-deficiency-related CAH is closely linked to the degree of enzyme deficiency. A defect in cortisol biosynthesis leads to a compensatory increase in pituitary production of corticotropin and hypothalamic production of corticotropin-releasing hormone (CRH) owing to a lack of the usual negative feedback by cortisol. Physiological glucocorticoid and mineralocorticoid replacement fails to replicate the close temporal relation between release of CRH, corticotropin, and subsequent cortisol pulses. Thus, supraphysiological doses of glucocorticoid are necessary in many patients to suppress excess adrenal production of androgens and oestrogens adequately.[18] Moreover, intrauterine glucocorticoid deficiency can affect postnatal sensitivity to feedback inhibition, thus blunting the central effects of treatment.[19] The resulting iatrogenic hypercortisolism, in combination with excess adrenal androgens and oestrogens, can stunt growth in children and cause damaging metabolic side-effects, resulting in insulin resistance, metabolic syndrome, and infertility (figure 1).

Increased expression of CRH may contribute to clinical manifestations of CAH, including psychological effects and changes in energy homoeostasis. Oversecretion of CRH has been found in states of anxiety and depression, and the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis characteristic of CAH might have negative psychological effects. Adrenocortical tumours have been found in high frequency compared with the general population, which suggests that chronic corticotropin stimulation has a role in formation of adrenocortical tumours.[20] These issues are currently being researched.

Carriers or heterozygotes for *CYP21* mutations have subtle abnormalities in the functioning of the HPA axis. After corticotropin stimulation, 50–80% of carriers show increased secretion of cortisol precursors, such as 17-hydroxyprogesterone, compared with healthy individuals.[21] Carriers also have higher testosterone concentrations,[22] lower 24 h urinary excretion of free cortisol,[23] and higher corticotropin secretion after CRH stimulation.[23] Carriers might be at risk of the development of clinically inapparent adrenal masses[20,24] and, according to one study, have increased vulnerability to psychological stress.[23] Carriers are mostly free of symptoms and do not experience adrenal crises, hyperandrogenic symptoms, or disorders of growth and puberty.

Glucocorticoids are essential in the development and the continuing regulation of the adrenal medulla, and the adrenomedullary system is impaired in 21-hydroxylase-deficient mice[19,25,26] and in severely affected patients.[27] Glucocorticoids stimulate the expression of phenylethanolamine-N-methyltransferase, the enzyme that converts norepinephrine to epinephrine.[28–31] Normal glucocorticoid secretion by the

zona fasciculata of the adrenal cortex is necessary for adrenomedullary organogenesis, and a developmental defect in the formation of the adrenal medulla has been shown in patients with salt-losing CAH.[27] In human 21-hydroxylase-deficient adrenal glands, we found that chromaffin cells formed extensive neurites expanding between adrenocortical cells (figure 2). These findings accord with those from in-vitro studies that adrenal androgens promote outgrowth, whereas glucocorticoids preserve neuroendocrine cells.[32,33]

The clinical implications of epinephrine deficiency in patients with CAH have been investigated lately. Measurement of adrenomedullary function could be a useful biomarker for disease severity in CAH. In one study, molecular genotype and plasma concentrations of free metanephrine, the O-methylated metabolite of epinephrine, predicted clinical phenotype with similar accuracy.[34] The usefulness of measuring plasma metanephrine concentrations in newborn infants has not been studied. Epinephrine has a role in glucose homoeostasis, especially in young children, and patients with CAH receiving standard glucocorticoid replacement therapy have decreased adrenomedullary reserves[27] and reduced epinephrine and blood-glucose responses to high-intensity exercise.[35] Administration of additional hydrocortisone (double dose) before exercise was not beneficial[36] and had no effect on the impaired metabolic response to exercise. Epinephrine deficiency most likely plays a major part in the hypoglycaemia observed in association with intercurrent illness in patients with CAH.[37–39] Production and possibly action of leptin is inhibited by epinephrine, and insulin resistance and raised serum leptin concentrations have been described in patients with CAH.[34] Hyperinsulinism has also been reported in patients with non-classic CAH, even before the institution of glucocorticoid therapy.[40] Hyperandrogenism is an independent risk factor for hyperinsulinism in adolescent girls[41] and in women[42] and might have a role in the development of insulin resistance or polycystic ovaries in patients with CAH. Thus, many endocrinopathies, including glucocorticoid and sex-steroid imbalances and adrenomedullary hypofunction, contribute to the metabolic disturbances observed in patients with CAH and theoretically put these patients at risk of development of the metabolic syndrome (figure 1).

Clinical features

The severity of CAH depends on the degree of 21-hydroxylase deficiency caused by *CYP21A2* mutations. The classic forms present in childhood and are characterised by striking overproduction of cortisol precursors and adrenal androgens. In the most severe form, concomitant aldosterone deficiency leads to loss of salt. In the mildest form, there is sufficient cortisol production, but at the expense of excess androgens.

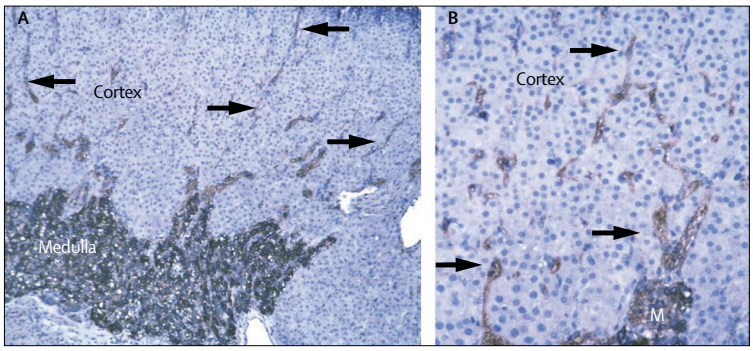

Figure 2: **Immunostaining of adrenal-gland tissue from a patient with classic 21-hydroxylase deficiency**
A: Hyperplasia, poorly defined zonation, and intermingling of the chromaffin and cortical cells (arrows) is shown in the adrenal gland of a patient with 21-hydroxylase deficiency; original magnification ×40. B: Chromaffin cells form long cellular extensions and neurite outgrowth (arrows); original magnification ×200. Chromaffin cells were stained with anti-synaptophysin. Reactions were visualised with 3-amino-ethylcarbazole and haematoxylin (reddish-brown).

Female infants with classic CAH typically have ambiguous genitalia at birth because of exposure to high concentrations of androgens in utero, and CAH due to 21-hydroxylase deficiency is the most common cause of ambiguous genitalia in 46XX infants (figure 3, A). Characteristic findings include an enlarged clitoris, partly fused and rugose labia majora, and a common urogenital sinus in place of a separate urethra and vagina. The internal female organs, the uterus, fallopian tubes, and ovaries, are normal; wolffian duct structures are not present. Boys with classic CAH have no signs of CAH at birth, except subtle hyperpigmentation and possible penile enlargement (figure 3, B). Thus, the age at diagnosis in boys varies according to the severity of aldosterone deficiency. Boys with the salt-losing form typically present at 7–14 days of life with vomiting, weight loss, lethargy, dehydration, hyponatraemia, and hyperkalaemia, and can present in shock. Girls with the salt-losing form, if not treated soon after birth, would also experience a salt-losing adrenal crisis in the neonatal period. However, the ambiguous genitalia typically lead to early diagnosis and treatment. Boys with the non-salt-losing form present with early virilisation at age 2–4 years (figure 3, C).

Patients with non-classic CAH do not have cortisol deficiency, but instead have manifestations of hyperandrogenism, generally later in childhood or in early adulthood.[43,44] These patients can present with early pubarche, or as young women with hirsutism (60%), oligomenorrhoea or amenorrhoea (54%) with polycystic ovaries, and acne (33%).[45] 5–10% of children with precocious pubarche[46,47] have been found to have non-classic CAH. Conversely, some women with non-classic CAH have no apparent clinical symptoms, and many men with non-classic CAH remain free of symptoms.[48] The proportion of patients with non-classic CAH who remain symptom-free is unknown, and women can go on to develop symptoms of hyperandrogenism later in

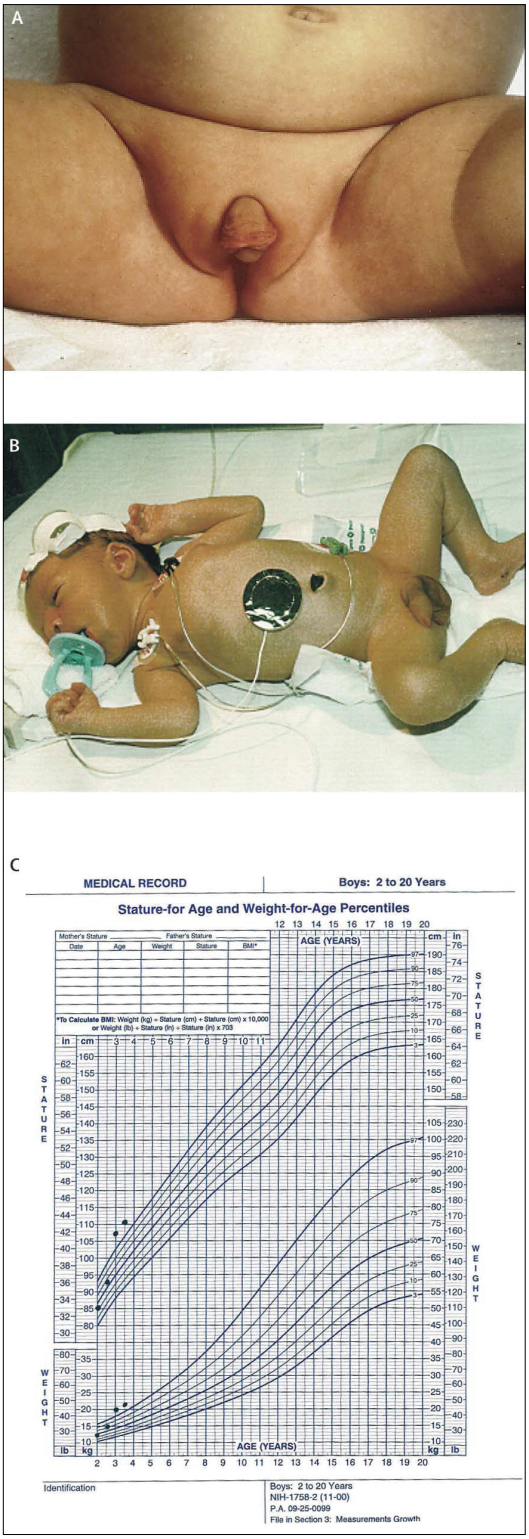

Figure 3: **Clinical presentation of classic 21-hydroxylase deficiency**
A: Female infants present at birth with ambiguous genitalia as a result of in-utero exposure to androgens. B: Boys with salt-losing CAH present at 7–10 days of age with a salt-losing adrenal crisis; some have hyperpigmentation on physical examination (note scrotal hyperpigmentation). C: Boys with the non-salt-losing form present with early virilisation and accelerated growth at age 2–4 years. Panels A and B reproduced with permission from Adis International Limited.

life.[45] Overall, the frequency of non-classic CAH among women with infertility or presenting with symptoms of androgen excess is 1–2%.[49,50] Although endocrinological testing reveals mild abnormalities in adrenal function, carriers typically do not have symptoms or signs of excess androgens and do not need treatment.[22]

Diagnosis

A very high concentration of 17-hydroxyprogesterone (more than 242 nmol/L; normal less than 3 nmol/L at 3 days in full-term infant) in a randomly timed blood sample is diagnostic of classic 21-hydroxylase deficiency.[51] Typically, salt-losing patients have higher 17-hydroxyprogesterone concentrations than non-salt-losers. False-positive results from neonatal screening are common with premature infants, and many screening programmes have established reference ranges that are based on weight and gestational age.[52,53] A corticotropin stimulation test (250 μg cosyntropin) can be used to assess borderline cases. Genetic analysis can be helpful to confirm the diagnosis.[54]

Randomly measured 17-hydroxyprogesterone concentrations can be normal in patients with non-classic CAH. Thus, the gold standard for diagnosis of the non-classic form is a corticotropin stimulation test, with measurement of 17-hydroxyprogesterone at 60 min. This test can be done at any time of day and at any time during the menstrual cycle. A stimulated concentration of 17-hydroxyprogesterone higher than 45 nmol/L is diagnostic of 21-hydroxylase deficiency. Many carriers have slightly raised concentrations of 17-hydroxyprogesterone (less than 30 nmol/L) after a corticotropin stimulation test.[51] An early-morning (before 0800 h) measurement can be used for screening,[55] but it is not as sensitive or specific as a corticotropin stimulation test. Early-morning 17-hydroxyprogesterone concentrations of less than 2·5 nmol/L in children and less than 6·0 nmol/L in women during the follicular phase rule out the diagnosis of non-classic CAH in most cases; higher values warrant a corticotropin stimulation test to establish the diagnosis.[55]

Medical treatment

In classic CAH, glucocorticoids are given in doses sufficient to suppress adrenal androgen secretion partly, without total suppression of the HPA axis; mineralocorticoids are given to return electrolyte concentrations and plasma renin activity to normal. Physiological cortisol secretion rates are about 6 mg/m²

daily,[56–58] and most patients have satisfactory control of androgen production with hydrocortisone doses of 12–18 mg/m² daily divided into two or three doses. The target 17-hydroxyprogesterone range is 12–36 nmol/L when measured in the early morning before medication. Adrenal androgen concentrations later in the day and after medication has been taken will be lower, but they should not be suppressed below the normal range because of risk of iatrogenic Cushing's syndrome.

Hydrocortisone is the glucocorticoid of choice during childhood.[59,60] Cortisone must be converted to cortisol for biological activity. Differences in the rate of conversion influence drug efficacy; thus, cortisone acetate is not recommended. Longer-acting glucocorticoids, such as prednisone (5·0–7·5 mg per day in two doses) and dexamethasone (0·25–0·50 mg at bedtime or in two doses), can be used in adults, but they are generally avoided in children because of concerns about growth suppression. However, the growth-suppressive effects of longer-acting glucocorticoid preparations could be dose related. A retrospective study of 17 children with CAH showed that once-daily administration of dexamethasone at a 70 to one relative potency to hydrocortisone could achieve normal growth,[61] and nine children with adrenal insufficiency had normal short-term (6-month) growth velocity when receiving prednisolone at a dose of 15 to one relative potency to hydrocortisone.[62] These relative potency ratios are substantially greater than previously suggested dose equivalencies. The use of longer-acting glucocorticoid preparations in children needs further study.

Mineralocorticoid replacement is achieved with fludrocortisone. The dose should be adjusted to maintain plasma renin activity in the mid-normal range. A typical daily dose of fludrocortisone ranges from 100 µg to 200 µg. The dose is independent of body size from childhood to adulthood, although higher doses are commonly needed in early infancy. The use of fludrocortisone therapy in patients with non-salt-losing classic CAH is recommended and allows management with lower doses of glucocorticoid.[18,59,60]

Infants with salt-losing CAH commonly need supplementation of sodium chloride (1–2 g daily). Routine salt supplementation is typically not needed after the first 6–12 months of life. However, patients should be encouraged to use salt freely to satisfy salt cravings. Additional salt intake may be needed with exposure to hot weather or with intense exercise.

Many patients with non-classic CAH do not need treatment. Treatment is recommended only for those with symptoms and aims to reduce hyperandrogenism.[59,60,63] Glucocorticoid treatment is indicated in children with androgen excess, whereas adult women might need adjuvant antiandrogen therapy. Dexamethasone and antiandrogen drugs should be used with caution and in conjunction with oral contraceptives in young women; both cross the placenta. When fertility is desired, ovulation induction might be necessary[63] and a glucocorticoid that does not cross the placenta (eg, prednisolone or prednisone) should be used.

Drugs that induce hepatic microsomal enzymes (CYP450), such as antiepileptic drugs, affect the metabolism of glucocorticoids and can greatly alter the appropriate glucocorticoid dose.[64] Flutamide, an antiandrogen, has also been reported to affect hydrocortisone metabolism.[65] A prudent approach includes close clinical monitoring and laboratory assessment 4–6 weeks after the patient starts taking a new medication long term.

Stress dosing

Patients with classic CAH cannot mount a sufficient cortisol response to physical stress and need pharmacological doses of hydrocortisone in situations such as febrile illness, surgery, and trauma. Dose guidelines include doubling or tripling the glucocorticoid maintenance dose for the whole day. If a patient is unable to take medication orally, hydrocortisone should be given intramuscularly, and medical advice about the need for intravenous hydration should be promptly sought. The combination of cortisol deficiency and epinephrine deficiency puts patients at risk of hypoglycaemia with illness or fasting. During illnesses, intake of carbohydrates and glucose-containing fluids should be encouraged and glucose monitoring should be considered, especially in children. Patients and parents should receive instructions for these types of emergencies. All patients should wear or carry medical alert identification specifying adrenal insufficiency.

There is no evidence that higher doses of glucocorticoid are needed in times of mental or emotional stress, and higher doses of glucocorticoid should be given only for physical stressors. Exercise, although a physical stressor, does not require increased dosing.[36] However, the normal exercise-induced rise in blood glucose concentrations is blunted in patients with CAH, and extra intake of carbohydrates might be useful with exercise.[36]

Patients with non-classic CAH do not need stress doses of hydrocortisone unless they have iatrogenic suppression of their adrenal glands by glucocorticoid treatment. Thus, a prudent approach is to treat patients with non-classic CAH who are receiving glucocorticoid therapy as if they have adrenal insufficiency.

Clinical challenges

Prenatal therapy

In pregnancies in which the fetus is at risk of classic CAH, maternal dexamethasone treatment has successfully suppressed the fetal HPA axis and reduced the genital ambiguity of affected female infants.[66,67] Masculinisation of the external genitalia begins by 8 weeks of gestation. Therefore, if treatment is desired, it

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