Fertility in patients with congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is the most frequently encountered genetic steroid disorder affecting fertility. Steroid hormones play a crucial role in sexual development and reproductive function; patients with either 21- hydroxylase or 11β-hydroxylase deficiency thus face immense challenges to their fertility. Given the relevance of CAH in reproductive medicine as well as the diagnostic challenges posed by the phenotypic overlap with polycystic ovary syndrome, we review the reproductive pahophysiology of both classic and nonclassic CAH and present contemporary treatment options. (Fertil Steril® 2014;101: 301–9. ©2014 by American Society for Reproductive Medicine.)

Key Words: CAH, infertility, 21 hydroxylase, 11b-hydroxylase, genotype, phenotype, steroidogenesis

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Congenital adrenal hyperplasia (CAH) is the most frequently encountered genetic steroid disorder affecting fertility. Approximately 1 in 16,000 individuals has classic CAH, and approximately 1 in 600 is affected with nonclassic disease, making it one of the most common recessive human genetic diseases (1). Given the critical role played by steroid hormones in sexual development and reproductive function, it is not surprising that individuals affected by these steroidogenic disorders often face immense challenges to their fertility. Moreover, the significant phenotypic overlap between nonclassic adrenal hyperplasia and polycystic ovary syndrome (PCOS) can lead to misdiagnoses that may carry important health consequences for the offspring of affected individuals. We review the pathophysiology of congenital adrenal hyperplasia arising from either 21-hydroxylase or 11β-hydroxylase deficiency, with a special emphasis on the reproductive phenotypes and fertility treatment options associated with each condition given the incidence of CAH and its relevance in reproductive disorders. The predominant focus will be on female infertility, with male infertility phenotypes and existing therapies concluding the discussion.

The most common form of congenital adrenal hyperplasia is caused by mutations in the *CYP21A2* gene. Classic disease leads to cortisol deficiency and virilization of the female genitalia in utero. The disease manifests along a spectrum of severity according to the extent of enzymatic deficiency. Salt-wasting CAH is a life-threatening condition characterized by nearly complete ablation of enzymatic activity, leading to deficiencies of both cortisol and aldosterone secretion. Patients with simple virilizing CAH preserve enough aldosterone synthesis to maintain electrolyte homeostasis. In contrast, nonclassic adrenal hyperplasia is most often asymptomatic but may occasionally be manifested by mild clitoromegaly in affected female infants or during childhood by premature adrenarche, acne, adult body odor, and/or accelerated somatic growth and skeletal maturation. Cortisol secretion is impaired or absent in classic CAH but may be normal in nonclassic cases. In all patients, however, supraphysiologic levels of androgen precursors are secreted from the adrenals, and these cause impaired fertility.

A rarer form of congenital adrenal hyperplasia (1 in 100,000 births in most populations) is caused by mutations in the *CYP11B1* (11β-hydroxylase) gene responsible for the conversion of 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone (Fig. 1). Such patients have impaired cortisol secretion and signs of androgen excess similar to those seen in 21-hydroxylase deficiency patients, but rather than being

Received October 9, 2013; revised and accepted November 1, 2013; published online December 17, 2013.
D.E.R. has nothing to disclose. P.C.W. has nothing to disclose. M.I.N. has nothing to disclose. Z.R. has nothing to disclose.
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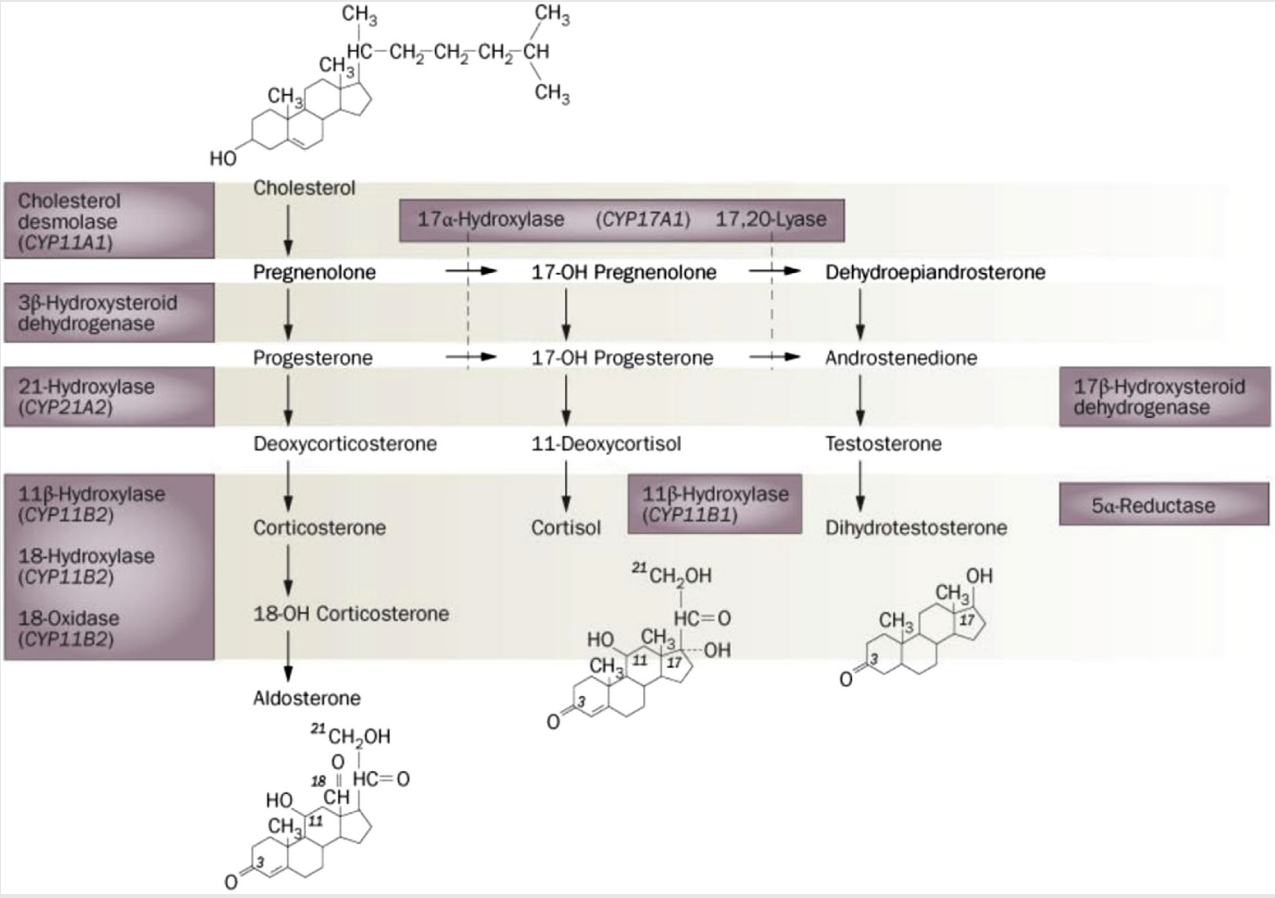
Fertility and Sterility® Vol. 101, No. 2, February 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.11.002

FIGURE 1



Adrenal steroidogenesis pathway (37).

Reichman. Fertility in patients with CAH. Fertil Steril 2014.

prone to salt-wasting crises owing to aldosterone deficiency, they are at risk for hypertension owing to excessive production of deoxycorticosterone and its metabolites (2).

In its classic form, 3β-hydroxysteroid dehydrogenase deficiency is an additional rare cause of CAH. In contrast with 21-hydroxylase or 11β-hydroxylase deficiency, it is associated with both adrenal and gonadal steroidogenesis defects. Many women with PCOS apparently have low 3β-hydroxysteroid dehydroxysteroid dehydrogenase activity, as measured by the ratio of dehydroepiandrosterone to androstenedione. The pathogenetic significance of this is uncertain, and such patients almost never carry mutations in the enzyme (3). Given that the treatment for infertility is similar to that of patients with 21-hydroxylase deficiency and that relatively little has been published regarding the reproductive functioning associated with the disorder, we will henceforth focus on 21- and 11β-hydroxylase deficiencies.

MOLECULAR GENETICS

The enzyme 21-hydroxylase, a member of the cytochrome P450 family, is encoded by *CYP21A2* located on the short arm of chromosome 6 (4). All variations of the disease are inherited in an autosomal recessive manner. *CYP21A2* disruption can arise from misalignment of sister chromatids during mitosis, misalignment of homologous chromosomes during meiosis, resulting in large-scale deletions (together accounting for over 90% of all 21-hydroxylase-related CAH cases), or from rare de novo disruptions arising from either somatic or germ-line mutations (5). Uniparental isodisomy, in which the child inherits two identical copies from a parent who is a carrier, can also lead to disease in rare cases (6).

CYP11B1, the gene encoding 11β-hydroxylase, is found on the long arm of chromosome 8. As with 21-hydroxylase deficiency, 11β-hydroxylase deficiency is inherited as an autosomal recessive disorder. At least 40 mutations among patients with 11β-hydroxylase deficiency have been described. Many patients of North African Jewish origin carry an Arg-448 to His, a mutational "hotspot" prone to cytosine methylation and subsequent deamidation (7). This missense mutation affects a region of known functional importance, inhibiting interactions with the enzyme's heme group. Other missense mutations (T318M, E71G, R374Q, R384Q) affect various regions critical to function, such as proton transfer to oxygen, binding of