REVIEW

# Why is management of patients with classical congenital adrenal hyperplasia more difficult at puberty?

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Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive condition in which deletions or mutations of the cytochrome P450 21-hydroxylase gene cause glucocorticoid and often mineralocorticoid deficiency. Despite optimal substitution therapy, control of classical CAH is often inadequate at puberty, and the problems encountered relate to hypocortisolism and/or hyperandrogenism. A number of physiological alterations in the endocrine milieu at puberty, which include alterations in the growth hormone/insulin-like growth factor axis, insulin sensitivity, as well as the activity of enzymes participating in cortisol metabolism and adrenal steroidogenesis, may account for the documented hypocortisolism and elevated androgen production, and may explain the difficulty in maintaining adequate adrenocortical suppression in pubertal patients with classical 21-hydroxylase deficiency.

Congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency is an autosomal recessive condition, in which deletions or mutations of the cytochrome P450 21-hydroxylase gene result in glucocorticoid and often mineralocorticoid deficiency. This leads to increased secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary, adrenal hyperplasia, and increased production of androgens and steroid precursors for which 21-hydroxylation is not necessary (fig 1).[1 2] Glucocorticoid substitution is given to suppress the excessive secretion of corticotrophin releasing hormone (CRH) and ACTH by the hypothalamus and anterior pituitary respectively, and to reduce the circulating concentrations of adrenal androgens. Treatment efficacy reflects the adequacy of adrenocortical suppression and is assessed by monitoring annualised growth velocity, the rate of skeletal maturation, and serum concentrations of androgen precursors.[1 2]

Despite adequate substitution therapy, however, control of classical 21-hydroxylase deficiency is often difficult and patients are at risk for developing in tandem iatrogenic hypercortisolism and/or hyperandrogenism, both of which are responsible for the main problems encountered in their management, such as compromised final height, obesity, hyperinsulinism, hirsutism, polycystic ovarian syndrome, poor fertility, and psychosexual identification problems.[1]

Limitations of current medical therapy include: (1) inability to control hyperandrogenism without employing supraphysiological doses of glucocorticoid and therefore inducing hypercortisolism; (2) hyperresponsiveness of the hypertrophied adrenal glands to ACTH following a small ACTH challenge in the event of escape from pituitary suppression; and (3) difficulty in suppressing the anterior pituitary with glucocorticoids, given that glucocorticoid feedback is only one of the mechanisms governing ACTH secretion.[3]

In addition to the above, a number of clinical observations suggest that puberty imposes greater difficulty in achieving and maintaining adrenal suppression despite optimal doses of substitution therapy. This difficulty in maintaining optimal control in pubertal patients with classical CAH has been attributed traditionally to non-adherence to medical therapy as a result of psychosocial factors relating to adolescence. At puberty, children often rebel against authority in an attempt to gain more control and independence over their world,[4] parental supervision over their medical therapy decreases with the expectation that adolescents will assume responsibility for the treatment tasks,[5] and conformity to peers increases, so that adolescents are inclined not to adhere to a treatment regimen in an attempt to become "normal" and to minimise the risk of rejection by their peers.[6 7] Regardless of age and developmental stage, adherence to medical therapy may also depend on the frequency of drug administration, the intensity of therapy, the side effects of certain medications,[8 9] the child's level of optimism, and the support provided by other members of the family.[9 10]

Non-adherence to medical therapy, however, only explains in part the problems encountered in the management of pubertal patients with classical CAH. There is increasing evidence to suggest that alterations in the endocrine milieu at puberty may influence cortisol pharmacokinetics and, consequently, the handling of hydrocortisone used as replacement therapy. Recent studies have

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**Abbreviations:** ACTH, adrenocorticotrophic hormone; BMI, body mass index; CAH, congenital adrenal hyperplasia; CRH, corticotrophin releasing hormone; GFR, glomerular filtration rate; GH, growth hormone; GnRH, gonadotrophin releasing hormone; HPA, hypothalamic–pituitary–adrenal; HSD, hydroxysteroid dehydrogenase; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein

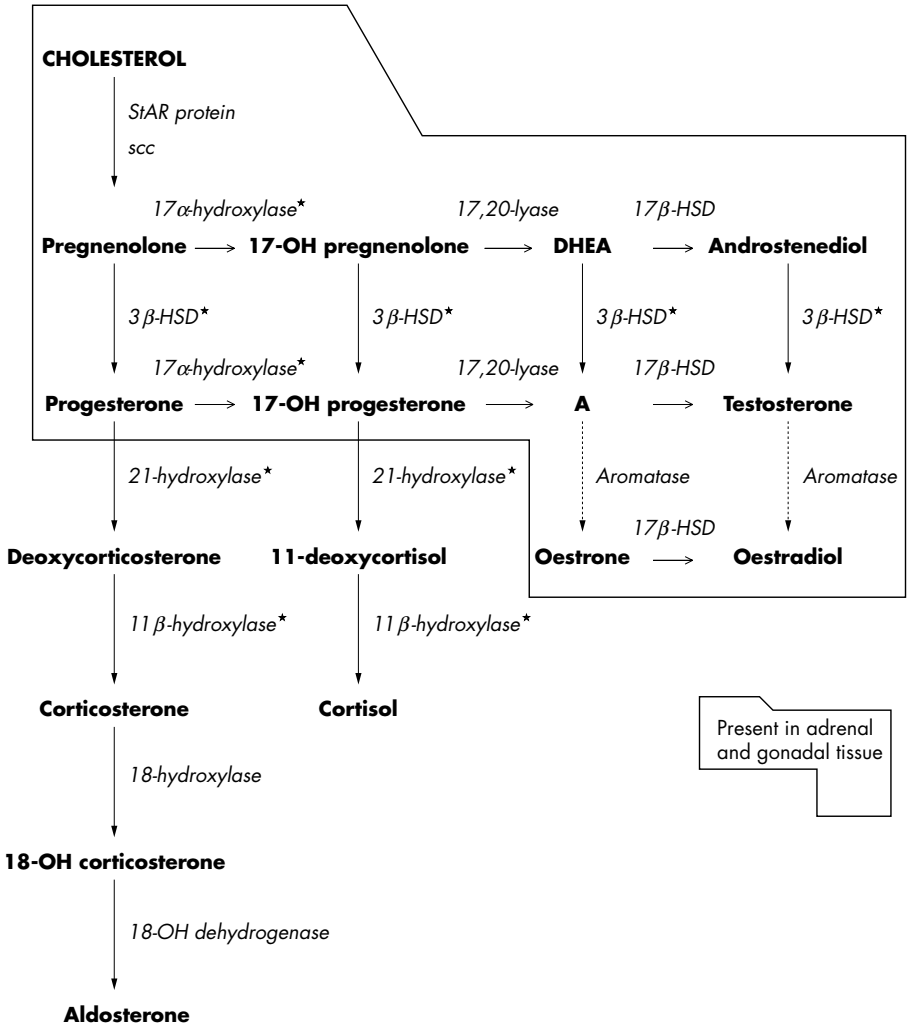


**Figure 1** Schematic representation of adrenal steroidogenesis. Solid line: major pathway. Dotted line: major pathway in ovaries and minor in adrenals. *Deficient enzymatic activity results in CAH. StAR, steroidogenic regulatory protein; scc, cholesterol side chain cleavage enzyme; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; DHEA, dehydroepiandrosterone; A, androstenedione.

shown a significant increase in cortisol clearance at puberty (fig 2A), and a shorter half life of free cortisol in pubertal females compared to their male counterparts (fig 2B).[11]

Puberty results from increased gonadotrophin secretion from the anterior pituitary in response to gonadotrophin releasing hormone (GnRH) secretion from the hypothalamus. The rise in sex steroid concentration is associated with increased growth hormone (GH) secretion from the anterior pituitary, which leads to increased insulin-like growth factor (IGF)-I concentrations and the pubertal growth spurt.[12–14] Associated with this there is a decrease in insulin sensitivity and a parallel elevation in insulin concentrations.[15] At the tissue level, insulin reduces IGF binding protein 1 (IGFBP-1) concentrations, altering tissue exposure to IGF-I.[16]

The increase in cortisol clearance at puberty is primarily the result of inhibition of the activity of 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) secondary to the alterations in the endocrine milieu.[11] 11β-HSD1 is one of the main hepatic enzymes participating in cortisol metabolism, which acts predominantly as an oxo-reductase, converting inactive cortisone to active cortisol.[17–19] The increase in GH, IGF-I, and oestradiol concentrations at puberty can have an independent or a combined effect in causing a decrease in the activity of 11β-HSD1.[20–22] The effect of IGF-I on 11β-HSD1 activity is further enhanced by the decrease in IGFBP-1 concentrations secondary to the raised insulin concentrations.[16] Inhibition of 11β-HSD1 activity effectively increases the metabolic clearance rate of cortisol.[20] An additional mechanism that results in increased cortisol clearance is the increase in renal clearance of cortisol secondary to an increase in glomerular filtration rate (GFR) in response to the raised GH and IGF-I concentrations. IGF-I increases GFR via a direct effect on the glomerular vasculature and a decrease in renal glomerular afferent and efferent arteriolar resistance, while the action of GH is likely to be mediated by IGF-I.[23–26]

The above changes in cortisol pharmacokinetics, if the administration schedule of oral hydrocortisone remains unchanged, will result in hypocortisolism, loss of control of the hypothalamic–pituitary–adrenal (HPA) axis, inadequate suppression of the adrenal cortex, and excessive production of androgens and steroid precursors. The increased secretion of adrenal androgens will be further amplified by the increased 17, 20 lyase activity and/or decreased 3β-hydroxysteroid dehydrogenase (3β-HSD) activity secondary to the rise in GH, IGF-I, IGF-II, and insulin concentrations at puberty.[27–31] Moreover, the increased insulin concentrations will suppress the synthesis of sex hormone binding globulin by the liver, further enhancing hyperandrogenism.[32 33] As androgens and androgen precursors are known to compete with exogenously administered glucocorticoids for the same receptors,[34] both hypocortisolism and hyperandrogenism will operate as independent factors to amplify the loss of control. Increased ACTH

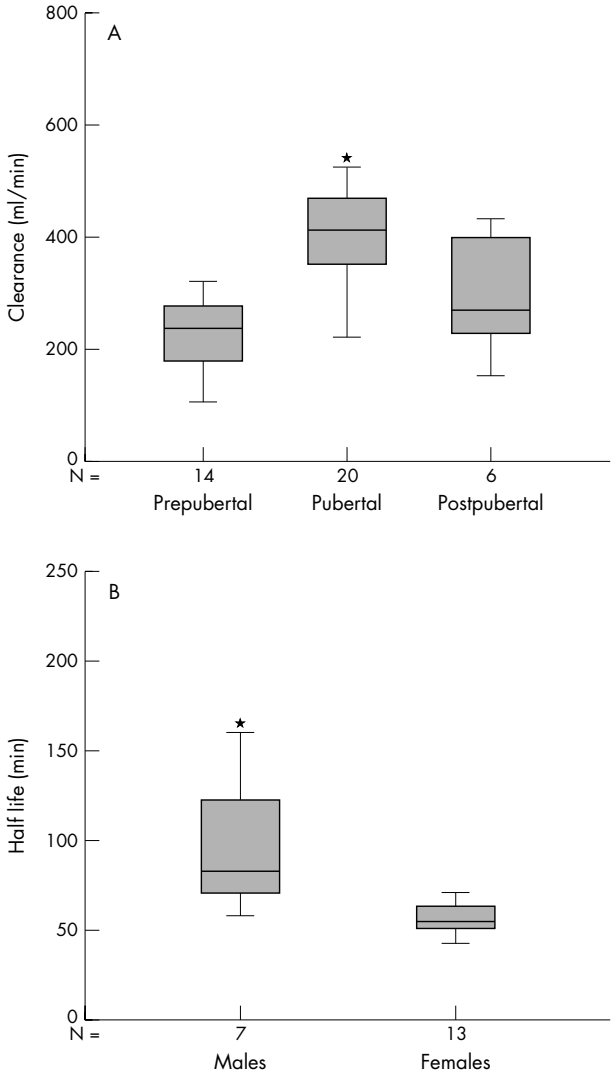


**Figure 2** Box plot schematic representation of (A) total cortisol clearance in prepubertal, pubertal, and postpubertal patients with classical 21-hydroxylase deficiency; and (B) half life of free cortisol in pubertal male and female patients with classical CAH. The line is drawn across the box at the median. The lower line of the box is at the first quartile (Q1) and the upper line is at the third quartile (Q3). The whiskers are the lines that extend from the top or the bottom of the box to the adjacent values within ± 1.5 × (Q3 – Q1). The asterisks indicate significant differences between groups (From Charmandari E, Hindmarsh PC, Johnston A, Brook CGD. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: alterations in cortisol pharmacokinetics at puberty. *J Clin Endocrinol Metab* 2001;**86**(6):2701–8).

secretion, in turn, may further potentiate hypocortisolism by increasing the metabolic clearance rate of cortisol.[35]

Besides the above alterations in cortisol pharmacokinetics at puberty, obesity is an important factor that contributes significantly to the problems encountered in the management of these patients. Children with classical 21-hydroxylase deficiency have significantly higher values of body mass index (BMI) and fat mass throughout childhood compared to their normal counterparts.[36] This most likely reflects the supraphysiological doses of glucocorticoid often employed in an attempt to suppress the adrenal cortex effectively, and/or the impaired adrenomedullary function and decreased catecholamine secretion documented in these patients.[37] Compared to normal subjects matched for age and BMI, children with classical CAH also have significantly higher serum insulin concentrations and insulin resistance index, as determined by the homoeostasis model assessment method.[38] This is probably the result of long standing adrenomedullary hypofunction in association with intermittent hypercortisolism and/or adrenal hyperandrogenism. Hyperinsulinism and insulin resistance, in turn, may further stimulate adrenal and ovarian steroidogenesis, and may play an important role in the development of polycystic ovary syndrome,[39] metabolic syndrome related atherosclerotic cardiovascular disease in adult life,[39 40] and adrenal incidentalomas.[41–43]

It is worth noting that the above alterations are expected to affect pubertal female patients more than males because of the sexually dimorphic patterns in GH secretion, the activity of 11β-HSD1, and the concentrations of corticosteroid binding globulin.[44–48] Recent studies have shown that the half life of free cortisol is significantly shorter in pubertal females with classical CAH compared to their male counterparts.[11] These observations may explain why management of female patients at puberty is often problematic, and indicate more frequent administration of oral hydrocortisone in these patients.

We conclude that in children with classical 21-hydroxylase deficiency, alterations in the endocrine milieu at puberty may result in inadequate suppression of the HPA axis despite optimal substitution therapy and adherence to treatment. The increase in GH secretion and the rise in IGF-I and oestradiol concentrations result in decreased conversion of cortisone to cortisol, and hypocortisolism. In addition, these alterations in association with the raised insulin concentrations at puberty lead to increased adrenal and ovarian androgen production. Both hypocortisolism and hyperandrogenism result in increased ACTH secretion, which, in turn, may further potentiate hypocortisolism by increasing the metabolic clearance rate of cortisol, thus establishing a vicious cycle. Administration of oral hydrocortisone should be more frequent than twice daily in pubertal patients with classical CAH, particularly in females.

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