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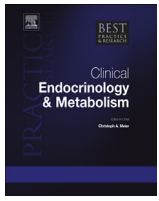

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Fetal endocrine therapy for congenital adrenal hyperplasia should not be done

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Prenatal treatment of congenital adrenal hyperplasia by administering dexamethasone to a woman presumed to be carrying an at-risk fetus remains a controversial experimental treatment. Review of data from animal experimentation and human trials indicates that dexamethasone cannot be considered safe for the fetus. In animals, prenatal dexamethasone decreases birth weight, affects renal, pancreatic beta cell and brain development, increases anxiety and predisposes to adult hypertension and hyperglycemia. In human studies, prenatal dexamethasone is associated with orofacial clefts, decreased birth weight, poorer verbal working memory, and poorer self-perception of scholastic and social competence. Numerous medical societies have cautioned that prenatal treatment of adrenal hyperplasia with dexamethasone is not appropriate for routine clinical practice and should only be done in Institutional Review Board approved, prospective clinical research settings with written informed consent. The data indicate that this treatment is inconsistent with the classic medical ethical maxim to 'first do no harm'.

Abbreviations: 3βHSD2, 3β-hydroxysteroid dehydrogenase, type 2; 3αHSD, one of several 3α-hydroxysteroid dehydrogenases; 17βHSD, one of several 17β-hydroxysteroid dehydrogenases; 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AMH, anti-müllerian hormone; C19, steroids containing 19 carbon atoms, usually androgens or androgen precursors; CAH, congenital adrenal hyperplasia; CLP, cleft lip with or without cleft palate; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; NCAH, non-classical CAH; P450c17, cytochrome P450 specific for steroid 17α-hydroxylation and 17,20 lyase activity; P450c21, cytochrome P450 specific for adrenal 21-hydroxylation.

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Introduction

Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency (CAH) is an autosomal recessive disorder affecting about 1 in 14,500 newborns [1,2]. Glucocorticoid (cortisol) and mineralocorticoid (aldosterone) synthesis are impaired, and affected females typically have virilized external genitalia. Practice guidelines covering broad aspects of the diagnosis and treatment of CAH, from fetus to adult, have been published [3,4]. Since the 1980s endeavors have been made to suppress the overproduction of adrenal androgens in female fetuses with CAH by administering dexamethasone to the mother prenatally [5–7]; however, all published practice guidelines from numerous medical societies caution that prenatal treatment of CAH with dexamethasone is at best experimental, and at worst contraindicated. Current knowledge of the molecular genetics of CAH, fetal adrenal physiology, and glucocorticoid actions permits a timely re-evaluation of this controversial experimental treatment.

Genetics and biology of CAH

CAH is caused by mutations in the *CYP21A2* gene that encodes the adrenal 21-hydroxylase, which is a specific microsomal cytochrome P450 enzyme termed P450c21 or CYP21. *CYP21A2* is part of an unusually complex gene cluster that lies in the middle of the major histocompatibility (HLA) locus on chromosome 6p21 [8]. In addition to adrenal P450c21, a number of other enzymes, notably in the liver, can also catalyze steroid 21-hydroxylation [9,10]. Cortisol synthesis by the adrenal zona fasciculata requires P450c21 to convert 17-hydroxyprogesterone (17OHP) to 11-deoxycortisol; in aldosterone synthesis by the zona glomerulosa, P450c21 converts progesterone to deoxycorticosterone. At least two liver enzymes, CYP2C19 and CYP3A4, can 21-hydroxylate progesterone but not 17OHP, potentially ameliorating salt-loss in adults [11]. Increased concentrations of 17OHP are used diagnostically because the adrenal makes 100–1000 times more cortisol than aldosterone. The genetics, biochemistry and disease-causing defects of steroidogenesis have been reviewed in detail [8].

CAH can present at different ages with a spectrum of clinical symptoms that are usually described as three different forms of CAH, with substantial overlap in their clinical behavior [2,4]. The most severe form, salt-wasting CAH, is characterized by deficiencies of both aldosterone and cortisol. Deficient fetal cortisol production leads to overproduction of ACTH, stimulating the disordered fetal adrenal to produce excess androgens, virilizing female fetuses at 7–12 weeks gestation. The virilization of a female fetus can lead to incorrect newborn sex assignment, hence CAH must be considered in apparently male infants with bilateral non-palpable gonads. Affected males have normal external genital development, and may escape initial diagnosis. Before the development of newborn screening programs, affected females were usually identified by their genital ambiguity whereas affected males presented later with a salt-losing crisis characterized by weight loss, poor feeding, dehydration, hyponatremia, hyperkalemia and acidosis. These symptoms of salt loss are rarely seen before the second week of life and will be fatal if not treated. Simple virilizing CAH results from milder mutations that permit production of enough aldosterone to prevent overt salt loss, but cortisol remains deficient, ACTH is high, the adrenal overproduces C19 androgens, and affected females are virilized. Males with simple virilizing CAH are anatomically normal and may escape diagnosis until they are older and present with phallic enlargement, premature sexual hair, tall stature, and advanced skeletal maturation. Salt-losing and simple virilizing CAH are often considered together as 'Classic CAH'. Non-classical CAH (NCAH) (sometimes termed late-onset CAH) may become apparent in adolescent or adult females with irregular menses, infertility, or hirsutism, or may have no symptoms at all; NCAH may be difficult to distinguish from the polycystic ovary syndrome [12]. Males with non-classical CAH are asymptomatic, but may be identified through family studies [13,14]. The incidence of NCAH is about 1:1000, but varies among populations. Newborn screening programs now permit early, life-saving diagnosis of most severely-affected infants; a detailed evaluation by a pediatric endocrinologist is then needed, as false positives are common, and other rare adrenal disorders may also yield positives.

Over 200 *CYP21A2* alleles have been identified (http://www.cypalleles.ki.se/cyp21.htm), largely because the *CYP21A2* locus is unusually complex [8]. Most individuals have both a *CYP21A1P* pseudogene and an adjacent *CYP21A2* gene on each allele, but normal individuals may have from 0 to 4 copies of a *CYP21* gene (usually the *CYP21A1P* pseudogene) on a single chromosome [15,16]. Because