

Infertility and Reproductive Function in Patients with Congenital Adrenal Hyperplasia

Pathophysiology, Advances in Management, and Recent Outcomes



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KEYWORDS

- 21-Hydroxylase deficiency • Congenital adrenal hyperplasia • Fertility • Pregnancy
- Testicular adrenal rest tumors (TART)

KEY POINTS

- Fertility data in CAH focus primarily on 21-hydroxylase deficiency.
- Fertility rates in women with CAH have improved over time. Current pregnancy rates approach 90% among those with classic disease seeking conception.
- Children born to mothers with CAH typically have no evidence of virilization.
- Fertility rates are decreased in men with classic CAH; testicular adrenal rest tumors are a common cause of infertility, require surveillance with repeated ultrasonography, and can respond to therapy with glucocorticoids.
- Suppression of adrenal androgen secretion represents the first treatment strategy toward spontaneous conception in both men and women with CAH.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) refers to a group of inherited autosomal recessive disorders that lead to defective steroidogenesis. Cortisol production in the zona fasciculata of the adrenal cortex occurs in several enzyme-mediated steps. Compromised enzyme function at each step leads to a characteristic combination of elevated

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precursors and deficient products that is distinctive for each form of CAH. The most common form of CAH, 21-hydroxylase deficiency, accounts for approximately 95% of all cases. It is further subdivided into salt-wasting and simple-virilizing 21-hydroxylase deficiency, both of which are considered to be classic CAH, and into nonclassic CAH. In salt-wasting CAH, aldosterone and cortisol are deficient and adrenal androgens are elevated, leading to development of atypical external genitalia. In simple-virilizing CAH, aldosterone production is adequate and salt wasting does not occur; however, androgens are elevated and females are also born with atypical genitalia. In nonclassic CAH, the enzymatic deficiency is mild; although androgens are also elevated, the elevation is not significant to cause genital abnormalities in utero.¹ Thanks to life-saving glucocorticoid therapy and newborn screening programs, patients with CAH are living longer. In fact, CAH has become a life-long chronic illness with multiple complications in adulthood, including impaired fertility.

Other forms of CAH include deficiencies of 11 β -hydroxylase, 3 β -hydroxysteroid dehydrogenase (HSD) or 17- α hydroxylase/17-20 lyase, congenital lipoid adrenal hyperplasia (steroidogenic acute regulatory protein), and cytochrome P450 oxidoreductase deficiency (POR). These rare forms of CAH are also associated with impaired fertility as presented in single case reports or small series of cases (Table 1). Most publications on

Congenital lipoid hyperplasia	<p>Severe form:</p> <ul style="list-style-type: none"> • Infertility is found in both 46XX- and 46XY-affected individuals. • Spontaneous puberty and menses have been observed in 46XX-affected individuals¹⁰⁶; there are anovulatory cycles with development of ovarian cysts.¹⁰⁷ • Successful pregnancies have been reported with reproductive assistance.¹⁰⁸ <p>Partial form: There is wide variation in gonadal function in both men and women.^{109,110}</p>
17 α -Hydroxylase/17,20-lyase deficiency	<p>Severe form: There is hypergonadotropic hypogonadism and infertility (impaired spermatogenesis and folliculogenesis) in both 46XX- and 46XY-affected individuals.¹¹¹</p> <p>Partial form:</p> <ul style="list-style-type: none"> • Case reports of girls with spontaneous puberty and irregular or regular menses. • Single pregnancy has been reported after IVF¹¹²; there are several other case reports of failed IVF.
3 β -HSD deficiency	<p>Infertility is usually seen in both 46XX- and 46XY-affected individuals, with isolated reports of spontaneous puberty and conception.¹¹³</p>
11 β -Hydroxylase deficiency	<p>Severe form: It resembles classic 21-hydroxylase deficiency.</p> <ul style="list-style-type: none"> • Successful pregnancies of affected women have been reported.¹¹⁴ • TART can develop in men.⁸³ <p>Mild or nonclassic form: It resembles nonclassic 21-hydroxylase deficiency.¹¹⁵</p>
P450 Oxidoreductase deficiency	<p>Sexual development during puberty is disturbed in patients of both sexes, but experience is limited.¹¹⁶</p>

Abbreviations: HSD, hydroxysteroid dehydrogenase; IVF, in vitro fertilization; TART, testicular adrenal rest tumor.

impaired fertility in CAH focus on 21-hydroxylase deficiency; unless otherwise indicated, in the authors' review the term *CAH* refers to 21-hydroxylase deficiency.

FERTILITY IN WOMEN WITH CONGENITAL ADRENAL HYPERPLASIA

Pregnancy and Fertility Rates

Estimates of spontaneous pregnancy and fertility in women with CAH correlate with the severity of the enzymatic defect, with the lowest reported rates in salt-wasting CAH and the highest reported rates in nonclassic disease. Older papers report extremely low spontaneous fertility rates (0%–10%) among women with salt-wasting CAH and moderately low rates (33%–60%) in women with the simple-virilizing type.^{2–6} However, these results do not take into account whether or not patients were actively pursuing conception. Indeed, compared with the general population, adult women with classic CAH are less sexually active and less likely to engage in heterosexual relationships or actively pursue motherhood.^{7,8} These facts are likely to contribute to the overall low fertility rates in this population. Reports of the pregnancy rate for women with classic disease actually trying to conceive are much more optimistic. A more recent evaluation of 106 women with classic CAH (81 with salt wasting and 25 with simple virilizing) showed that of the 23 who actively pursued conception, 91.3% achieved pregnancy. Pregnancy rates were similar in the salt-wasting (88.9%) and simple-virilizing (92.9%) groups, but those with simple-virilizing CAH were more likely to seek pregnancy.⁹

Fertility in patients with nonclassic (NC)-CAH seems to be mildly reduced. Cumulative pregnancy rates at 6 and 12 months among treated and untreated women who want pregnancy have been reported at little less than the general population at 67% and 76%, respectively.¹⁰ Pregnancy rates may vary according to a study, from approximately 65% up to a normal rate of 95% among those seeking conception.^{8,11–13} These studies involve women who came to medical attention either because of symptoms of hyperandrogenemia or infertility and, therefore, are likely to represent a more severe phenotype. The true fertility rate in nonclassic women is difficult to assess because many nonclassic patients with mild symptoms never seek medical attention and remain undiagnosed.

Proposed Factors Contributing to Reduced Fertility

Both classic and nonclassic congenital adrenal hyperplasia

Chronic anovulation and endometrial dysfunction have been described in women with CAH.^{14,15} The most salient factor that can lead to these abnormalities in both classic and nonclassic CAH is adrenal androgens excess, including adrenal hypersecretion of progesterone. Elevated serum androgens can negatively affect reproductive function by several complex mechanisms that include alterations of the hypothalamic-pituitary-gonadal (HPG) axis and a direct effect on the ovary itself.^{14,16}

Although the exact mechanisms by which elevated serum androgen may affect the HPG axis remain unclear, animal studies and studies in women with polycystic ovarian syndrome (PCOS) suggest that elevated androgens may alter normal central feedback pathways or interfere with the gonadotropin-releasing hormone (GnRH) pulse generator, thus, hindering ovulation.^{17–19} Timing of the exposure to androgens, that is, during puberty, may also be important.¹⁹ Estrogens produced from aromatization of excess androgens have also been proposed to suppress the HPG axis, thus, leading to anovulation and irregular menstrual cycles.²⁰ Regardless of the mechanism, luteinizing hormone (LH) pulsatility and secretion abnormalities have been reported in women with CAH. Compared with controls, women with nonclassic CAH have increased LH pulse amplitude but normal intervals.²¹ In women with classic CAH,

perinatal androgenization of the neuroendocrine function has been proposed to lead to LH hypersecretion.²² More recently, poor adrenal control was found to be associated with reduced LH pulse frequency and amplitude.²³ Finally, elevated serum androgens have been proposed to affect folliculogenesis directly and to modulate ovarian hormone secretion by several pathways, including inhibition of follicle-stimulating hormone (FSH)-stimulated LH receptor formation in granulosa cells.²⁴

Ovarian hyperandrogenism with secondary PCOS is a common finding in both classic and nonclassic CAH²² because of chronic exposure to excess adrenal androgens, which can impair hypothalamic sensitivity to progesterone and subsequently cause LH hypersecretion. PCOS can hinder fertility through ovarian androgen production, anovulation, and irregular menstrual cycles.^{16,25,26}

Another postulated factor contributing to decreased fertility is increased adrenal progesterone production in CAH. The elevated progesterone levels may potentially impede ovulation and implantation by altering GnRH pulsatility and interfering with endometrial development.²⁷ Other reported effects of excess progesterone are diminished sperm motility and thickening of cervical mucus, thereby acting as a form of contraception. Continuous high levels of progesterone (in contrast to the normal biphasic pattern in a healthy woman) have been documented in CAH and may adversely affect both the quality of oocytes and implantation.^{10,14,16,28}

Although testicular adrenal rests are a relatively common finding in men with CAH, ovarian adrenal rests have been infrequently reported in women with CAH.^{29–33} Ovarian adrenal rest tumors are difficult to identify with conventional imaging,³⁴ however, so it is possible that they are a more significant contributor to impaired fertility than currently estimated.

Factors unique to classic congenital adrenal hyperplasia

Women with classic CAH may face additional challenges related to their sexual and reproductive function. In these women, the excessive adrenal androgen secretion in utero affects the development of the external genitalia, including the presence of a urogenital sinus, labial fusion, and varying degrees of clitoral hypertrophy. Depending on the introital width, vaginal length, and clitoral integrity, sexual intercourse may be prohibitively uncomfortable and, thus, reduce chances for pregnancy.¹⁴

Women with classic CAH report being less sexually active and engaging in relationships less frequently than the general population.⁷ Postsurgical difficulties may contribute to these behaviors. A study of adult women with classic CAH who had undergone genital surgery reported reduced clitoral sensation, vaginal stenosis, and painful intercourse, negatively affecting intercourse frequency.³⁵ Short-term results on younger patients who have undergone newer surgical techniques, such as nerve-sparing ventral clitoroplasty, have shown improved innervation and clitoral sensation.^{36,37} Further studies in this cohort are needed to document if fecundity rates improve along with the evolution of surgical techniques.

Psychosexual development and psychological factors may also play a role in the reduced pregnancy rates in women with classic CAH. Prenatal exposure to high adrenal androgens seems to affect typically gender-related behavior. Girls with classic CAH have been shown to have more masculine interests in terms of sports, toys, and play behavior.³⁸ They also report low interest in getting married and performing a traditional child-care role, which may be an important factor.³⁹ Although behavior may be more masculinized, most adult women with CAH have a clearly female sex identity and gender dysphoria is rare. Most patients report a heterosexual orientation, but there is an increased rate of homosexual and bisexual orientation compared with the general population.³⁸

Women with primary adrenal insufficiency also have reduced fertility⁴⁰; therefore, cortisol deficiency itself may affect folliculogenesis and, thus, impact fertility in women with classic CAH. Glucocorticoid receptors have been shown to be present in the ovary,^{14,41} and *in vitro* fertilization (IVF) success rates are increased with higher cortisol/cortisone ratios.⁴² A direct role of cortisol on oocyte maturation or reproductive potential, however, is not clear.

Fertility Treatments

Almost all patients with classic CAH require glucocorticoid replacement in order to ovulate, and salt wasters require mineralocorticoid replacement as well. Therefore, spontaneous conception without any treatment in this patient group is exceedingly low.¹⁴ Nonclassic patients diagnosed because of symptoms of hyperandrogenemia are also likely to benefit from therapy, although spontaneous pregnancies without any glucocorticoid replacement have been reported in rates close to 57% to 65% in this population.^{10,13}

Women with CAH may conceive while on routine maintenance therapy. However, some patients may require higher doses of glucocorticoids in order to adequately suppress adrenal androgen and progesterone secretion.¹⁴ Serum progesterone concentrations, in particular, may remain elevated despite adequate suppression of 17-hydroxyprogesterone,⁴³ a situation that may require treatment with higher glucocorticoid doses than routine replacement. Indeed, using a regimen of prednisolone 2 to 5 mg 3 times per day to decrease circulating progesterone levels to less than 2 nmol/L during the follicular phase, Casteras and colleagues⁹ were able to attain high spontaneous pregnancy rates among women with classic disease.

For patients who remain anovulatory despite appropriate glucocorticoid and mineralocorticoid therapy and satisfactory androgen and progesterone suppression, ovulation can be induced with injectable gonadotropins or clomiphene.⁴⁴ As many adults with CAH suffer from obesity and insulin resistance,⁴⁵ an adjunct therapy with metformin can be considered, although data on its effects on androgen secretion and ovulation are limited at the moment. A decrease in circulating adrenal androgen concentrations was documented in a recent small study using metformin in diabetic women with nonclassic CAH.⁴⁶ Ovulation rates were not studied in this report.

Bilateral laparoscopic adrenalectomy is a controversial but potentially effective treatment for rare cases in which adequate adrenal androgen and progesterone suppression cannot be attained with medical therapy alone.⁴⁷ Although adrenalectomy will effectively remove the adrenal source of excess androgens, it also increases the risk for adrenal crisis, especially if patients are not completely compliant with medical therapy.⁴⁸ An increase in adrenocorticotrophic hormone (ACTH) may also stimulate any adrenal rest tumors present in the ovaries.

IVF is another option if other fertility treatments are ineffective. For women with CAH whose partners are carriers, preimplantation genetic diagnosis can be performed to determine if CAH is present in embryos before they are transferred to the uterus. With this method, the parents have the option of selecting embryos unaffected by CAH for implantation.⁴⁹

PREGNANCY AND ITS OUTCOMES

A growing body of literature reports on practice management and outcomes of women with CAH who achieve pregnancy.^{5,9,15,43,50} Spontaneous miscarriages have been reported at higher rates among glucocorticoid-untreated women than in the general population. These rates reach those of the general population with steroid

therapy.^{9,10,13} A single report suggests that women with CAH may be at high risk for gestational diabetes.⁵ This finding has not been confirmed by other studies, although it is unclear if and how patients were screened for this complication in various publications. Rates of preeclampsia or premature delivery do not seem to be affected.⁹ Stress doses of glucocorticoids are recommended for labor and delivery, using similar protocols as in primary adrenal insufficiency. Finally, cesarean section is usually performed in individuals with prior genital reconstructive surgery, although vaginal deliveries have also been reported.^{15,50}

Maternal use of dexamethasone to prevent virilization of the external genitalia of a female fetus affected with CAH remains a topic of heated debate, the details of which are outside the scope of this review. For women with CAH who carry an unaffected baby, hydrocortisone, prednisone, or prednisolone are the preferred steroids as these medications are inactivated by the placental 11 β -hydroxysteroid dehydrogenase type 2 and, therefore, do not affect the fetus. However, there is no consensus or established guidelines on the management of glucocorticoid and/or mineralocorticoid doses during pregnancy.^{43,50} One approach is to maintain prepregnancy doses and adjust them as needed based on clinical symptoms. Alternatively, therapy can be adjusted to maintain serum adrenal androgen concentrations in the upper normal range for laboratory-established pregnancy norms. Regardless, management of a pregnant woman with CAH can be challenging for multiple reasons. Symptoms of fatigue, nausea, and vomiting are common in pregnancy and overlap with those of adrenal insufficiency. Overtreatment with steroids can lead to fluid retention, excessive weight gain, and hypertension. In addition, optimal adrenal suppression during pregnancy in CAH is difficult to assess because of the multiple changes in steroidogenesis that occur during pregnancy.^{4,50,51} They include a significant increase in adrenal steroid secretion along with altered steroid clearance, an increase in sex hormone-binding globulin and an increase in placenta aromatization during the third trimester. Despite all of these concerns, many pregnancies do not require an increase in prepregnancy glucocorticoid doses⁹ and few obstetric problems have been reported thus far under the care of a multidisciplinary team.

Fetal outcomes are thus far reassuring. Current experience includes reports on approximately 190 babies born to mothers with classic disease.^{4-7,9,52-54} No virilization was observed with the exception of 2 babies born to untreated or poorly treated mothers.^{55,56} The lack of fetal masculinization is attributed to the protective effect of placental aromatase, which converts maternal androgens into estrogens. However, one should remain aware that the placental capacity for aromatization can be overcome in cases of extreme hyperandrogenemia, such as seen with maternal luteomas. Beyond this concern, fetal growth restriction and fetal distress have been linked to poorly treated adrenal insufficiency^{57,58} and can be applicable to CAH pregnancies. Higher rates of babies born small for gestational age were observed in one study in CAH,⁵² but the findings have not been replicated by others. Finally, long-term follow-up data remain limited at the moment^{5,52} and raise no particular concerns but need to be validated by future studies.

FERTILITY IN MEN WITH CONGENITAL ADRENAL HYPERPLASIA

Fertility and Fecundity Rates

Although the subject of fertility in CAH is more frequently addressed in the literature from the female perspective, fertility remains an important topic of investigation in affected men. Earlier reports failed to show impairment in fertility.⁵⁹ However, more recent studies from Europe document significantly reduced fecundity and fertility rates

in men with classic disease compared with age-matched controls or the general population.^{60,61} Similar results were observed in another large study of 65 adult men with classic CAH. In this cohort, only 37% of affected men attempted fertility and 67% of them were successful, rates again significantly lower than in the general population.⁸ The largest reported series to date looking at men with CAH is from a French group and includes 219 men. In those who reported cohabitation with a female partner, 51% stated that they had at least one child, a rate that is significantly lower than the French general population whereby 79% had fathered a child.⁶²

Little is known about fertility rates in men with nonclassic disease. There are several case reports of men with nonclassic CAH and reduced fertility because of low sperm counts, which was reversed with glucocorticoid treatment.^{63–66} However, in a recent study of 222 men who underwent a fertility evaluation because of abnormal sperm parameters, none were diagnosed with CAH.⁶⁷ Of interest, study participants were of mixed Jewish backgrounds, a population with high prevalence for nonclassic CAH. The authors do not know of any large studies directly investigating fertility in men with nonclassic CAH.

Factors Contributing to Reduced Fertility

Testicular adrenal rest tumors (TARTs) have been widely described in men with CAH and are considered to be the main culprit in reduced fertility in this population. Dysregulation of the HPG axis, Sertoli and Leydig cell dysfunction, glucocorticoid overtreatment, elevated body mass index (BMI), as well as psychological factors have also all been described as contributing factors. In addition, men with 46, XX karyotype who have CAH are unable to conceive.

Testicular adrenal rest tumors

TARTs are benign tumors, histologically resembling adrenocortical tissue and typically found in the rete testes, located at the hilum of the testicle (mediastinum testis). The rete testis consists of a network of interconnecting tubules that carry sperm from the terminal part of the seminiferous tubules to empty it into the efferent ducts. Because of their location, even small sized tumors can cause obstruction of the terminal seminiferous tubules, resulting in mechanical oligospermia or azoospermia.

Wilkins and colleagues⁶⁸ published the first case of TART in 1940. Multiple case reports followed.^{66,69–72} The reported prevalence of TARTs varies widely between 0% and 94%,^{8,59,60,62,73,74} depending on the age, hormonal control of the patients, and the surveillance method that was used. A limited number of studies in the pediatric population has indicated that these tumors are already present in early childhood, with a prevalence anywhere from 18% to 43%, in patients as young as few weeks of age.^{69,75–79} Attempts to link the presence of TART with the *CYP21A2* genotype have demonstrated no particular association, with tumors being detected in patients with salt-wasting *null* and *I2splice* mutations,^{61,80,81} simple virilizing *I172N* mutation,^{73,82} and even in men with nonclassic disease.⁶¹ TARTs have also been described in men with 11- β hydroxylase deficiency^{79,83} and 3- β hydroxysteroid dehydrogenase deficiency forms of CAH.⁶¹

The cause of TART is not completely understood, although recent studies have shed some light on the subject. It has been proposed that TARTs originate from ectopic adrenal cells that descend with the testes during fetal life and grow under ACTH stimulation; however, this hypothesis has been challenged by recent data.⁸⁴ Clinical evidence demonstrates that tumor growth is promoted in conditions whereby ACTH levels are high, such as in poorly controlled CAH and Nelson syndrome, and is reduced with high doses of glucocorticoids, suggesting the presence of ACTH

receptors on tumor cells.^{66,85} Recent molecular studies have supported the presence of ACTH and angiotensin II receptors as well as adrenal-specific enzymes, such as CYP11B1 and CYP11B2, directly on the tumor cells.⁸⁶ In addition, adrenal-specific steroids have been detected in blood from gonadal veins of men with TARTs⁸⁷ suggesting that these tumors have steroidogenic capacity similar to adrenals. Interestingly, some men with CAH never develop TART, despite poor adrenal control, suggesting complete regression of testicular adrenal cells prenatally. Conversely, others do not respond to intensifying glucocorticoid treatment with a reduction in tumor size.^{88,89} Furthermore, Reich and colleagues⁹⁰ failed to observe an association between adrenal hormone control and TART development, again suggesting that factors other than ACTH may contribute to tumor growth. More recently, gene expression studies from TART-derived tissue revealed the presence of both adrenal cortex and Leydig cell-specific genes and expression of ACTH, angiotensin II, and LH/human chorionic gonadotropin (hCG) receptors.⁸⁴ The results provide evidence that cells in TART derive from totipotent embryonic cells that resemble fetal Leydig cells. Growth of these cells under ACTH stimulation in prenatal and postnatal life in patients with CAH and further proliferation by increased LH secretion during puberty have been proposed to lead to TART formation in men with CAH.⁸⁴

Leydig cell dysfunction

Decreased testosterone levels have been described in several studies investigating men with CAH.^{73,74,82} Although direct intratesticular mechanisms, such as TART, can cause Leydig cell damage, inadequately controlled adrenal androgens and their conversion to estrogens can suppress gonadotropins, primarily LH secretion. Cross-sectional studies as well as isolated case reports have demonstrated that men with CAH may have high androstenedione and estradiol levels along with low LH and testosterone levels, indicating an HPG axis dysregulation,^{66,73,74,82,91} whereas others may have normal LH levels and low testosterone levels, indicating that TARTs may impair Leydig cell function either mechanically or by local steroid production.^{74,82} In turn, impaired Leydig cell function leads to reduced semen volume and sperm number.^{74,79,82} In the largest study to date, sperm analysis was performed in 71 men with classic CAH; more than 40% were found to have significant oligospermia or azoospermia, and TART was a major risk factor.⁶² In one study looking at men with classic CAH, all but one patient had normal GnRH stimulation test results, indicating that HPG axis dysfunction can be overcome by stimulation and should be reversible.⁸² LH suppression along with low testosterone has also been described in men with nonclassic CAH.^{63–66}

Sertoli cell dysfunction

Serum inhibin B levels, which serve as a reliable marker of Sertoli cell function and number as well as seminiferous tubule damage,^{92–94} have been demonstrated to be lower in men with CAH.^{61,62,82,95} Inhibin B levels showed a strong positive correlation with all semen parameters, including decreased sperm count, decreased concentration, abnormal morphology, and lower motility.⁸² TARTs have been shown to cause testicular parenchymal damage and seminiferous tubule obstruction in adult men with CAH, and the prevalence of TART has been shown to be significantly higher in men with low inhibin B levels than in men with normal inhibin B levels.⁶² Inhibin B levels have also been shown to be lower in prepubertal boys with CAH who have no evidence of TART, implying that these patients may have had impaired Sertoli cell development independent of tumor effect.⁷⁸

Glucocorticoid overtreatment

Overtreatment with glucocorticoids in CAH has been associated with suppression of the HPG axis^{82,96} and increased BMI.^{8,97,98} Obesity in itself is associated with an increased likelihood of abnormal semen parameters and reduced fertility in otherwise healthy men,^{99,100} likely caused by aromatization of androgens to estrogens in the adipose tissue and subsequent dysregulation of the HPG axis.⁹⁹ Mirroring the studies in the general population, patients with CAH who have abnormal semen parameters demonstrate increased total and abdominal body fat and greater fat to lean mass ratio compared with men with CAH with normal semen.⁶¹ Furthermore, metabolic syndrome in CAH has been linked to both high glucocorticoid replacement doses⁸ and lower fertility and fecundity rates.⁶¹

Psychological factors and quality of life

It is unclear if psychological factors and issues contributing to quality of life have a similar impact on male fertility and fecundity rates as they do in women with CAH. The rate of marriage has been reported to be the same⁶¹ or even higher than in healthy controls.¹⁰¹ Men with CAH have been shown to have lasting employment rates comparable with healthy controls; however, they were reported to be on sick leave and receive disability pension more often than healthy controls,¹⁰¹ which may play a role in their desire to have children. Anxiety and depression scores were also increased.⁸ Further studies are needed to determine whether these factors influence fecundity rates in men with CAH.

Diagnostic Approach and Evaluation

The work-up of impaired fertility in a men with CAH is multifold and should include an assessment of adrenal hormone secretion and function of the HPG axis, measurement of inhibin B concentrations, as well as semen analysis. Because TART is the most common cause of infertility, men with CAH should be screened for these tumors early on in the evaluation. As the tumors are embedded within the rete testes, practitioners should not rely on palpation alone for TART detection. Typically tumors greater than 2 cm can be palpated; however, imaging techniques, such as MRI and ultrasonography, can pick up tumors only a few millimeters in diameter.^{74,89} Because ultrasound is quick, noninvasive, and inexpensive, it is the study of choice for TART screening and monitoring. The age at which screening should start has not been established, but some clinics propose imaging in boys as young as 8 years of age.⁹⁶

It is important to note that TART may be mistaken for Leydig cell tumors, and cases of unnecessary orchiectomy have been reported.^{8,102} Although the tumors may be difficult to differentiate, several clinical features can aid in the differential. Up to 80% of TARTs are bilateral, whereas only 3% of Leydig cell tumors are present in both testes. Reinke crystals are found in 25% to 40% of Leydig cell tumors and are absent in TARTs. Reassuringly, malignant degeneration has never been described in TARTs; however, it occurs in 10% of Leydig cell tumors.⁹⁶

A TART classification system has been proposed by Claahsen-van der Grinten and colleagues⁹⁶ and is summarized in **Table 2**. Beyond an effect on fertility, large TARTs can cause significant discomfort and pain.

Fertility Treatments

Because TART is the most common cause of impaired fertility in men with CAH, most of the treatment efforts aim at tumor reduction. Intensifying glucocorticoid treatment is the mainstay of medical therapy; however, there are no specific treatment protocols in place, and glucocorticoid dosing and treatment outcomes have mostly been reported

Table 2**Classification of TART**

Stage 1	Adrenal rest cells present within the rete testes and are not detected on ultrasound. No treatment necessary is necessary.
Stage 2	Adrenal rest cells become visible on ultrasound as one or more small hypoechoic lesions. Optimizing glucocorticoid therapy frequently leads to tumor regression.
Stage 3	There is further growth of adrenal rest cells with compression of the rete testes. Because of obstruction of the seminiferous tubules, oligospermia and azoospermia may already be present and hormonal gonadal dysfunction is evident. Tumor size can be temporarily reduced with high glucocorticoid dosing, but tumor growth will typically resume when the dose is lowered again.
Stage 4	There is further tumor growth with progressive obstruction of the rete testes with fibrosis and focal lymphocytic infiltrates. Glucocorticoid therapy is typically not effective, and testes-sparing surgery is the treatment of choice.
Stage 5	There is irreversible damage of testicular parenchyma.

Adapted from Claahsen-van der Grinten HL, Hermus AR, Otten BJ. Testicular adrenal rest tumors in congenital adrenal hyperplasia. *Int J Pediatr Endocrinol* 2009;2009:624823; with permission.

Table 3**TART treatment strategies: case report summary**

Case Report	Original Dosage	TART Treatment	Outcome
23-y-old man with well-controlled SV-CAH, bilateral TART, and azoospermia ¹¹⁷	Hydrocortisone 30 mg divided twice daily (16 mg/m ²)	Dexamethasone 0.75 mg divided 3 times daily Two 7-mo courses	<ul style="list-style-type: none"> • Successful pregnancy with each course of therapy • Cushingoid features
30-y-old man with poorly controlled SW-CAH, 1.5-y history of infertility, bilateral TART, and poor sperm quality ⁹⁵	Hydrocortisone 10 mg daily Fludrocortisone 0.05 mg daily	Hydrocortisone 10 mg TID Dexamethasone 0.1 mg daily	<ul style="list-style-type: none"> • Partial bilateral TART regression after 1.5 mo and complete regression on one side after 2 y • 6 mo on treatment semen quality significantly improved and spontaneous conception occurred • Adrenal androgens well controlled • No cushingoid features
26-y-old man with poorly controlled SW-CAH, 4-y history of infertility, bilateral TART, and azoospermia ⁷¹	Not described	Dexamethasone 0.5 mg twice daily Fludrocortisone 0.05 mg twice daily	<ul style="list-style-type: none"> • Spontaneous conception approximately after 3 mo of therapy (repeat semen analysis and paternity testing not performed) • Complete regression of TART
37-y-old man with previously undiagnosed SV-CAH, infertility, unilateral TART, and azoospermia ⁷²	None	Dexamethasone 0.5 mg daily	<ul style="list-style-type: none"> • Complete regression of TART within 1 y • Normal sperm parameters

Abbreviations: SV, simple virilizing; SW, salt-wasting.

as individual cases, a selection of which is summarized in **Table 3**. High-glucocorticoid dosing has side effects and is, therefore, not acceptable to some patients. Because angiotensin II may stimulate tumor growth, mineralocorticoid therapy in patients with salt-wasting (SW)-CAH should also be optimized.⁸⁶ Surgical treatment has been reserved for more advanced TART staging, such as stage 4, whereby glucocorticoid treatment is no longer effective and testes-sparing tumor removal may prevent further testicular damage. Surgery for stage 5 tumors does not reverse testicular damage and has not been demonstrated to improve pituitary-gonadal function; therefore, surgery is primarily performed to reduce pain and discomfort.^{86,96,103} Claahsen-van der Grinten and colleagues,⁹⁶ a Danish group with significant TART experience, recommends conducting a testicular biopsy before surgery to evaluate the surrounding testicular parenchyma and the extent of gonadal damage.

Traditional infertility treatments, such as clomiphene citrate,¹⁰⁴ combination of hCG and FSH,¹⁰² and intracytoplasmic sperm injection,¹⁰⁵ have been described in men with CAH. Glucocorticoid dosing should be optimized because overtreatment with steroids can both suppress the HPG axis and lead to weight gain and metabolic syndrome, further compromising fertility. Men with CAH who have an elevated BMI should aim to lose weight. As testicular damage secondary to TART can be progressive and because there may be additional risk factors that can lead to infertility in men with CAH, perhaps the idea of semen analysis and sperm cryopreservation should be discussed with families early on in the clinical course.

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