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Reproductive and fertility challenges in adolescents with congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) carries reproductive implications that begin to manifest in childhood and adolescence and extend into adulthood. This review examines the reproductive challenges that emerge during adolescence in individuals with CAH and discusses strategies to optimize long-term reproductive outcomes. In females, reproductive outcomes are shaped by endocrine dysregulation, psychosexual development, prior genital surgery and psychosocial factors, with women with classic CAH showing reduced birth rates compared to the general population and more severe genotypes associated with poorer outcomes. In classic CAH, androgen excess and elevated 17-hydroxyprogesterone impair ovulation, menstrual regularity and endometrial receptivity. In non-classic CAH, fertility is generally less affected, although delayed diagnosis and untreated hyperandrogenism may still contribute to subfertility. Psychosexual development poses additional challenges in females with classic CAH, shaped by prenatal androgen exposure, surgical interventions and body image concerns. In males with classic CAH, fertility impairment arises primarily from hypogonadotropic hypogonadism and testicular adrenal rest tumors, which often develop during puberty and may compromise spermatogenesis. In contrast, fertility issues in males with non-classic CAH are uncommon. Adolescence is a particularly sensitive period, with potential delays in sexual development, relationship formation, and heightened psychosocial vulnerability. Therefore, it represents a critical window for anticipatory guidance and transition care, encompassing early discussion of fertility, genetic counseling and future reproductive options. Optimized hormonal treatment before conception is central to improving reproductive outcomes. Overall, a multidisciplinary, developmentally sensitive approach is essential to support long-term reproductive health and quality of life in patients with CAH.

KEYWORDS

adolescence, congenital adrenal hyperplasia, fertility, testicular adrenal rest tumor, transition

Introduction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders characterized by impaired cortisol biosynthesis due to defects in adrenal steroidogenic enzymes (1). In approximately 90% of cases, CAH is caused by mutations in the gene encoding 21-hydroxylase, resulting in 21-hydroxylase deficiency (21OHD) (1, 2). The clinical spectrum depends on residual enzyme activity and ranges from the severe classic salt-wasting (SW) form, typically presenting in the neonatal period, to

the simple virilizing (SV) form with partial cortisol deficiency and the milder non-classic CAH (NCCAH), which often remains undiagnosed until later in life (3). Reduced cortisol production leads to chronic adrenocorticotrophic hormone (ACTH) stimulation and consequent adrenal androgen excess, which underlies many of the clinical manifestations of the disease (1).

Diagnosis of CAH is primarily based on measurement of 17-hydroxyprogesterone (17OHP), the steroid precursor that accumulates in 21OHD. Newborn screening using dried blood spot 17OHP allows early detection of classic CAH and timely prevention of adrenal crises. Serum 17OHP concentrations >240 nmol/L are diagnostic of classic CAH. In patients with mildly elevated basal 17OHP concentrations or a high clinical suspicion, an ACTH stimulation test is recommended to confirm the diagnosis and distinguish between classic and non-classic forms. A stimulated 17OHP concentration >30 nmol/L supports the diagnosis of NCCAH, whereas values >300 nmol/L are typically observed in classic CAH. Additional steroid profiling and molecular genetic testing may help distinguish 21OHD from rarer forms of CAH and confirm the underlying genotype (1, 4).

While the diagnosis and early management of classic CAH are often established shortly after birth, adolescence represents a critical and often under recognized phase in the disease trajectory. During this period, the long-term consequences of chronic hyperandrogenism, glucocorticoid therapy and prior surgical interventions become increasingly apparent. In females, androgen excess may disrupt pubertal development, menstrual cyclicity and ovulation, whereas in NCCAH, a milder but persistent androgen excess frequently results in a phenotype resembling polycystic ovary syndrome, including hirsutism, acne and menstrual irregularities (5). In males, pubertal development may be complicated by hypogonadotropic hypogonadism and the development of testicular adrenal rest tumors, both of which may impair future fertility (6).

Beyond endocrine disturbances, psychosocial and psychosexual aspects are central to adolescence and adulthood. Individuals with CAH may face challenges related to body image, gender identity, sexual development and interpersonal relationships (7–10). In females with classic CAH in particular, prior genital surgery, genital appearance and concerns about sexual function may affect self-esteem and intimacy (11–14). Moreover, emerging awareness of reproductive potential may give rise to uncertainty and anxiety. Chronic disease burden, including lifelong medication, frequent medical evaluations and adrenal crises, may further influence psychosocial development and quality of life.

Fertility impairment has been documented in both women and men with CAH and arises from both endocrine

dysregulation and psychosocial factors. Adrenal-derived steroids can interfere with the hypothalamic–pituitary–gonadal axis, leading to ovulatory dysfunction in females and hypogonadism in males (6, 15–17). Epidemiological studies suggest reduced reproductive rates in affected individuals, particularly in women with classic CAH, although outcomes have improved with optimized treatment and early diagnosis (11, 18). Importantly, reproductive decision-making is not solely biologically determined but is also influenced by psychosocial factors, including partnership formation, sexual health and personal reproductive goals (19).

This review summarizes the reproductive, psychosexual and psychosocial challenges arising during adolescence in patients with CAH and discusses their implications for fertility, pregnancy planning and long-term reproductive outcomes, highlighting opportunities for early intervention and multidisciplinary care.

Fertility and fecundity in women with classic and non-classic CAH

Reproductive function in females with CAH is shaped by both endocrine and psychosocial determinants (Figure 1), with slight differences between classic and non-classic disease, and overall lower birth rates compared to the general population. In a Swedish population-based cohort including 272 women with CAH, only 25.4% had at least one child, and affected women also had fewer children and were older at the birth of their first child than controls (20). Similar findings of reduced fertility, pregnancy rates, and live birth rates have been described in other cohorts (21, 22). Disease severity is also a contributing factor, with more severe genotypes associated with lower birth rates (22).

In classic CAH, impaired fecundity is largely attributable to endocrine dysregulation. Menstrual disturbances occur in more than 30% of women not receiving hormonal contraception (23–26). Excess adrenal androgens impair follicular maturation and ovulation (15, 16). In addition, elevated 17OHP, a hallmark of 21OHD, exerts progesterone-like effects either through direct binding to the progesterone receptor or via conversion to progesterone, thereby impairing endometrial development, altering cervical mucus and contributing to anovulation, effectively creating a milieu similar to that induced by progestin-only contraception (15, 27, 28). Elevated androgen and progesterone concentrations may also disturb luteinizing hormone pulsatility, thereby further compromising menstrual cyclicity (29). Nevertheless, adequate glucocorticoid replacement can restore hormonal balance and fecundity can approach that of the general population in well-controlled patients (22).

By contrast, reproductive outcomes in NCCAH are usually more favorable. Most women with NCCAH conceive spontaneously (30, 31), although reduced fertility is still reported in 10%–30% of women of reproductive age (30, 32, 33). The main mechanism of subfertility is anovulation, as reflected by the good response to ovulation induction (28, 34). Similar to classic CAH, however, elevated adrenal-derived progesterone and 17OHP may adversely affect cervical mucus and endometrial receptivity and thus reduce implantation

Abbreviations

11-OHA4, 11 β -hydroxyandrostenedione; 11-OHT, 11 β -hydroxytestosterone; 11-KA4, 11-ketoandrostenedione; 11-KT, 11-ketotestosterone; 17OHP, 17-hydroxyprogesterone; 21OHD, 21-hydroxylase deficiency; ACTH, Adrenocorticotrophic hormone; CAH, Congenital adrenal hyperplasia; FSH, Follicle-stimulating hormone; hCG, Human chorionic gonadotropin; HPG axis, Hypothalamic–pituitary–gonadal axis; LH, Luteinizing hormone; NCCAH, Non-classic Congenital adrenal hyperplasia; SHBG, Sex hormone-binding globulin; SV, Simple virilizing; SW, Salt-wasting; TART, Testicular adrenal rest tumor.

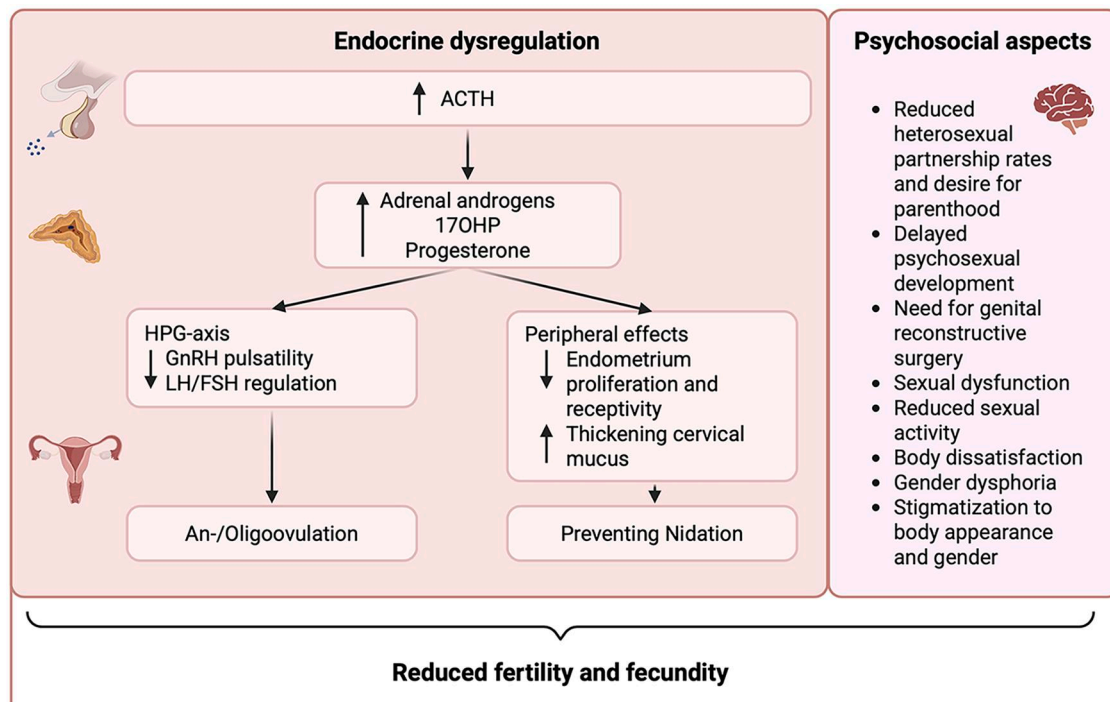


FIGURE 1

Mechanisms contributing to impaired fertility in females with CAH. Schematic overview of endocrine and psychosocial factors contributing to reduced fertility in females with CAH. CAH, congenital adrenal hyperplasia; ACTH, adrenocorticotropic hormone; 17OHP, 17-hydroxyprogesterone; HPG-axis, hypothalamic–pituitary–gonadal-axis; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

potential (28). Early diagnosis and treatment improve outcomes, with higher live birth rates reported in women diagnosed before conception than in those diagnosed only after pregnancy (86% versus 69%) (30). Likewise, miscarriage rates decrease from about 25% before diagnosis to around 10% after diagnosis and treatment (30, 33).

Psychosocial factors further modify reproductive outcomes, particularly in classic CAH. Lower birth rates in these women may partly reflect reduced desire for parenthood rather than absolute infertility, especially in the SW phenotype (22). In a study by Casteras et al. (21), only 23.6% of women with classic CAH expressed a wish for pregnancy, whereas this proportion was closer to 50% in women with NCCAH (30, 33). NCCAH is also frequently diagnosed during infertility work-up, underlining its relevance in reproductive medicine. In a retrospective multicenter study by Auer et al. (26) of 72 adult women with different CAH phenotypes, time to pregnancy was often prolonged, with a median ranging from 8 to 24 months, and 25.6% required fertility-enhancing medication and 30.8% underwent assisted reproductive techniques (26). Despite this, live birth numbers per woman and miscarriage rates were similar across phenotypes and broadly comparable to the general population (26).

Psychosexual challenges in women with classic CAH

Psychosexual outcomes also influence fertility and fecundity in females with classic CAH and arise from prenatal androgen

exposure, chronic endocrine imbalance, genital surgery and psychosocial influences. These factors emerge early in life and continue to affect sexual function, body image, gender identity and intimate relationships throughout adolescence and adulthood.

Genital reconstructive surgery remains a central concern in girls with classic CAH and has important implications for later sexual and reproductive health. Depending on the degree of virilization, surgery may be necessary to reduce urogenital complications such as infections associated with a persistent urogenital sinus and to create anatomical conditions that may permit future sexual intercourse and spontaneous conception (35). Although many procedures are performed in infancy, repeated surgery is often required in later childhood or adolescence (36). These repeated procedures carry significant psychological burden and require careful interdisciplinary decision-making and access to psychological support.

Compared with controls, females with CAH report higher rates of sexual dysfunction (11, 36, 37). Persistent vaginal stenosis, reduced lubrication, diminished genital sensitivity, dyspareunia and difficulties with penetrative intercourse have all been described, often together with lower sexual activity (11, 12, 38–40). In one cohort, more than one-third of women with CAH had never engaged in vaginal intercourse at all (11). At the same time, more recent data suggest that sexual quality of life may be acceptable in some operated women despite objective functional limitations, with satisfactory cosmetic and functional outcomes being reported (36). Genotype severity is also relevant, as patients with null mutations have reported lower sexual satisfaction and more surgical complications (13). These findings highlight the need to identify vulnerable

subgroups early, particularly during childhood and adolescence, and to discuss sexual health proactively rather than waiting until adulthood.

Most 46,XX individuals with CAH who are raised as females later identify as female, but a minority experience gender-related distress or dysphoria (9, 10). A review by Dessens et al. (41), found that 94.8% of such individuals maintained a female gender identity, with 5.2% reporting gender identity-related difficulties. Higher rates of gender-related problems were reported in chromosomal females raised as males (41). A meta-analysis by Babu and Shah (42) similarly found gender identity disorder in approximately 4% of CAH females raised as females, compared with substantially higher rates in those raised as males. Although these data generally support female sex assignment at birth in 46,XX CAH, management should remain individualized, especially in highly virilized cases (41, 43). Factors associated with later gender dysphoria include marked virilization, delayed diagnosis and poor hormonal control (44). Documented cases of gender dysphoria in children and adolescents emphasize the importance of repeated and developmentally appropriate psychological assessment throughout childhood and adolescence (45).

Sexual orientation represents another relevant dimension, although findings in the literature are inconsistent. Most females with CAH identify as heterosexual and some cohorts report rates similar to those in the general population (12, 36). Other studies have suggested a higher prevalence of bisexual or homosexual orientation, possibly linked to prenatal androgen exposure and masculinization of behavior (46), whereas other reports did not confirm this association (47–49). Irrespective of orientation, adolescence is a vulnerable period for psychosexual development. Girls with CAH may initiate romantic relationships and sexual experiences later than their peers and may show delayed development in social and intimate domains (22, 50). These patterns may extend into adulthood, with lower rates of partnerships and marriage reported in adulthood (47, 49, 51). Reduced sexual activity, apprehension regarding intimacy and stigmatization related to both body appearance and gender have also been reported (8, 49).

Beyond sexual function and orientation, girls and women with CAH often face broader psychosocial challenges. More male-typical interests and behaviors have been reported, including occupational preferences and recreational activities, possibly reflecting the organizational effects of prenatal androgen exposure on neurodevelopment (52). Chronic illness itself may also contribute, as repeated hospitalizations, lifelong medication and regular examinations during childhood and adolescence may affect social and psychosexual development independently of androgen exposure. Comparative work suggests that some delays in dating and sexual experiences may be attributable to chronic illness more generally, rather than CAH alone (39). Disease severity is also relevant, as women with SW CAH have reported greater concerns regarding sexuality and relationships than those with less severe forms (13, 47, 53).

Body image represents a further important dimension, closely linked to psychosexual health and overall quality of life. Women with CAH frequently report dissatisfaction with their general appearance and their genitalia (14, 40, 50). While repeated surgery has been associated with body dissatisfaction in some

studies, others have reported acceptable postoperative cosmetic results (54, 55). Recent evidence indicates poorer body image and reduced physical, psychological and social quality of life in women with CAH compared with healthy controls (7). Importantly, support during childhood and adolescence is particularly relevant, as satisfaction with professional care and family support during these years predicts better adult quality of life and body image (7, 54). Thus, adolescence is not merely a period when challenges emerge, but also a critical window in which supportive multidisciplinary care may alter long-term outcomes.

Non-classic CAH in girls and women

Whereas classic CAH is usually diagnosed in the neonatal period, as mentioned above, NCCAH often remains clinically silent during infancy and early childhood. Most affected girls have normal external genitalia and become symptomatic only later, typically in late childhood or adolescence, when hyperandrogenic features emerge (5). Compared with classic CAH, NCCAH is characterized by milder but still increased adrenal androgen production and an exaggerated ACTH-stimulated androgen response. Dehydroepiandrosterone sulfate levels are usually normal, whereas androstenedione and testosterone are elevated and may overlap with levels seen in polycystic ovary syndrome (56–59). Ovarian dysfunction and peripheral conversion of steroid precursors further contribute to the phenotype and are often accompanied by polycystic ovarian morphology (60, 61).

In childhood, the first manifestation is most often premature pubarche, which may occur very early in life. In one study of girls younger than 10 years, 92% presented with premature pubarche (32), whereas earlier data suggested premature adrenarche in up to 60% of children with NCCAH (62). During adolescence, hirsutism, acne, alopecia, clitoromegaly and menstrual disturbances become more prominent (3, 32). In a cohort of 220 adolescents, 56% presented with irregular menses and 9% with primary amenorrhea (32). These features highlight that NCCAH often first becomes clinically relevant during adolescence, when reproductive endocrine function is becoming established.

In adulthood, women with NCCAH typically present with hyperandrogenic symptoms and hypothalamic-pituitary-ovarian dysfunction, including menstrual irregularities, ovulatory dysfunction and polycystic ovarian morphology (32, 60, 63–65). Delayed diagnosis may lead to prolonged hyperandrogenism, menstrual dysfunction and later subfertility, underscoring the importance of recognizing NCCAH during adolescence, when counseling and treatment can be initiated before reproductive issues become clinically pressing.

Fertility issues in men with CAH

Disturbances of the hypothalamic-pituitary-gonadal (HPG) axis and subnormal testosterone levels are commonly observed in males with 21OHD, with reported prevalence ranging from 20% to 52% (17, 66–68). In line with this, impaired semen

quality and reduced sperm concentrations have been described in up to two-thirds of affected individuals (17, 68–72). Data on semen quality in adolescents and young males with CAH remain however scarce (73). Epidemiological evidence further suggests that fertility rates may be reduced in individuals born before the introduction of neonatal screening, whereas outcomes appear comparable to the general population in those diagnosed and treated early (18).

The pathophysiology of subfertility in males with CAH is complex and involves both central and testicular mechanisms, as depicted in Figure 2. On the one hand, chronic excess of adrenal-derived steroids suppresses the HPG axis via negative feedback, while on the other hand testicular adrenal rest tumors (TARTs) may directly compromise testicular function and spermatogenesis.

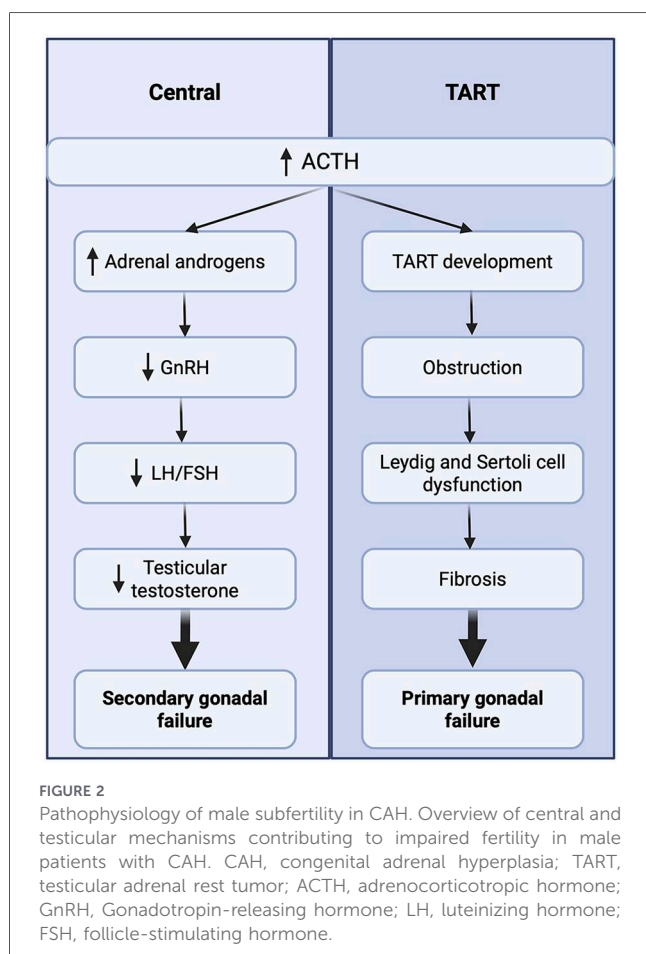
Most patients present with hypogonadotropic or normogonadotropic hypogonadism (17) as multiple adrenal-derived steroids can contribute to HPG-axis suppression: testosterone via the androgen receptor, androstenedione following aromatization to estradiol via the estrogen receptor and 17OHP and progesterone via the progesterone receptor.

More recently, 11-oxygenated adrenal androgens have emerged as important further contributor to androgen excess in CAH (74–76). These steroids, defined by an oxygen group at carbon position 11 (77), are primarily derived either from androstenedione (originating from 17OHP in 21OHD) or via 21-deoxycortisol (77–79). Key representatives include 11 β -

hydroxyandrostenedione (11-OHA4), 11 β -hydroxytestosterone (11-OHT), 11-ketoandrostenedione (11-KA4) and 11-ketotestosterone (11-KT). Notably, 11-KT and its derivative 11-ketodihydrotestosterone exert androgenic effects comparable to classical androgens and could therefore further contribute to HPG-axis suppression (75). In line, elevated levels of these 11-oxygenated androgens have been demonstrated in men with hypogonadotropic hypogonadism and insufficient disease control (24, 80). This finding may however also help explain the clinical observation that some patients with low circulating testosterone do not necessarily exhibit typical symptoms of androgen deficiency.

Because adrenal and testicular testosterone are biologically indistinguishable, the androstenedione/testosterone ratio can be useful to identify the primary source of testosterone in men with 21OHD. Values >0.5 suggest relevant adrenal androgen contribution, whereas ratios ≥ 1 indicate predominantly adrenal testosterone production and are commonly associated with subnormal testosterone (17). Biochemically, this constellation is often further characterized by decreased inhibin B levels (17, 68).

While secondary hypogonadism is often reversible and fertility may improve with adequate glucocorticoid therapy (81, 82), it must be kept in mind that excessive glucocorticoid exposure can also impair gonadal function (66, 71). In rare cases, prolonged androgen excess may lead to persistent suppression of the HPG-axis, even when biochemical control is achieved, resembling the effects seen with long-term exogenous androgen use. In such cases, testosterone replacement therapy may be required. In particular, semen quality appears to depend not only on current hormonal control but also on prior disease management (73).

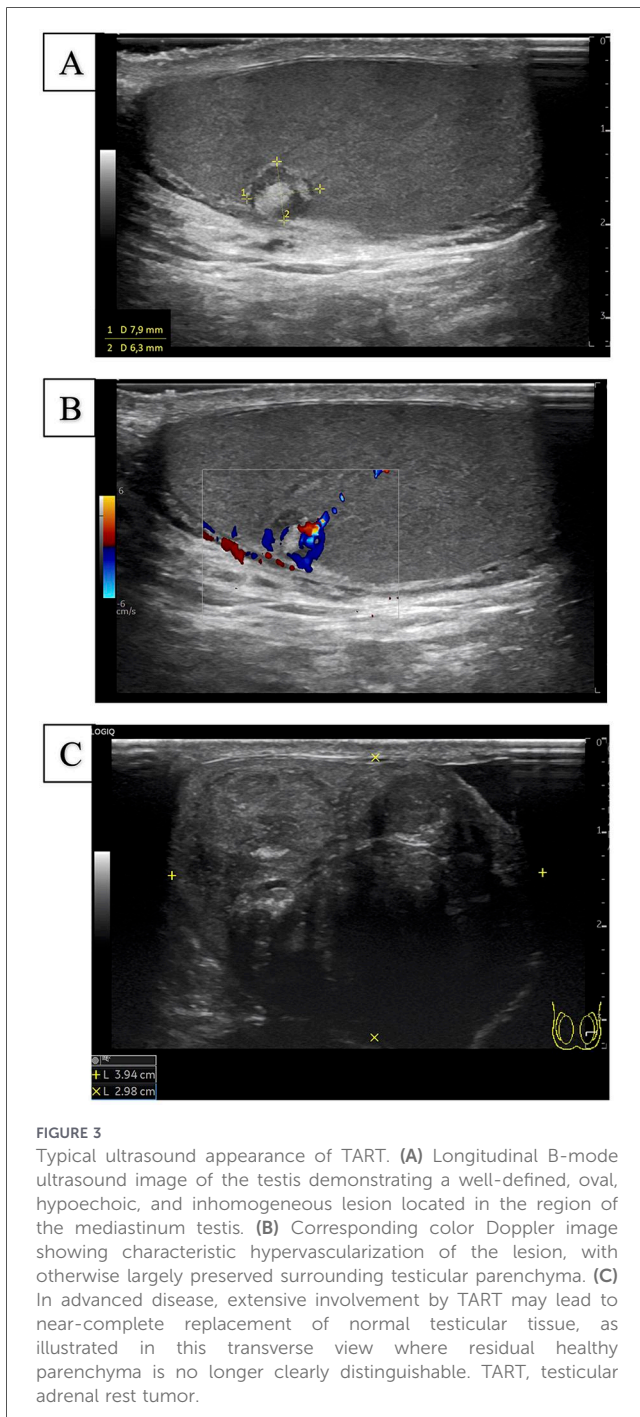


Testicular adrenal rest tumors (TART)

TART are benign lesions that histologically resemble adrenocortical tissue. They typically originate in the rete testis and can progress from small, solitary hypoechoic nodules to multiple lesions and, eventually, to larger conglomerate masses located near the mediastinum testis (83). Due to their central location, lesions smaller than 2 cm are usually not detectable by palpation, making scrotal ultrasound the diagnostic modality of choice. Typical sonographic appearance of TART is depicted in Figure 3. Magnetic resonance imaging does not provide relevant diagnostic advantages and is therefore not routinely recommended.

The prevalence of TART is estimated at 30%–50% in adolescent boys and adult men with classic CAH (63, 69, 84–86), with bilateral occurrence in approximately 80% of cases (87). Traditionally, TARTs were thought to arise from ectopic adrenal cells that migrate with the gonads during embryonic development. More recent evidence, however, suggests that they may originate from pluripotent steroidogenic cells with features of both adrenal and testicular lineage, possibly representing fetal Leydig cells or their precursors (88). Their development is likely initiated during fetal life, potentially driven by elevated ACTH levels (89–91).

In line with this concept, TARTs are more frequently observed in patients with severe genotypes, particularly those with null mutations and are rare in NCCAH (17, 73, 83, 92, 93). While



adrenal rest usually regresses spontaneously in early infancy, persistent ACTH stimulation as in CAH promotes their proliferation (24). Consistently, their presence is associated with poor biochemical control and chronic ACTH excess (73, 94). Although TARTs can be detected in childhood, they predominantly develop during puberty (73, 83, 95, 96), suggesting an additional role of luteinizing hormone (LH) in promoting tumor growth (97). Notably, new TART development in adulthood is uncommon, even in the setting of inadequate treatment, possibly due to depletion or apoptosis of precursor cells (66).

Larger TARTs may lead to mechanical obstruction of the seminiferous tubules, Sertoli cell dysfunction and germ cell damage and subsequent subfertility or infertility (87).

Accordingly, impaired semen parameters and azoospermia are more frequently observed in patients with larger tumors (73). Overall, biochemical hypogonadism appears however to be a stronger determinant of impaired spermatogenesis than local tumor effects alone (17, 72, 85).

In addition to mechanical effects, TARTs are capable of steroidogenesis due to their adrenal-like enzymatic profile (87, 98). They can produce androgens, including testosterone and 11-oxygenated androgens, which may negatively affect spermatogenesis via paracrine mechanisms (95, 99). Elevated levels of 11-oxygenated androgens have also been associated with the presence of TART (24, 80). However, it remains unclear whether these steroids directly contribute to impaired fertility or primarily reflect ACTH-driven tumor growth in poorly controlled patients.

Male patients with NCCAH are rarely clinically recognized. Although NCCAH is autosomal recessive and would be expected to occur equally in both sexes, males are underrepresented in clinical cohorts, most likely because they are often asymptomatic (3, 61). As occurrence of TART in male NCCAH is much less common than in classic CAH and fertility-relevant manifestations are rare, NCCAH plays only a minor role in the discussion of reproductive challenges in adolescence.

Important aspects for pregnancies and partner pregnancies

Genetic counseling

Genetic counseling is an essential component of reproductive care and should be offered to all patients with CAH (100–103). Because CAH is inherited in an autosomal recessive manner, reproductive risk depends on the carrier status of both partners. Classic 21OHD occurs in approximately 1:10,000 to 1:15,000 newborns, whereas NCCAH is considerably more common, with an estimated prevalence of around 1:1,000 and higher frequencies in some ethnic groups (104–106). Carrier frequency has been estimated at roughly 1:55 in the general population, although higher frequencies have also been reported (107). Because biochemical screening is insufficiently reliable for identifying carriers, genetic testing remains the preferred approach (108, 109).

If both partners carry a pathogenic variant, the probability of an affected child is 25%, with 50% of offspring being carriers. If one parent is affected and the other partner's status is unknown, the estimated risk of having a child with classic CAH is approximately 1:120, with a lower risk in NCCAH (110). These inheritance patterns have direct implications for family planning and prenatal counseling and should therefore be addressed well before conception. Counseling should begin in adolescence as part of structured transition care, so that young people with CAH understand inheritance, partner testing and reproductive risks before pregnancy is being considered.

The importance of counseling is further highlighted by the possible consequences of androgen excess in affected female fetuses. Cortisol deficiency leads to an ACTH overproduction, causing fetal adrenal androgen excess, which can result in

varying degrees of virilization of the external genitalia, including clitoromegaly, labial fusion and urogenital sinus formation, occasionally complicating sex assignment at birth (111–117). Because the severity of virilization correlates with genotype (118), counseling also helps families understand why prenatal and postnatal outcomes may differ between disease forms. Given the later surgical, sexual, urinary and psychosocial sequelae that may follow genital virilization and corrective procedures, these complications are directly relevant to the reproductive future of adolescents with CAH and their offspring (7, 8, 11, 36, 119–122).

Prenatal dexamethasone treatment

Prenatal dexamethasone treatment aims to prevent or reduce virilization of the external genitalia in female fetuses affected by classic CAH. Unlike hydrocortisone or prednisolone, dexamethasone is not inactivated by placental 11 β -hydroxysteroid dehydrogenase type 2 and therefore reaches the fetus, where it can suppress ACTH secretion and subsequent adrenal androgen excess (123). To be effective, treatment must begin before gestational week 8, that is, before differentiation of the external genitalia begins (124).

Despite its biological rationale, prenatal dexamethasone remains highly controversial. As definitive prenatal diagnosis is often only available later in the first trimester, many fetuses who cannot benefit from treatment, especially unaffected females and male fetuses, are exposed unnecessarily (3, 125). Although newer non-invasive strategies have reduced unnecessary treatment, only a minority of treated pregnancies ultimately derive direct benefit (126, 127). In addition, concerns exist regarding possible maternal adverse effects and long-term fetal consequences, including neurocognitive, behavioral, and metabolic outcomes, although the evidence remains limited and in part conflicting (128–135). Current recommendations therefore limit this intervention to specialized centers and preferably to research settings (136). Even so, this topic warrants discussion with adolescents with CAH, as awareness of prenatal therapeutic options, their limitations, and their ethical implications should be established before reproductive decision-making begins.

Optimal treatment in women to achieve and maintain pregnancy

For women with CAH who wish to conceive, endocrine optimization is the cornerstone of management. The main goal is to suppress excess adrenal androgens and reduce 17OHP and progesterone concentrations sufficiently to restore ovulation and a receptive endometrium (100). Hydrocortisone is generally preferred because of its short half-life and partial mineralocorticoid activity (136). However, some patients require treatment intensification or the addition of prednisolone to suppress steroid excess more consistently over 24 h (21, 137). Adequate mineralocorticoid replacement should also be ensured, as this may improve fertility even in patients without overt SW (21, 138). In women with NCCAH, conception is often spontaneous, but low-dose glucocorticoid therapy may be needed in selected cases, particularly in the setting of anovulation or hyperandrogenism (30, 33). If conception is not achieved despite

optimized endocrine treatment, ovulation induction and assisted reproductive techniques can be considered (21).

Pregnancy should ideally be managed in specialized centers. Biochemical monitoring is complicated by physiological changes in steroid levels, so treatment is often guided more by clinical assessment than by laboratory targets (136, 137). In general, pre-pregnancy glucocorticoid and mineralocorticoid doses can often be continued during early pregnancy, with moderate glucocorticoid dose increases considered later in gestation (123, 137). Hydrocortisone and prednisolone are inactivated by the placenta and are therefore preferred, whereas dexamethasone should be avoided during pregnancy unless specifically used for prenatal treatment (117), as outlined above. Overall, maternal and neonatal outcomes are generally favorable when care is optimized, although higher cesarean section rates and variable risks of miscarriage, small-for-gestational-age infants and gestational diabetes have been reported (20, 139).

Optimal monitoring and treatment in men

Male patients with classic CAH should undergo regular screening for TART by scrotal ultrasound starting at around 8 years of age, followed by annual assessments during childhood and less frequent monitoring (e.g., every 2–5 years) in adulthood (1, 69).

Assessment of gonadal function should include measurements of LH, follicle-stimulating hormone (FSH), testosterone and sex hormone-binding globulin (SHBG), as well as inhibin B where available. Since normal testosterone and gonadotropin levels do not exclude gonadal dysfunction, the androstenedione/testosterone ratio should be calculated to distinguish between adrenal and testicular androgen sources.

Even in the absence of an immediate desire for paternity, sperm cryopreservation should be offered when TARTs are detected, given the risk of progression and the uncertain reversibility of testicular damage. Intensification of glucocorticoid therapy aimed at suppressing ACTH has been shown to reduce tumor size and, in some cases, restore testicular function and fertility (70, 140–143). This approach appears to be more effective in younger patients, whereas long-standing TARTs may become less responsive due to fibrotic changes (87). Therapeutic strategies may include the addition of low-dose dexamethasone in the evening (e.g., 0.25–0.5 mg) (95), although temporary higher glucocorticoid doses may be required in selected cases (0.5 mg three times daily) (144). There is preliminary evidence that the new modified release hydrocortisone (Efmody®) can result in significant improvements in sperm quality and gonadal function in general without increasing overall glucocorticoid exposure (145).

Experimental approaches, including the use of mitotane, have been reported but are limited by significant toxicity and should be reserved as a last-line option in refractory cases (146, 147) and therefore not in adolescents. Testis-sparing surgical resection has not been shown to improve fertility outcomes and should generally only be considered for patients with significant pain or local discomfort (148).

In patients with persistent hypogonadotropic hypogonadism, treatment with human chorionic gonadotropin (hCG) combined with FSH may improve spermatogenesis and fertility (149).

TABLE 1 Practical recommendations for reproductive and transition care in adolescents with congenital adrenal hyperplasia.

Age/life stage	Recommended assessment	Clinical purpose
11–13 years early adolescence	Introduce the transition programme, assess transition readiness, provide education regarding CAH (medication adherence, stress dosing, use of emergency medication) and gradually promote patient autonomy.	Establish self-management skills early and prepare for transition.
13–15 years	Regular assessment of pubertal development, biochemical control, psychosocial wellbeing, treatment adherence and readiness for increasing responsibility. Begin age-appropriate discussions on puberty, sexuality, fertility and reproductive health.	Optimize disease control while preparing adolescents for adult care.
Throughout male puberty	Clinical assessment of gonadal function with consideration of testicular ultrasound for TART surveillance, particularly in patients with poor hormonal control or abnormal examination findings.	Early identification of TART and preservation of fertility.
15–18 years	Repeat transition readiness assessment, reinforce adherence, discuss fertility preservation, contraception, pregnancy planning, inheritance and possible genetic counselling.	Facilitate informed reproductive decision-making before transfer.
16–19 years or according to readiness	Joint paediatric–adult transition clinic whenever possible, comprehensive medical summary, appointment with adult endocrinologist within 3–6 months after transfer and continued follow-up by a transition coordinator if available.	Minimize loss to follow-up and ensure continuity of care.
Any age when indicated	Referral to: - reproductive medicine for infertility or gonadal dysfunction - psychology for impaired adherence, body image concerns, psychosexual difficulties, anxiety, depression or reduced quality of life	Multidisciplinary management of reproductive and psychosocial complications.

Based on recommendations by the European Society for Paediatric Endocrinology (ESPE), European Society of Endocrinology (ESE) and the Endocrine Society (1, 150).

Once an adequate sperm quality has been achieved, cryopreservation of sperm should be considered to preserve fertility potential for future use.

In the long term, if semen quality remains poor or azoospermia persists into adulthood, assisted reproductive techniques such as intracytoplasmic sperm injection, with or without testicular sperm extraction (micro-TESE), may be considered (72).

Transition to adult care

Given that many of the reproductive, psychosexual and endocrine challenges discussed above emerge during adolescence and require lifelong management, structured transition to adult care represents a critical component of comprehensive CAH care. Rather than a single transfer, transition should be a gradual, multidisciplinary process beginning in early adolescence that promotes continuity of care, self-management, autonomy and psychosocial development. Accordingly, both the European Society for Paediatric Endocrinology (ESPE)/European Society of Endocrinology (ESE) transition guideline and the Endocrine Society recommend lifelong follow-up by experienced multidisciplinary teams to optimize endocrine control, reproductive health and long-term outcomes (1, 150).

Transition planning should begin in early adolescence and be individualized according to transition readiness rather than chronological age. Transition clinics should promote treatment adherence and self-management while providing age-appropriate counselling on sexuality, fertility, contraception, pregnancy planning and genetic counselling within a multidisciplinary team. Psychological support should be integrated throughout the transition process to address body image, emotional well-being, and treatment-related challenges (1, 150). Practical

recommendations for reproductive monitoring, fertility counselling, and transition care throughout adolescence are summarized in Table 1.

Conclusion

Adolescents with CAH face reproductive challenges long before parenthood becomes an immediate concern. In girls and young women, endocrine dysregulation, menstrual disturbance, genital surgery, body image concerns, delayed psychosexual development, and uncertainty regarding future fertility may all emerge during adolescence and influence reproductive trajectories into adulthood. In boys and young men, impaired gonadal function and TART may already develop during puberty, making early surveillance and intervention essential. Across both sexes, reproductive outcomes are strongly shaped not only by biological disease severity and hormonal control, but also by psychosocial support, structured transition care, and timely counseling. Adolescence therefore represents a decisive window for anticipatory guidance, including discussion of fertility, sexuality, genetic inheritance, partner pregnancy, prenatal options, and future pregnancy management. A multidisciplinary, developmentally sensitive approach is essential to optimize both reproductive health and long-term quality of life in patients with CAH.

Author contributions

LT: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition. MA: Writing – original draft, Writing – review & editing. HN: Writing – original draft, Writing – review & editing, Funding acquisition. NR: Writing –

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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