Fertility Treatment in Men with Classical and Nonclassical Congenital Adrenal Hyperplasia

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Abbreviations

17-OHP	17-Hydroxyprogesterone
A/T	Androstenedione-to-testosterone
ACTH	Adrenocorticotropic hormone
ART	Assisted reproductive technologies
CAH	Congenital adrenal hyperplasia
CI	Confidence interval
CYP11B1	Cytochrome P450 family 11 subfamily B member-1
CYP11B2	Cytochrome P450 family 11 subfamily B member-2
DSD	Disorder of sex development
FSH	Follicle-stimulating hormone
hCG	Human chorionic gonadotropin
HPG	Hypothalamic–pituitary–gonadal
HSD17B3	Hydroxysteroid 17-beta dehydrogenase-3
ICSI	Intracytoplasmic sperm injection
INSL3	Insulin-like-3
IVF	In vitro fertilization
LH	Luteinizing hormone
MC2R	Melanocortin-2 receptor
micro-TESE	Microsurgical testicular sperm extraction
MRI	Magnetic resonance imaging
NCAH	Nonclassical congenital adrenal hyperplasia
OR	Odds ratio
TARTs	Testicular adrenal rest tumors

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Introduction

Although female infertility and its treatment is an extensively studied topic, male fertility issues in patients with congenital adrenal hyperplasia (CAH) are less described [1]. Indeed, both the disorder per se (e.g., multiple genotypes and phenotypes) and the male infertility make the individualized approach a challenging task.

Small studies in 1970s have failed to demonstrate an association between CAH and male infertility [2]. On the contrary, most recent studies have reported a significant impact of CAH on fecundity and fertility outcomes [1, 3–5]. More specifically, in a French national survey, 51% of patients with CAH have been reported to have at least one child, a prevalence significantly lower compared with the French general population (79%) [3]. A British study has reported that almost 40% of males with CAH have used fertility treatment services (24/65) with a success rate of 67% [4]. From another perspective, an analysis of the Swedish CAH registry (n = 221) has demonstrated that the odds ratio (OR) of being a biological father of at least one child has been 0.5 [95% confidence interval (CI) 0.4–0.7] for CAH males compared with controls matched for year, place of birth, and migration status [5]. An interesting point raised by the same study is that the introduction of neonatal CAH screening in Sweden has not significantly changed the likelihood of having a child, even though the OR is doubled (OR_{before} = 0.5 versus OR_{after} = 1.0) [5]. The previous study has also provided data specific for patients with non-classical adrenal hyperplasia (NCAH), a group for which evidence is even more scarce in literature [5]. More specifically, the OR of being a biological father has been 3.7 (95% CI 0.9–15) for NCAH males compared with matched controls from general population [5]. The difference between the two forms of the disease has been attributed to a variety of factors. Compared with the classical form, NCAH may not be diagnosed as often, thus hampering a properly powered estimation of infertility in these individuals [5]. Another reason can be that testicular adrenal rest tumors (TARTs), one of the most common reasons for male infertility, constitute a rather rare entity in patients with NCAH [6]. In line with this finding, the routine ultrasound screening for TARTs in patients with NCAH is not included in the Endocrine Society's most recent clinical practice guidelines [7].

An essential prerequisite of infertility treatment in men with CAH is the identification of its possible causes (Fig. 1). Some of them are attributed to the disease per se. The causes include TARTs, primary (hypergonadotropic) hypogonadism resulting from testicular dysfunction and secondary (hypogonadotropic) hypogonadism. Furthermore, sexuality problems may be related to the disease per se, given its effect on male sexuality [8]. Glucocorticoid administration may lead to increased body weight or even hypogonadism by suppressing gonadotropin secretion [8]. Finally, other infertility aspects (e.g., sexually transmitted infections, obesity, medications) may also accompany. Hence, accurate diagnosis of all comorbidities is of utmost importance in infertile men with CAH.

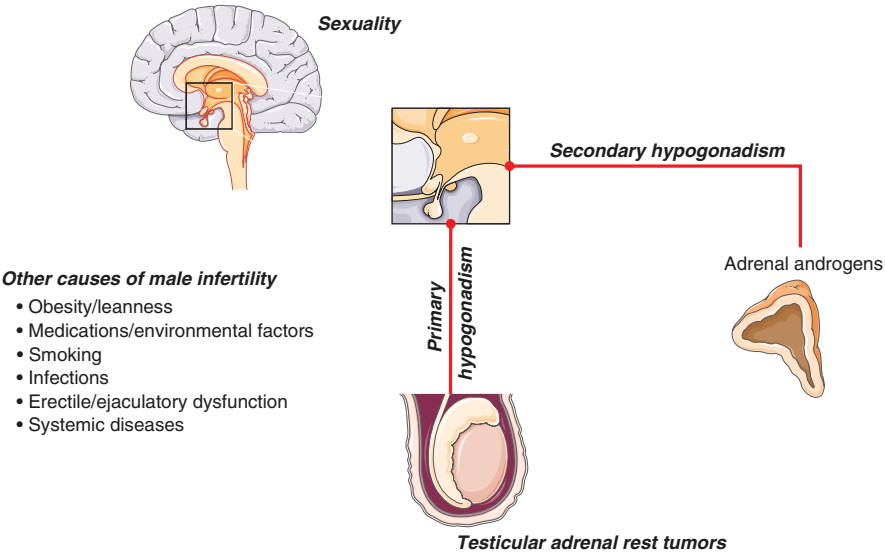

Fig. 1 The multifactorial etiology of infertility in congenital adrenal hyperplasia (CAH). Four mechanisms specific for CAH patients are identified (bold letters). Other causes of male infertility need to be taken into consideration. Parts of the figure were based on images by Servier Medical Art by Servier licensed under a Creative Commons Attribution 3.0 Unported License

Testicular Adrenal Rest Tumors

Testicular adrenal rest tumors (TARTs) constitute the most common cause of male infertility among CAH patients. These tumors are benign, mostly bilateral, and require early detection to prevent permanent testicular damage [9]. There are case reports in current literature stressing on the importance of these lesions in CAH, as TARTs can be the only manifestation [10].

Embryology

The pathophysiology of TARTs development has been studied extensively in the past years. The interplay between a specific primordial cell type nesting in rete testis during fetal development and exposure to growth factors pre- and postnatally constitute the main mechanism [9].

As far as cellular types are concerned, some authors have proposed primordial adrenal cells, while others have suggested that fetal Leydig cells may divide into TARTs, as the latter also express receptors and enzymes found in TARTs [9, 11]. A seminal paper by Val et al. has introduced a new concept in the embryology of TARTs [12]. More specifically, fetal and adult mouse testes have been demonstrated

to possess adrenal-like cells, expressing adrenal-specific markers; cytochrome P450 family 11 subfamily B member-1 (Cyp11B1) and Cytochrome-21 (Cyp21), and responding to adrenocorticotropic hormone (ACTH) and human chorionic gonadotropin (hCG). The authors have suggested that a common steroidogenic progenitor, originating in the area between the mesonephros and the gonad, can be responsible for TARTs formation in CAH [12]. Based on these findings, Engels et al. have hypothesized the presence of a pluripotent steroidogenic cell in humans, as well [11].

In line with the theory of pluripotent steroidogenic progenitor in humans, a study by Smeets et al. has provided molecular evidence that characteristics of both adrenal and gonadal cells are present in TARTs [13]. In gene expression analysis of TARTs, the authors have identified 1000- to 10,000-fold higher adrenal enzymes expression compared with testis. Those have been CYP11B1, cytochrome P450 family 11 subfamily B member-2 (CYP11B2), and melanocortin-2 receptor (MC2R). On the other hand, insulin-like-3 (INSL3) and hydroxysteroid 17-beta dehydrogenase-3 (HSD17B3) produced in Leydig cells have been expressed in TARTs at significantly higher levels compared with adrenal tissues. This complex steroidogenic profile can only be attributed to a less differentiated embryonic progenitor [13].

Considering growth factor exposure, ACTH's proliferative effect on primordial adrenal cells has been proposed as a possible contributor to TARTs development [9]. Compatible with the theory mentioned above, patients with NCAH rarely present with TARTs, probably because ACTH is only moderately increased. Engels and colleagues have stressed that ACTH exposure's timing is crucial and have reported that not all CAH patients with increased ACTH present with TARTs [11]. Nevertheless, TARTs have also been described even in patients with low ACTH concentrations [9]. Apart from ACTH, recent molecular analyses of TARTs tissues have suggested that angiotensin II and luteinizing hormone (LH) exposure, the latter appearing during puberty, can also play a role in the development and progression of these tumors [13].

Prevalence

A recent pooled analysis of 1315 patients by Engels and colleagues has estimated an overall prevalence of almost 40% (489 cases) [11]. Main factors associated with the presence of TARTs are patient's age, method of detection, and severity of the disease. In general, TARTs are more prevalent as the patient's age increases from puberty to adulthood [11]. Even though TARTs are considered rarer in children, a review of autopsy studies has reported seven CAH patients younger than 8 weeks, three of whom have demonstrated bilateral TARTs. Of note, TARTs have been identified in all patients older than 14 months of life [14]. More recent evidence is in line with these findings, suggesting that boys present with TARTs more frequently than expected, gonadal function [determined by follicle-stimulating hormone (FSH), LH, testosterone, and inhibin B concentrations] has not been impaired in any of the patients with TARTs compared with those without. As a result, the authors have concluded that gonadal function impairment may occur as the age progresses [15].

Furthermore, different diagnostic methods modify the estimated prevalence rates of TARTs [11]. More specifically, clinical examination fails to identify small tumors (see Diagnosis). On the other hand, ultrasonography and magnetic resonance imaging (MRI) can identify small size tumors; thus, imaging modalities have an important place in TARTs diagnosis. Finally, TARTs prevalence increases in parallel with disease severity. A genotype-specific association has been described, with salt-wasting forms demonstrating higher prevalence compared with the simple virilizing forms [11].

As far as NCAH is concerned, anecdotal reports occur [6]. Still, the review by Engels and colleagues has provided no specific estimate of TARTs in patients with NCAH [11]. Therefore, one can conclude that they constitute a rare entity.

The aforementioned data has been related to 21-hydroxylase deficiency (21-OHd). Even fewer data are available for other forms of CAH. In a study of boys and adolescent males, three out of five patients with 11-β hydroxylase deficiency have presented with TARTs. All subjects have demonstrated a suboptimal control of the disease [16]. In these patients, TARTs are associated with oligo- and azoospermia as in patients with 21-OHd [17]. Further assumptions are hard to be drawn, as evidence on TARTs and 11-β hydroxylase deficiency remains scarce.

Association with Hormonal Parameters

Given that TARTs have been described in patients with ACTH overproduction, such as Cushing's or Nelson's syndromes [18, 19], and TARTs have demonstrated ACTH-responsiveness [20], a series of studies have evaluated hormonal parameters as determinants of TARTs. More specifically, some authors suggest that the control of the disease (demonstrated by hormonal concentrations) play a role in the development of TARTs. According to Engels' pooled estimates, 58% of cases with TARTs have demonstrated inadequate hormonal control [11].

In line with the "poor control" concept, evidence is driven mostly from cross-sectional studies. Increased ACTH concentrations have been associated with TARTs presence [21]. Furthermore, in a recent multicentric European study of 121 patients, 17-hydroxyprogesterone (17-OHP) concentrations two times higher than the upper limit of the reference range have resulted in an OR for having TARTs of 28.0 (95% CI 3.1–252.5), while simply exceeding the reference range led to an OR of 18.7 (95% CI 2.2–158.1) compared with concentrations within the reference range [22]. The authors have also demonstrated that androstenedione concentrations above the reference range has been associated with 3.6 times greater odds of having TARTs (95% CI 1.0–12.7, significance not reached) [22].

Despite the evidence from cross-sectional studies on disease control parameters, a longitudinal analysis of 50 patients with classical 21-hydroxylase deficiency has failed to demonstrate any significant correlation. Pregnanetriol and serum 17-OHP concentrations have not been related to TARTs presence [23]. Similar observations have been made for long-term clinical control parameters, namely testicular volume, Tanner stage for pubic hair, and bone age [23].

As a conclusion, caution is required in the interpretation of clinical data connecting disease control with TARTs development. Most studies providing data are cross-sectional, and hence, the association should not necessarily imply causation. Furthermore, the number of patients enrolled in these studies is rather small, decreasing the power of estimates produced by them. Importantly, one needs to bear in mind that TARTs can be present even in patients with optimal hormonal control. Hence, more robust evidence is required for producing definitive conclusions, even though multifactorial etiology cannot be excluded [11].

Diagnosis

Clinical examination allows diagnosing TARTs larger than 2 cm. Ultrasonography is considered to be the diagnostic method of choice. Data on MRI stem from case reports and are rather scarce. Most TARTs are located in the rete testis and can affect one or both testicles [11]. A variety of ultrasonographic features characterizes TARTs: they can be round, lobular, or even irregular in shape, clearly defined from the testicular parenchyma [24]; the majority of them are hypoechogenic (without excluding hyperechogenic lesions) and usually demonstrate increased vascularity in color Doppler scans [24, 25].

It is important to mention that TARTs need to be differentiated from Leydig cell tumors of the testis. Their bilateralism, typical adrenal steroid secretion profile, response to glucocorticoids, and solely benign potential are characteristic features. However, Leydig cell tumors can be malignant in 10% of cases, and they exhibit Reinke crystals in pathologic specimens [11].

Staging

Even though TARTs are benign, histopathologic studies have proven that they can progress in size and cause irreversible obstructive pathology demonstrated as oligo- or azoospermia. Residual parenchyma biopsies following testis-sparing surgery (see Management options) have demonstrated impaired spermatogenesis [26]. This obstructive damage has been attributed to decreased tubular diameters, thickening of the lamina propria, peritubular fibrosis, and hyalinization [9, 26]. Furthermore, toxic damage to Sertoli and germ cells via paracrine hormone secretion by the tumor has also been implicated [9]. Apart from direct effects on testes, endocrine mechanisms have also been postulated [27]. More specifically, steroid production directly by TARTs can interfere with hypothalamic–pituitary–gonadal (HPG) axis. Blumberg-Tick and colleagues have demonstrated the secretion of 11-β-hydroxylated steroids in gonadal veins of patient with TARTs [27]. Adding to this, presence of TARTs has been correlated with increased concentrations of 11-oxygenated androgens (11-β-hydroxyandrostenedione, 11-β-hydroxytestosterone, 11-ketoandrostenedione, and 11-ketotestosterone) [28].

Table 1 Histopathologic classification of TARTs

Stage	Description	Clinical information
Stage 1	Microscopic detection of TARTs cells in the rete testes	• Regression during infant life • Clinically undetectable lesions
Stage 2	Proliferation and hypertrophy of TARTs cells	• Ultrasonographic detection
Stage 3	Continuation of proliferation, rete testes compression, testicular dysfunction	• Oligo- or azoospermia • Decreased inhibin B, increased FSH, LH • Glucocorticoids still effective
Stage 4	Lymphocytic infiltration focally, fibrosis (peritubular and in tumor)	• Glucocorticoids no longer effective
Stage 5	Irreversible damage to the testicular parenchyma: • Peritubular fibrosis • Tubular hyalinization Replacement of tumor with adipose tissue	

FSH follicle-stimulating hormone, *LH* luteinizing hormone, *TARTs* testicular adrenal rest tumors. Source: [9]

Claahsen-van der Grinten and colleagues have attempted to classify the histopathologic stages of TARTs to predict long-term sequelae better and guide therapy [9] (Table 1). Note that late stages provide little space for treatment, as testicular damage becomes irreversible.

Management Options

There are primarily two goals in the management of TARTs. The first is early detection via ultrasound screening in early stages of the disease, and the second is the reduction of tumor size with subsequent prevention of testicular failure.

As far as the first goal is concerned, informing patients about TARTs and subsequent risk of infertility remains an essential prerequisite of effective screening [11]. Moreover, periodically scanning males with classical CAH to assess TARTs development have been stressed in the most recent recommendations by the Endocrine Society [7]. Specific details, such as age at initial screening or screening frequency, remain uncaptured, as clinical data are scarce.

Based on the observation that children with CAH may present with TARTs, Claahsen-van der Grinten and colleagues have suggested that ultrasound screening must begin in childhood [29]. Engels and colleagues have proposed that screening should be conducted annually, starting at 8 years of age until adulthood. From adulthood on, biennial or triennial controls are sufficient [11]. In addition, as TARTs may cause progressive, irreversible gonadal failure, authors have advocated in favor of sperm cryopreservation in pubertal or young adult males with TARTs [11, 29, 30].

Intensification of glucocorticoid treatment is considered as the primary choice for treatment of TARTs [9, 11, 29]. The prevailing theory behind fertility

improvement is tumor shrinkage resulting from ACTH decrease after glucocorticoid administration [29]. It is important to stress that no prospective evidence is currently available [11].

Patients with second- or third-stage TARTs have been reported to achieve a decrease in TARTs size, reversal of azoospermia, normalization of hormonal profile, and pregnancies after recommencing, increasing the dosage, or altering glucocorticoid treatment to a longer-acting one [9, 31–33]. Regimens used include hydrocortisone combined with dexamethasone [31], dexamethasone [32], and fludrocortisone [33]. Prednisone may also be used [29]. Of note, patients presenting with salt-wasting phenotypes require additional mineralocorticoid replacement [34].

Glucocorticoid administration comes with certain restrictions. First of all, adverse effects need to be discussed with the patients before deciding on intensification. These include Cushingoid effects (e.g., body weight gain, striae) and reduced height (pubertal administration) [30, 32]. Of note, weight gain may also deteriorate the negative effects of CAH on fertility [6]. Furthermore, tumor shrinkage and therapeutic benefits may only be temporary for as long as intensified treatment is administered [9]. Finally, stage 4 TARTs are resistant to glucocorticoid treatment, while other treatment options remain of dubious value [9].

Surgical treatment constitutes another possible choice. Historically, orchiectomies have been considered the treatment of choice for patients with CAH, because the diagnostic conundrum between Leydig cell tumors and TARTs has prevailed. Given that orchiectomies have been radical, and the testis cannot be preserved, testis-sparing surgery has been quickly employed in TARTs surgery. Walker and colleagues have reported three cases of steroid-resistant TARTs treated with tumor enucleation resulting in a viable testis [35]. Still, the effect of surgery on fertility parameters has not been addressed [35]. A more recent study has examined testis-sparing surgery's effect on gonadal function in eight patients with stage 5 TARTs [36]. Tumor enucleation has resulted in no improvement of semen parameters, 6 and 22 months after the operation. As far as hormonal parameters are concerned, various changes have occurred, even though inhibin B concentrations have remained low in all patients. Two patients have demonstrated decrease in testosterone concentrations, indicating further gonadal damage attributed to surgery [36]. Based on the findings mentioned above, the role of surgery in the restoration of fertility remains uncertain. Hence, until new evidence is produced, surgical treatment should only be considered in cases of pain or discomfort caused by the tumor [11].

Apart from TARTs-specific treatments, classical assisted reproductive technologies (ART) have been applied in patients with TARTs. Yang and colleagues have reported the successful use of clomiphene citrate (25 mg daily) in a patient with TARTs treated with dexamethasone (initially 2 mg for 7 days, and then 0.25 mg daily) who has been unable to achieve pregnancy solely with steroid therapy. The patient's sperm number and volume have increased, and after five cycles of intrauterine insemination, the couple has achieved pregnancy [37]. Rohayem and colleagues have described the use of gonadotropin administration (hCG 1500 IU twice a week and FSH 150 IU three times a week) in a patient with persistent hypogonadotropic hypogonadism and TARTs despite steroid administration [38].

Murphy and colleagues have described intracytoplasmic sperm injection (ICSI) in a patient on prednisolone with azoospermia and TARTs. Spermatozoa have been obtained via testicular needle aspiration (TESE) and used for ICSI, which has resulted in live birth [39]. Microsurgical testicular sperm extraction (micro-TESE) has also been described in non-responsive cases with functional testicular parenchyma [30]. Kavoussi and colleagues have reported two patients with TARTs accompanied by orchialgia and azoospermia despite gonadotropic stimulation [40]. Resection of TARTs followed by TESE and ICSI leading to live birth has been reported in one patient, while the other has been opted for cryopreservation. The pain subsided in both patients [40].

In 2014, Bry-Gauillard and colleagues have reported mitotane use for fertility restoration in a 29-year-old male with azoospermia and bilateral TARTs [41]. Mitotane, a regimen inducing "chemical adrenalectomy," has resulted in normalization of hormonal profile (decrease in 17-OHP, increase in FSH, LH, inhibin B). The TARTs sizes have decreased, and 8 months after treatment, sperm counts have increased. In vitro fertilization (IVF) after ovarian stimulation has resulted in birth of a neonate, heterozygous to the mutation of the father. As the authors have concluded, mitotane can constitute as a "last resort" in patients with large, unresponsive tumors and severe sperm disorders (azoospermia) [41]. Of course, more data are required to produce definitive evidence on the drug's effectiveness in infertility treatment.

Disturbances of HPG Axis

Apart from TARTs, dysfunction of HPG axis may also cause male infertility. Hypogonadism remains a challenging concept, as males with CAH may present with normal or even increased testosterone concentrations, instead of decreased, due to excessive adrenal androgen production [42].

Given that no methods to differentiate adrenal from testicular androgens have been described, Engels and colleagues have proposed using androstenedione-to-testosterone (A/T) ratio to categorize patients in three categories based on androgen production source [22]. Those with testicular androgen production present with A/T values <0.5, those with adrenal origin present with values ≥ 1, while cases in between represent significant adrenal involvement [22].

Primary Hypogonadism

The principal cause of primary (hypergonadotropic) hypogonadism in patients with CAH is TARTs causing testicular dysfunction. A study of 50 men with CAH due to 21-hydroxylase deficiency has detected increased FSH concentrations in 11 patients [30]. Nine of them (82%) have presented with TARTs, whereas only two (12%) have

had no abnormalities in testicular ultrasound [30]. Similar findings have been observed in the study by Bouvattier and colleagues [3]. Increased FSH concentrations have been associated with TARTs presence. Seminal abnormal parameters have further demonstrated testicular damage and markedly decreased inhibin B levels.

Secondary Hypogonadism

Apart from eugonadism and primary hypogonadism, secondary (hypogonadotropic) hypogonadism seems to be a common entity among patients with CAH [3, 23, 30]. Adrenal steroids, produced in excess because of CAH, can be aromatized to estrogens and interfere with gonadotropic secretion. As a result, infertility may occur [43].

The exact prevalence of hypogonadotropic hypogonadism varies among studies. Variability in definitions leads to heterogeneity in prevalence estimation. In the study by Bouvattier and colleagues, 62 of 164 (37.8%) men have presented with decreased LH concentrations [3]. King and colleagues have reported that 26 of 50 patients (52%) have had at least one low LH value [30]. A study on 22 CAH patients have demonstrated that eight of them have had decreased serum testosterone concentrations with three have also exhibited low basal LH concentrations [23]. Finally, Engels and colleagues have reported that 12 of 90 patients with CAH have presented with low LH concentrations [22]. In the same study, an A/T ratio value >1.0 have been associated with reduced gonadotropin concentrations (OR 39.3, 95% CI 2.1–732.4). Therefore, the authors have stressed the role of adrenal androgens in the pathogenesis of secondary hypogonadism. Given the retrospective nature of the data, caution is required in their interpretation [22].

As far as treatment options are concerned, even though no prospective evidence for hypogonadotropic hypogonadism exists, retrospective data suggest that commencement, intensification, or altering glucocorticoid treatment seems to restore hormonal, seminal parameters, and fertility (nine patients) [30]. This has also been demonstrated in cases with NCAH (see below). Of note, glucocorticoid administration has uncovered a hypergonadotropic hypogonadism in one patient [30]. In nonresponsive cases, gonadotropin administration and ICSI with or without micro-TESE constitute possible alternatives [30].

Nonclassical CAH (NCAH) data is less abundant, mainly there are four case reports. Augarten and colleagues have reported secondary infertility in a patient with hypogonadotropic hypogonadism and poor semen quality. Treatment with prednisolone 10 mg daily has resulted in normalization of hormonal and seminal profile and fertility restoration, resulting to his second child a few months after treatment [44]. Wischusen and colleagues have stressed the reversible nature of NCAH-related hypogonadotropic hypogonadism and infertility in a patient receiving 0.5 mg dexamethasone daily, whose spouse has achieved pregnancy [45]. Finally, Trakakis and colleagues have reported a couple with NCAH and two failed IVF attempts, both wife and the husband have been treated with hydrocortisone

30 mg daily, and pregnancy has been achieved. As the authors stated, ART should only be reserved for patients unresponsive to glucocorticoid administration [46].

Disturbances in HPG axis and semen production can be attributed to overtreatment with glucocorticoids [23]. They may be the consequence of glucocorticoids' direct effect or weight gain [34]. Increased body weight alone can lead to hypogonadotropic hypogonadism, semen disturbances, and infertility in otherwise healthy males [47]. This observation has been shown in males with CAH, as well [6]. More specifically, males with CAH and abnormal semen parameters exhibit increased total and truncal fat mass and fat/lean mass ratio compared with males with CAH and normal semen [6]. Consequently, establishing optimal glucocorticoid dosage, when intensification is not required, constitutes an important step in infertility management [34]. Weight loss and adoption of a healthy lifestyle can also support fertility [6].

Sexuality Disorders

Even though CAH constitutes a disorder of sexual development (DSD) in women, primarily due to androgen excess in fetal period, its exact effect on male sexuality remains unknown [48]. Data are limited for robust conclusions to be drawn. Apart from fertility, sexuality disorders can greatly impair well-being and quality of life [4]. Hence, identifying and treating them should be a part of CAH clinical care.

A recent multinational European cohort study of patients with CAH treated in specialized centers has demonstrated comparable age of sexual debut, frequency of intercourse and sexual satisfaction with the general population [49]. Of note, disease severity (attributed to genotype) has been shown to negatively associate with sexual activity. Furthermore, a slightly increased prevalence of sexual desire problems has been reported in the cohort. More specifically, lack of sexual desire has been reported in 17.6% of males with CAH, compared with 11.7–15.7% in general population. Excessive desire has also been more frequent (23.1% versus 5–10%, respectively). As far as premature ejaculation is concerned, it has been reported by 25% of the patients [49].

Erectile dysfunction has been also studied. The aforementioned study has reported a slightly increased prevalence (18.7%) compared with the general population (12–23%, mean 16.2%) [49]. Other studies have reported increased estimates (55% and 41%) [4, 50]. Such differences can be attributed to different methods used to measure erectile dysfunction (standardized questionnaires or self-reports). Nevertheless, patients with CAH should be screened and treated for erectile dysfunction.

In conclusion, men with CAH constitute a distinct population displaying dysfunctional aspects of sexuality. These include desire problems and erectile dysfunction. In the future, larger studies can provide more precise estimates, focus on addressing confounding factors interacting with sexuality, and assess the efficacy of different treatment methods.

Conclusion

Infertility constitutes a common problem among males with CAH. A treatment algorithm is provided in Fig. 2. Additional causes of male infertility should always be sought for and treated. The management begins in adolescence at latest with ultrasonographic controls for TARTs and sperm cryopreservation if required. The specific TARTs stage leads to appropriate therapeutic approaches. These include glucocorticoid intensification, surgery for pain relief, and classical ART strategies. Lifestyle changes may facilitate fertility. Despite TARTs, patients with CAH present with different forms of hypogonadism with variable testosterone concentrations; hence, the A/T ratio should be used for the diagnosis. Finally, sexual history should be obtained, and sexual disorders need to be addressed.

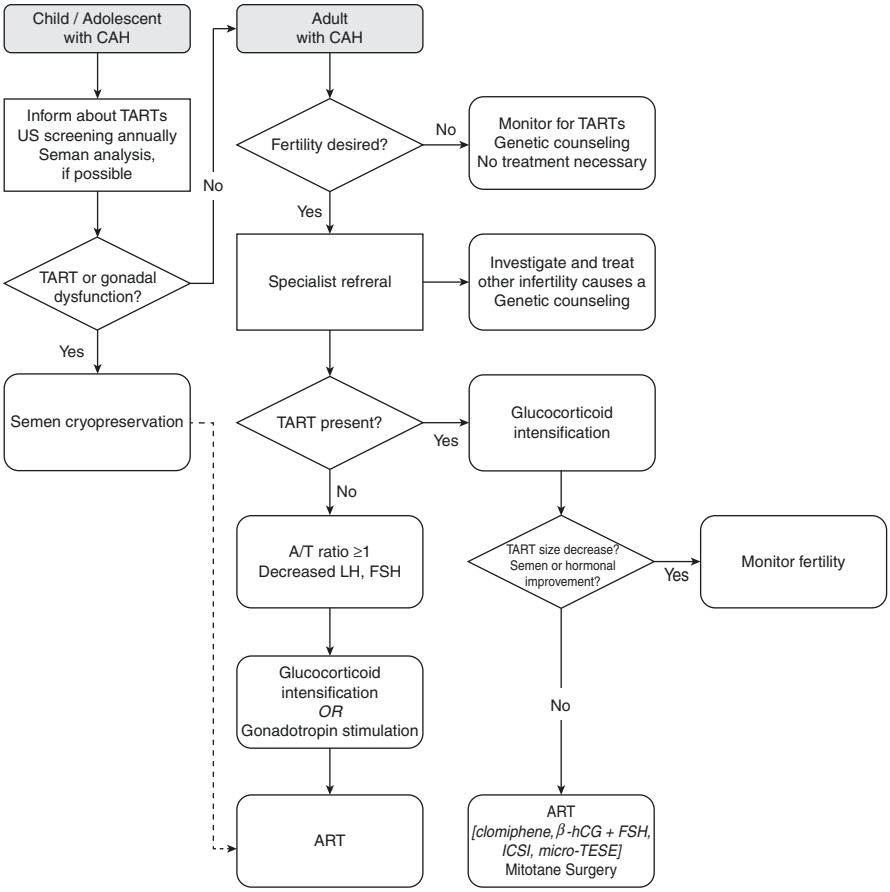

Fig. 2 Proposed CAH management algorithm for children and adults seeking fertility. [a]See Fig. 1. *ART* assisted reproductive technologies, *A/T* androstenedione-to-testosterone, *β-hCG* beta-human chorionic gonadotropin, *CAH* congenital adrenal hyperplasia, *FSH* follicle-stimulating hormone, *ICSI* intracytoplasmic sperm injection, *LH* luteinizing hormone, *TARTs* testicular adrenal rest tumors, *TESE* testicular sperm extraction

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