# Introduction: Contemporary perspectives on congenital adrenal hyperplasia: impacts on reproduction

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Congenital adrenal hyperplasia, an endocrine autosomal recessive disorder caused by several deficiencies of enzymes and/or proteins involved in adrenal cortisol biosynthesis, is often associated with reproductive dysfunction. While the most common disorder is due to 21-hydroxylase deficiency, several other enzymes in the steroidogenesis pathway have been described, all of which can result in a range of reproductive disorders in both males and females. Although for many enzymes the phenotypic presentation is associated with a particular genotype, the severity of disease cannot always be predicted. (Fertil Steril® 2019;111:4–6. ©2018 by American Society for Reproductive Medicine.)

**Key Words:** Congenital adrenal hyperplasia, 21-hydroxylase deficiency, steroidogenesis, reproductive disorders



Congenital adrenal hyperplasia (CAH), an endocrine autosomal recessive disorder caused by several deficiencies of enzymes and/or proteins involved in adrenal cortisol biosynthesis, is often associated with disorders of reproductive function. While the most common disorder is due to 21-hydroxylase deficiency, several other enzymes in the cortisol pathway have been described, all of which can result in reproductive disorders in both males and females. Figure 1 represents advances and milestones in the development of our understanding of steroid biochemistry and related endocrine CAH disorders. In this Views and Reviews, we present four contemporary papers by authorities in the field discussing current diagnostic approaches and treatments for this important endocrine disorder.

Gomes and colleagues (1) describe classical CAH, which is caused by several genetic mutations in steroidogenesis. The severe mutations include 21-hydroxylase deficiency, 11-hydroxylase deficiency, 3B-hydroxysteroid dehydrogenase deficiency, 17-hydroxylase deficiency, 17/20 lyase deficiency and congenital lypoid adrenal hyperplasia, and P450 oxireductase deficiency. The authors characterize the prevalence, phenotype, and associated mutations in each of these classical forms. For instance, in the classical form of 21-hydroxylase deficiency, the authors describe how genitalia in the affected female fetus are usually ambiguous and can be completely masculinized (Prader V). The 17-hydroxylase mutation is one of the few forms of CAH in which genital ambiguity occurs in the male rather than the female fetus. This abnormal development of male genitalia is a result of deficient testosterone secretion. The authors also address the impact of these variants on fertility and the mechanism by which they impair each of these classical steroid disorders.

In their in-depth review of nonclassical CAH, New and colleagues (2) explain how the mutations causing this mild form of 21-hydroxylase deficiency result in a much less severe phenotype than those in classical CAH. The nonclassical form has an extraordinarily high prevalance in particular ethnic groups and is sometimes mistaken by clinicians as polycystic ovary syndrome because of the shared presence of hyperandorgenemia and the absence of both salt wasting and genital ambiguity at birth in affected females. While the classical form requires treatment with glucocorticoids, added salt to the diet,

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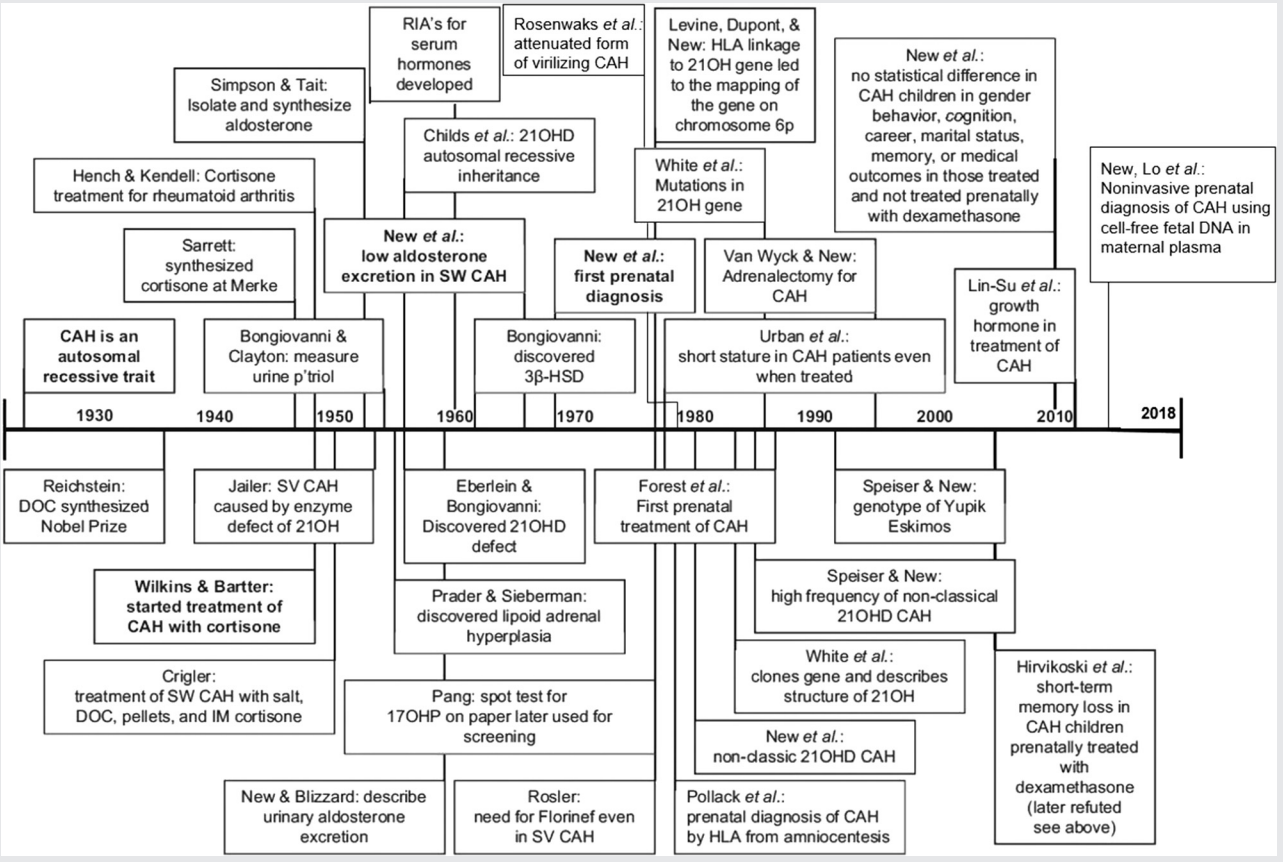
## FIGURE 1




Advances in steroid endocrinology. (Figures 1 and 2 modified from New MI. Chapter 1: Introduction. In: New MI, Yuen TT, Parsa A, Lekarev O, eds. Genetic steroid disorders. New York: Elsevier, 2014.)

*New. Contemporary perspectives on CAH. Fertil Steril 2018.*

and salt-retaining mineralocorticoids, nonclassical CAH does not require salt-retaining steroid treatment because the mineralococrtiocid pathway is rarely affected. However, due to hyperandrogenemia and the high prevalence of this mutation, nonclassical CAH is a common cause of impaired fertility in affected females.

Simpson et al. (3) describe new developments in prenatal diagnosis and treatments of adrenal steroid disorders. Prenatal diagnosis with chorionic villus sampling and amniocentesis involve an invasive procedure required to obtain placental tissue and/or amniotic cells. Noninvasive tests have been developed based on the novel discovery by Dr. Dennis Lo of cell-free fetal DNA in the maternal plasma circulation. Cell-free fetal DNA prenatal testing can be performed as early as the sixth week of gestation, thus making it possible to avoid unnecessary maternal prenatal treatment when there is a male fetus, while allowing for early initiation of treatment when there is a female fetus. Finally, for parents who want to avoid having a subsequent child with the same genetic mutation as a previous child, in vitro fertilization with preimplantation genetic diagnosis allows for the transfer of unaffected embryos prior to establishing pregnancies. While there has been progress in the various methods of prenatal testing for all the steroid disorders, there are nonetheless many pitfalls and challenges with all the testing methods described, as can be gleaned from the last contribution by Narasimhan et al. (4), who describe various forms of genotype-phenotype non-concordance in CAH.

In the final contribution, Narasimhan et al. (4) describe mutations in the CYP21A2 gene resulting in 21-hydroxylase deficiency—the most common form of CAH. Indeed, as discussed by Simpson et al., it is evident that prenatal diagnosis depends on the accuracy of the genetic diagnosis in predicting the phenotype. However, the correlation of the genotype-phenotype associated with different combinations of CYP21A2 mutations remains the most important and challenging determinant in prenatal diagnosis and counseling of the expectant couple at risk for CAH. Reproductive endocrinologists must be well-versed in steroid endocrinology and the genetics of steroidogenesis to accurately diagnose and thus recommend the appropriate treatment.

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