REVIEW

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Long-term Complications and Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia

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Abstract

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency accounts for approximately 95% of all CAH cases and is one of the most common inborn errors of metabolism. While glucocorticoid therapy has significantly improved patient outcomes, the focus has shifted towards managing the long-term effects. Numerous adverse outcomes have been associated with CAH, including those resulting from supraphysiological doses of glucocorticoid and mineralocorticoid replacement, excessive adrenal androgen secretion, and elevated levels of steroid precursors and adrenocorticotropic hormone. Despite advances in treatment, long-term complications persist due to the inability to replicate physiological hormone secretion fully. In this review, we explore critical aspects of managing CAH, focusing on cardiometabolic health, bone integrity, fertility, and other significant long-term consequences, informed by the latest literature.
Keywords: Congenital adrenal hyperplasia, complications, long term, outcome

Introduction

The management of congenital adrenal hyperplasia (CAH) during the transition from childhood to adulthood requires careful consideration. Key objectives include achieving normal growth and puberty, minimizing virilization, preparing for fertility, and preventing metabolic complications, all important for improving quality of life in adulthood (1). Early diagnosis and treatment are essential for preventing morbidity and mortality. The primary goal of treatment is to ensure adequate glucocorticoid and mineralocorticoid replacement while effectively controlling androgen excess. In clinical practice, glucocorticoid doses are often administered supra-physiologically or sub-physiologically to suppress androgen excess. However, excessive glucocorticoid and mineralocorticoid therapy may lead to adverse outcomes, such as short stature, osteoporosis, obesity, and increased cardiovascular risk. Conversely, inadequate glucocorticoid treatment or poor compliance can result in androgen excess, leading to infertility and the development of adrenal rest tumors (2,3). One significant complication in male patients with CAH is the development of testicular adrenal rest tumors (TART), which are the leading cause of infertility in these individuals. The prevalence of TART varies, but averages around 40%. However, rates as high as 94% have been reported in adults depending on detection methods, patient age, and disease severity (4,5).

Since TART can lead to infertility in adulthood, early diagnosis and adequate treatment during childhood are important. The preservation of gonadal function is directly related to tumor size, as an increase in tumor diameter over time may compromise gonadal function and fertility. TARTs smaller than 2 cm are challenging to detect by physical examination, making early imaging and differential diagnosis from Leydig cell tumors important considerations.

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Histopathologically, TART can be classified into five stages, with stage 5 representing irreversible damage characterized by hyalinization, loss of testicular parenchyma, and obstructive azoospermia, ultimately resulting in infertility (6).

The etiopathogenesis of TART has not been fully elucidated. Recent studies have explored the genotype-phenotype correlation, indicating a higher prevalence of TART, particularly in salt-wasting forms of CAH (7).

This evidence-based review, which includes good practice points, was developed by the Adrenal Working Group of the Turkish Society for Pediatric Endocrinology and Diabetes. We developed this evidence-based review for the management of long-term complications, including TARTs in children and adolescents with CAH.

Final Height

Patients with CAH often fail to reach their target height. Factors determining the final height at the time of diagnosis include chronological age, bone age, the adequacy of treatment, and the degree of hormonal control. Inadequate treatment can result in androgen excess and early epiphyseal closure. In addition, high-dose steroid use, especially in infants and during puberty, can suppress growth and impact final height (8,9,10). In a cohort study of 104 subjects divided into three age groups: early childhood (0-5 years), middle childhood (5-10 years), and adolescence (10-15 years), every 1 mg/m^2/day increase in hydrocortisone dose was associated with a 0.37 cm decrease in predicted height. In this study, hydrocortisone doses ranged from 9.4 mg/m^2/day to 39.2 mg/m^2/day and this effect was observed in cases receiving hydrocortisone doses above the lowest dose of 9.4 mg/m^2/day (11). A meta-analysis evaluating 35 studies on final height found that patients receiving mineralocorticoid treatment had better final height than those who did not. However, it was highlighted that this difference could be due to patients with a diagnosis of simple virilizing CAH receiving a delayed diagnosis compared to those with a salt-wasting CAH diagnosis. Furthermore, recent improvements in patient care, better nutrition or general health care, and changes in treatment dosage and preparation have been suggested as effective factors in improving patients' height (12). Bone age is commonly used as a clinical marker for metabolic control in CAH, and accelerated bone age indicates inadequate glucocorticoid treatment (13). It is recommended that annual bone age in cases under the age of two years be assessed until they reach adult height (14,15).

Obesity, Metabolic Issues, and Cardiovascular Risks

Cardiovascular outcomes related to steroid treatment in CAH patients are uncertain. CAH patients have been observed to exhibit increased systolic blood pressure, diastolic blood pressure, insulin resistance, and carotid intima thickness compared to the normal population. However, no differences have been found in fasting blood glucose and lipids. Cardiometabolic risk factors are associated with an increased risk of future cardiac problems. Factors contributing to this include high-dose glucocorticoid and mineralocorticoid treatment and uncontrolled androgen excess. Children and adolescents with CAH tend to have increased fat accumulation, which is also a contributing factor to obesity. The primary factor leading to obesity is the use of supra-physiological doses of glucocorticoids (16). The key factors in reducing these risks include the administration of glucocorticoids close to physiological doses and using the lowest necessary mineralocorticoid doses (15,16,17). Maintaining a healthy body weight and body mass index associated with normal blood pressure is key. However, CAH patients with accompanying hypertension from the time of diagnosis and those who develop obesity during follow-up may need to be evaluated for these comorbidities earlier than recommended by standard guidelines.

Bone Health

Gonadal and adrenal androgens stimulate the proliferation and differentiation of osteoblasts in both genders. Dehydroepiandrosterone sulfate (DHEAS) affects bone by binding to the androgen receptor and stimulating osteoblast growth and differentiation. DHEAS and other adrenal androgens particularly impact bone metabolism during adrenarche and throughout life. In children with classical CAH, there is no physiological increase in DHEAS (18). Glucocorticoids, which are the most important drugs causing secondary osteoporosis, lead to decreased bone mineral density (BMD) in CAH patients receiving lifelong glucocorticoid replacement therapy (19). Glucocorticoid treatment affects BMD through multiple mechanisms that result in increased bone resorption and reduced bone formation, leading to decreased BMD. It also causes secondary hyperparathyroidism by reducing intestinal calcium absorption and increasing renal calcium excretion (20). A lack of physiological increase in DHEAS at puberty, coupled with high-dose glucocorticoid treatment, represents a significant contributing factor to the observed decline in BMD. There are publications reporting that long-term glucocorticoid replacement therapy in CAH patients results in normal BMD (21). In adulthood, it is noted that low-dose glucocorticoid treatment is associated with normal BMD, and prednisolone treatment leads to greater BMD reduction compared to hydrocortisone treatment (22). During the

transition to adulthood, baseline BMD measurement can be conducted. To maintain good bone health, weight-bearing exercises should be combined with age-appropriate vitamin D and calcium intake (14).

Good practice points:

1. In the follow-up of patients, it is appropriate to carefully evaluate the growth rate and adjust the treatment dose. In terms of final height, it is appropriate to evaluate the growth rate, metabolic control and bone age (1⊕⊕OO).

2. Patients with CAH should be provided with standard lifestyle advice (ungraded good practice steatment).

3. Routine screening for cardiac and metabolic diseases is not recommended (ungraded good practice steatment).

4. CAH patients should be monitored for the development of metabolic and cardiac diseases according to standard guidelines applied to the general population (1⊕⊕OO).

5. There is no data to provide recommendations regarding bone health in childhood for individuals with CAH, and routine screening of BMD is not recommended in adults. However, assessment of BMD is appropriate for adults who have been exposed to above-average glucocorticoid doses for an extended period or have experienced non-traumatic fractures (2⊕OOO).

Testicular Adrenal Rest Tumors

Diagnosis

Ultrasonography (USG) is the preferred method for diagnosing and monitoring TARTs, as it can detect nodules as small as <2 mm. Annual testicular ultrasound is recommended from early childhood due to its accessibility, non-invasive nature, and the potential for TART to affect young children, particularly in those with poorly controlled CAH. This approach is supported by evidence of disease progression without obvious clinical symptoms.

One study reported a TART prevalence of 18.3% in patients with 21-hydroxylase deficiency aged 2-18 years, making it one of the few studies to provide long-term follow-up data. Notably, the youngest case reported in the literature was a 2-year-old patient. The frequency of TART increases with age, becoming more common during and after puberty (4,23,24). In addition, magnetic resonance imaging has not demonstrated any significant advantages over ultrasound for detecting or monitoring TART.

The Relationship Between TART and Specific CAH Phenotypes/Genotypes

The association between TART and specific CAH phenotypes/genotypes has not been definitively established. There may be a bias towards diagnosing TART in patients with salt-wasting CAH, as these individuals face greater health risks and are more challenging to manage in terms of hormonal balance. On the other hand, patients with simple virilizing CAH are often diagnosed later, and treatment may be less stable, particularly in low- and middle-income countries.

In our published series, approximately 83% of the 40 TART cases in patients with 21-hydroxylase deficiency were of the salt-wasting type. The *CYP21A2* variants detected in this cohort primarily belonged to groups 0 and A (variants in CYP21A2 are classified into four groups: Group 0, A, B, and C, based on residual 21-hydroxylase activity. Group 0 and Group A are associated with the salt-wasting form. Group 0 (null variants) exhibit 0% enzyme activity, while Group A variants have minimal residual activity (<1%). Group B variants retain approximately 2% residual enzyme activity, and Group C variants have 20-50% residual activity (37) with the mutations c.293-13C>G and c.955C>T (p.Gln319Ter) being the most common (7,17). In addition, in cases of TART associated with 11β-hydroxylase deficiency, the most frequently detected variant was c.896T>C (p.Leu299Pro). The fact that TART is reported more frequently in the classical forms of CAH compared to non-classical forms supports this observation. However, it is important to note that TART does not develop in all poorly controlled patients (7,25,26).

Treatment

The presence of high concentrations of adrenocorticotropic hormone (ACTH) receptors in TART tissues stimulates tumor growth, making ACTH suppression crucial in preventing the development of TART. Currently, no definitive and effective treatment exists for TART, and future research should focus on identifying potential drug targets. There are no clear guidelines for the treatment or prevention of TART, and current treatment strategies primarily focus on restoring fertility in adult patients. However, there are no prospective studies investigating the effect of intensified glucocorticoid therapy on TART, and high doses are associated with adverse effects, including hypertension, striae, weight gain, and impaired final height (27).

Testicular adrenal hyperplasia or small tumors have been shown to respond better to high-dose glucocorticoid therapy, leading to a reduction or disappearance of the tumor when monitored regularly by USG or Doppler scans

(25). Treatment modulation in well-managed patients may not be straightforward, as TART resolution typically requires higher steroid doses, which have implications for growth and other side effects. In cases where patients are non-compliant, on sub-therapeutic doses, or inconsistently taking prescribed hormones, resuming proper therapy has often been sufficient.

Mitotane has been used to restore fertility in adult patients with TART. However, it leads to irreversible chemical adrenalectomy and is recommended only as a last-resort treatment for fertility (28). Follicle stimulating hormone (FSH) and human chorionic gonadotropin have been administered to CAH patients with TART and hypogonadotropic hypogonadism, resulting in the restoration of testicular testosterone production and fertility. Successful testicle-sparing surgeries have been reported in small cohorts of CAH patients with TART, but gonadal function did not significantly improve after surgery. TART can cause pain due to compression of the testicular parenchyma, though malignancy has not been reported in any cases. Since TART lacks malignancy markers, such as high mitotic rates or atypical mitoses, surgery is only indicated for severe pain, as it does not improve fertility (29).

Treatment Follow-up

Poor hormonal control has been reported in approximately 58 % of TART patients (30,31,32,33). However, not all studies indicate a direct relationship between poor control and the development of TART. TART has also been reported in well-controlled CAH cases. ACTH, 17-hydroxyprogesterone, and androstenedione can be used as indicators of poor hormonal control and are thought to contribute to the development of TART (27,28,29). The presence of TART in rare cases of non-classical CAH suggests that poor control is not the only factor involved in its etiopathogenesis. Patients with the severe salt-wasting form of CAH are likely at higher risk of TART formation due to prolonged exposure to elevated ACTH concentrations (33).

This also highlights the relationship between specific variants and TART development. In Turkey, *CYP21A2* mutations c.293-13C > G and c.955C > T (p.Gln319Ter), and the *CYP11B1* mutation c.896T > C (p.Leu299Pro), have been associated with a predisposition to TART (7). Patients with these mutations require more careful monitoring.

Gonadal Function-fertility

There is no definitive predictive parameter for identifying which patients will develop TART, but it remains a significant cause of infertility in male CAH patients. Gonadal dysfunction and infertility, often becoming apparent during puberty, are adverse outcomes associated with TART. In men, gonadal dysfunction can stem from primary gonadal failure caused by TART or secondary gonadal failure due to hypothalamic suppression as a result of poor hormonal control.

Studies have shown a positive correlation between total functional testicular volume and sperm parameters, as well as inhibin B levels. Recent findings indicate that semen quality in men with CAH is highly compromised, with 100 % of cases considered pathological according to World Health Organization criteria (34). Given the risk of irreversible testicular damage with the development of TART, sperm cryopreservation is recommended. Guidelines suggest that sperm storage should be considered before TARTs enlarge significantly (33). There is evidence linking elevated FSH and low luteinizing hormone (LH) levels to oligospermia (25). In some cases, successful conception has been reported following sperm preservation during TART surgery in azospermic azoospermic patients (31,35,36).

Further research is needed to determine whether specific variants in *CYP21A2*, *CYP11B1*, or other regulatory genes contribute to TART development and infertility risk, independent of poor hormonal control. Understanding the genetic basis of TART and its association with infertility may help identify new treatment strategies.

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (37).

Good practice points:

1. In the pediatric population, TART screening with testicular USG every two years starting from the age of 8 years and annually during the peripubertal period would be appropriate (2⊕⊕OO).

2. The incidence of TART is higher in CAH patients with salt-wasting phenotypes; therefore, close monitoring of these cases is appropriate (ungraded good practice steatment).

3. Since ACTH plays a role in TART development, lowering ACTH may prevent TART formation in CAH patients, and treatment should focus on this goal (2⊕⊕OO).

4. It is appropriate to closely monitor CAH patients with poor hormonal control with a specific hormone profile, such as ACTH, 17-hydroxyprogesterone and androstenedione (2⊕OOO).

5. Spermiogram and sperm cryopreservation should be considered in TART patients due to the high risk of infertility (2⊕OOO).

6. Annual evaluation of gonadal function is advised by measuring LH, FSH, testosterone, and inhibin B levels as appropriate (ungraded good practice steatment).

Footnotes

Authorship Contributions

Surgical and Medical Practices: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Concept: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Design: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Data Collection or Processing: Aylin Kılınç Uğurlu, Elif Özsu, Analysis or Interpretation: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Literature Search: Aylin Kılınç Uğurlu, Elif Özsu, Writing: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan.

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References

1. Kim JH, Choi JH, Kang E, Kim YM, Lee BH, Yoo HW. Long-term consequences of congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency in adolescents and adults. Exp Clin Endocrinol Diabetes. 2017;125:196-201. Epub 2017 Jan 10
2. Ellaithi M, de LaPiscina IM, de La Hoz AB, de Nanclares GP, Alasha MA, Hemaida MA, Castano L. Simple virilizing congenital adrenal hyperplasia: a case report of sudanese 46, XY DSD male with G293D variant in CYP21A2. The Open Pediatric Medicine Journal. 2019:9.
3. Han TS, Walker BR, Arlt W, Ross RJ. Treatment and health outcomes in adults with congenital adrenal hyperplasia. Nat Rev Endocrinol. 2014;10:115-124. Epub 2013 Dec 17
4. Aycan Z, Bas VN, Cetinkaya S, Yilmaz Agladioglu S, Tiryaki T. Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clin Endocrinol (Oxf). 2013;78:667-672.
5. Turcu AF, Auchus RJ. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2015;44:275-296.
6. Claahsen-van der Grinten HL, Otten BJ, Hermus AR, Sweep FC, Hulsbergen-van de Kaa CA. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia can cause severe testicular damage. Fertil Steril. 2008;89:597-601. Epub 2007 Jun 4
7. Aycan Z, Keskin M, Lafcı NG, Savaş-Erdeve Ş, Baş F, Poyrazoğlu Ş, Öztürk P, Parlak M, Ercan O, Güran T, Hatipoğlu N, Uçaktürk SA, Çatlı G, Akyürek N, Önder A, Kılınç S, Çetinkaya S. Genotype of congenital adrenal hyperplasia patients with testicular adrenal rest tumor. Eur J Med Genet. 2022;65:104654. Epub 2022 Nov 4
8. Mnif MF, Kamoun M, Mnif F, Charfi N, Kallel N, Ben Naceur B, Rekik N, Mnif Z, Sfar MH, Sfar MT, Hachicha M, Keskes LA, Abid M. Long-term outcome of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Am J Med Sci. 2012;344:363-373.
9. Eugster EA, Dimeglio LA, Wright JC, Freidenberg GR, Seshadri R, Pescovitz OH. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. J Pediatr. 2001;138:26-32.
10. Nebesio TD, Eugster EA. Growth and reproductive outcomes in congenital adrenal hyperplasia. Int J Pediatr Endocrinol. 2010;2010:298937. Epub 2010 Feb 1
11. Sarafoglou K, Addo OY, Turcotte L, Otten N, Wickremasinghe A, Pittock S, Kyllo J, Lteif AN, Himes JH, Miller BS. Impact of hydrocortisone on adult height in congenital adrenal hyperplasia-the Minnesota cohort. J Pediatr. 2014;164:1141-1146. Epub 2014 Feb 20
12. Muthusamy K, Elamin MB, Smushkin G, Murad MH, Lampropulos JF, Elamin KB, Abu Elnour NO, Gallegos-Orozco JF, Fatourechi MM, Agrwal N, Lane MA, Albuquerque FN, Erwin PJ, Montori VM. Clinical review: Adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis. J Clin Endocrinol Metab. 2010;95:4161-4172.
13. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, Arlt W, Auchus RJ, Falhammar H, Flück CE, Guasti L, Huebner A, Kortmann BBM, Krone N, Merke DP, Miller WL, Nordenström A, Reisch N, Sandberg DE, Stikkelbroeck NMML, Touraine P, Utari A, Wudy SA, White PC. Congenital adrenal hyperplasia-current ınsights in pathophysiology, diagnostics, and management. Endocr Rev. 2022;43:91-159.
14. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:4043-4088. Erratum in: J Clin Endocrinol Metab. 2019;104:39-40.
15. P Prentice P. Guideline review: congenital adrenal hyperplasia clinical practice guideline 2018. Arch Dis Child Educ Pract Ed. 2021;106:354-357. Epub 2020 Dec 3
16. Improda N, Barbieri F, Ciccarelli GP, Capalbo D, Salerno M. Cardiovascular health in children and adolescents with congenital adrenal hyperplasia due to 21-hydroxilase deficiency. Front Endocrinol (Lausanne). 2019;10:212.
17. Tamhane S, Rodriguez-Gutierrez R, Iqbal AM, Prokop LJ, Bancos I, Speiser PW, Murad MH. Cardiovascular and metabolic outcomes in congenital adrenal hyperplasia: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2018;103:4097-4103.
18. El-Maouche D, Collier S, Prasad M, Reynolds JC, Merke DP. Cortical bone mineral density in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol (Oxf). 2015;82:330-337. Epub 2014 Jun 28
19. Falhammar H, Frisén L, Hirschberg AL, Nordenskjöld A, Almqvist C, Nordenström A. Increased prevalence of fractures in congenital adrenal hyperplasia: a Swedish population-based National Cohort Study. J Clin Endocrinol Metab. 2022;107:475-486.
20. Falhammar H, Filipsson Nyström H, Wedell A, Brismar K, Thorén M. Bone mineral density, bone markers, and fractures in adult males with congenital adrenal hyperplasia. Eur J Endocrinol. 2013;168:331-341.
21. G Gussinyé M, Carrascosa A, Potau N, Enrubia M, Vicens-Calvet E, Ibáñez L, Yeste D. Bone mineral density in prepubertal and in adolescent and young adult patients with the salt-wasting form of congenital adrenal hyperplasia. Pediatrics. 1997;100:671-674.
22. Koetz KR, Ventz M, Diederich S, Quinkler M. Bone mineral density is not significantly reduced in adult patients on low-dose glucocorticoid replacement therapy. J Clin Endocrinol Metab. 2012;97:85-92. Epub 2011 Oct 12
23. Lisieux Eyer de Jesus 1, Ana Paula Paz de Oliveira 2, Luiza Coutinho Porto 2, Samuel Dekermacher 2 testicular adrenal rest tumors - epidemiology, diagnosis and treatment2024 J Pediatr Urol. 2024;20:77-87. Epub 2023 Oct 7.
24. Claahsen-van der Grinten HL, Stikkelbroeck NM, Otten BJ, Hermus AR. Congenital adrenal hyperplasia--pharmacologic interventions from the prenatal phase to adulthood. Pharmacol Ther. 2011;132:1-14. Epub 2011 May 18

25. King TF, Lee MC, Williamson EE, Conway GS. Experience in optimizing fertility outcomes in men with congenital adrenal hyperplasia due to 21 hydroxylase deficiency. Clin Endocrinol (Oxf). 2016;84:830-836. Epub 2016 Feb 15

26. Engels M, Gehrmann K, Falhammar H, Webb EA, Nordenström A, Sweep FC, Span PN, van Herwaarden AE, Rohayem J, Richter-Unruh A, Bouvattier C, Köhler B, Kortmann BB, Arlt W, Roeleveld N, Reisch N, Stikkelbroeck NMML, Claahsen-van der Grinten HL; dsd-LIFE group. Gonadal function in adult male patients with congenital adrenal hyperplasia. Eur J Endocrinol. 2018;178:285-294. Epub 2018 Jan 16

27. Bayhan GI, Cetinkaya S, Cinar HG, Aycan Z. Testicular adrenal rest tumor in a patient with 11beta-hydroxylase deficient congenital adrenal hyperplasia. J Pediatr Endocrinol Metab. 2010;23:729-732.

28. Bry-Gauillard H, Cartes A, Young J. Mitotane for 21-hydroxylase deficiency in an infertile man. N Engl J Med. 2014;371:2042-2044.

29. Rich MA, Keating MA. Leydig cell tumors and tumors associated with congenital adrenal hyperplasia. Urol Clin North Am. 2000;27:519-528.

30. Dumic M, Duspara V, Grubic Z, Oguic SK, Skrabic V, Kusec V. Testicular adrenal rest tumors in congenital adrenal hyperplasia-cross-sectional study of 51 Croatian male patients. Eur J Pediatr. 2017;176:1393-1404.

31. Yılmaz R, Şahin D, Aghayev A, Erol OB, Poyrazoğlu Ş, Saka N, Yekeler E. Sonography and magnetic resonance ımaging characteristics of testicular adrenal rest tumors. Pol J Radiol. 2017;82:583-588.

32. Yu MK, Jung MK, Kim KE, Kwon AR, Chae HW, Kim DH, Kim HS. Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia. Ann Pediatr Endocrinol Metab. 2015;20:155-161. Epub 2015 Sep 30

33. Falhammar H, Nyström HF, Ekström U, Granberg S, Wedell A, Thorén M. Fertility, sexuality and testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia. Eur J Endocrinol. 2012;166:441-449. Epub 2011 Dec 9

34. Reisch N, Flade L, Scherr M, Rottenkolber M, Pedrosa Gil F, Bidlingmaier M, Wolff H, Schwarz HP, Quinkler M, Beuschlein F, Reincke M. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2009;94:1665-1670. Epub 2009 Mar 3

35. Chougar T, Laanani M, Ferreux L, Chalas C, Wolf JP, Bertherat J, Bouvattier C, Polak M, Bachelot A, Dulon J, Touraine P, Patrat C, Drouineaud V. Sperm cryopreservation in young males with congenital adrenal hyperplasia (CAH). Clin Endocrinol (Oxf). 2022;97:860-862. Epub 2022 Jul 7

36. Claahsen-van der Grinten HL. How to manage puberty and prevent fertility disorders in men with CAH? Ann Endocrinol (Paris). 2022;83:186-187. Epub 2022 Apr 15

37. Odabaşı Güneş S, Peltek Kendirci HN, Ünal E, Buluş AD, Dündar İ, Şıklar Z. Clinical, biochemical and molecular characteristics of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Res Pediatr Endocrinol. 2025;17(Suppl 1):3-11.