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Pediatric Complete Androgen Insensitivity Syndrome (CAIS): Clinical Presentation, Hormonal Profiles, and Gonadal Management

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ABSTRACT

Objective: Complete androgen insensitivity syndrome (CAIS) is caused by mutations in the *androgen receptor (AR)* gene, leading to androgen resistance. Early recognition is critical for optimal management. To evaluate clinical presentations, hormonal profiles, genetic characteristics, and decisions regarding gonadectomy in pediatric CAIS. Factors influencing gonadectomy, including malignancy risk, gonadal function, and psychological well-being were assessed.

Methods: Medical records of 16 children with genetically confirmed CAIS patients, aged 3 days-18 years, diagnosed between 2004 and 2024 at a tertiary referral center were retrospectively reviewed. Clinical, hormonal, genetic, and histological data were analyzed.

Results: Twelve patients (75%) were diagnosed prepubertally, most commonly due to inguinal hernia. Familial recurrence occurred in four cases (25%). Novel pathogenic AR variants not previously reported in public databases were identified in three patients. Prepubertal patients with hormone data (n=5) demonstrated Anti-Müllerian hormone>150 pM. Pubertal patients (n=9) had markedly elevated testosterone levels [median at 1361.3 ng/dL, range 367-3460 ng/dL]. Gonadal biopsy was performed in three cases (19%). Gonadal preservation was recommended in 11 children (69%), while five (31%) underwent gonadectomy followed by estrogen replacement therapy.

Conclusion: Most CAIS cases in this pediatric cohort were detected early through inguinal hernia or family screening. Delayed gonadectomy allowed spontaneous pubertal development and feminization. While gonadectomy results in lifelong hormone dependence and may raise identity-related concerns, surveillance-based gonadal preservation appears safe during childhood. The identification of novel *AR* variants expands the mutational spectrum of CAIS and highlights the need for multicenter registries and improved biomarkers to optimize individualized care.

Keywords: Androgen-insensitivity syndrome, amenorrhea, castration

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What is already known on this topic?

Complete androgen insensitivity syndrome (CAIS) arises from *androgen receptor (AR)* gene mutations in 46,XY individuals, causing a female phenotype with common presentations of inguinal hernia in infancy and primary amenorrhea in adolescence. Prophylactic gonadectomy timing is debated because of the low prepubertal malignancy risk and benefits of spontaneous pubertal development.

What this study adds?

This cohort of 16 pediatric CAIS patients shows that delaying gonadectomy until after spontaneous puberty under structured surveillance yielded no malignancies, supported natural estrogenization, and enhanced psychological outcomes. Familial AR mutation inheritance patterns and detailed hormonal profiles inform personalized gonadal management.

Introduction

Complete androgen insensitivity syndrome (CAIS) is a condition classified as a difference of sex development (DSD) caused by mutations in the X-linked *androgen receptor* (*AR*) gene (1). The disorder is primarily inherited from a heterozygous carrier mother, though *de novo* mutations occur in about 30% of cases (2,3). These mutations lead to a loss of function, preventing the androgen receptor from responding to androgens, primarily testosterone (T) and dihydrotestosterone (DHT). As a result, individuals with a 46,XY karyotype develop a female phenotype (4,5). Globally, the prevalence of CAIS is estimated at 1 in 20,000 to 1 in 100,000 live births (4,6). Due to androgen resistance, the Wolffian ducts fail to develop into male internal and external genitalia, Anti-Müllerian hormone (AMH) which acts independently, prevents the formation of typical female reproductive structures like the uterus and fallopian tubes, and the upper part of the vagina (7,8). The testes are typically undescended and may be located in various positions along the path of normal testicular descent, failing to descend into the scrotum. Common locations for undescended testes in CAIS include the abdomen, inguinal canal, suprapubic area, or labia majora, which may mimic labial swelling (2,9). During puberty, high levels of T produced by Leydig cells, are converted to oestradiol, resulting in the development of a phenotypic female with breast development. Peripheral androgen resistance limits the development of pubic and axillary hair (5,10).

The diagnosis of CAIS may first be suspected in infancy or early childhood, especially when inguinal hernias are observed in individuals with a female phenotype (4). In such cases, patients are referred for diagnostic hormonal evaluation and may require surgical intervention, occasionally including gonadal biopsy. In adolescence, clinicians should consider CAIS in patients presenting with primary amenorrhea, a shortened vagina, absence of a uterus and sparse body hair (11). CAIS can also be diagnosed prenatally when there is a discrepancy between the phenotypic sex and a 46,XY karyotype identified during foetal screening (9). Definitive confirmation of CAIS is achieved through molecular genetic testing, which identifies a hemizygous mutation in the *AR* gene on the X chromosome in individuals with a 46,XY karyotype. This molecular confirmation is vital for establishing the clinical diagnosis of CAIS. However, the optimal management of gonadal tissue in CAIS remains a matter of debate. The aim of this study was to evaluate the clinical presentation, hormonal profile, and genetic characteristics of genetically confirmed CAIS patients and assess the impact of gonadectomy decisions, considering oncological risks, endocrine function, and psychological well-being (2,3).

Methods

This retrospective study analysed a cohort of CAIS patients managed at the Department of Endocrinology and Diabetology at The Children's Memorial Health Institute, Warsaw, Poland, between 2004 and 2024. The aim was to characterize the clinical presentation, hormonal profile, and genetic findings in individuals with CAIS and evaluate the factors influencing gonadal management decisions, including the rationale for gonadectomy, histological findings, and long-term outcomes. In addition, the study explored the endocrine and psychological aspects related to gonadal preservation. Inclusion criteria included a confirmed diagnosis of CAIS based on genetic testing (46,XY karyotype with a pathogenic *AR* gene mutation) and clinical features. Eligible patients exhibited at least one of the following clinical characteristics: (1) typical female external genitalia at birth despite a 46,XY karyotype; (2) primary amenorrhea in adolescence; (3) inguinal hernia containing gonadal tissue in infancy or childhood; (4) absence of Müllerian structures (uterus, fallopian tubes) on imaging; and/or (5) elevated AMH levels within the male reference range during infancy or prepuberty.

Medical records were reviewed to collect data on key clinical parameters, including age at presentation, reasons for endocrine consultation, history of surgical interventions (particularly inguinal hernias and gonadectomies), and family history of similar conditions. These data were used to assess trends in clinical presentation and decision-making regarding gonadal management.

Clinical examination included final height measurements using a stadiometer, expressed in standard deviations (SD) compared to the mean height of both adult females and males and in comparison to height predictions based on mid-parental height. Psychological outcomes and quality of life were assessed retrospectively from clinical follow-up notes and patient/parent reports, including emotional well-being, self-acceptance of CAIS diagnosis, body image perception, and concerns related to fertility and gender identity. No validated psychometric questionnaires were applied. Moreover, clinical follow-up notes were reviewed for reports of anxiety, depression, or psychosocial distress associated with gonadal management decisions.

Laboratory investigations were categorized into three age ranges: first six months of life; prepubertal (six months to breast development at Tanner stage 2); and pubertal (Tanner stage 2 and higher). Hormonal evaluations were conducted using immunoassays to measure levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), T, estradiol (E2), dehydroepiandrosterone sulfate, 17-hydroxyprogesterone (17-OHP), and AMH. AMH levels typically exceeded the maximum detection limit, so the highest measured value was recorded. Given the limited assay sensitivity at high AMH concentrations, the potential variability in extreme values was acknowledged in data interpretation.

A human chorionic gonadotropin (hCG) stimulation test was performed in selected cases to assess the presence of functional Leydig cells. The test protocol included intramuscular administration of 2000 units of hCG/m^2, with blood samples collected before injection and 96 hours post-stimulation to measure T levels. A rise above 60 ng/dL was considered indicative of Leydig cell function.

All patients underwent ultrasound (US) examinations to assess gonadal position and morphology. In selected cases, magnetic resonance imaging was performed to further characterize gonadal structures, delineate size and composition, and assess their relation to adjacent anatomical structures.

For patients who underwent gonadectomy, detailed data were collected, including age at surgery, histological analysis of gonadectomy specimens, and details of hormone replacement therapy (HRT).

The study protocol was approved by the Research Ethics Committee of The Children's Health Memorial, Warsaw, Poland on 25.04.2024 (approval no.: 12/KBE/2024). Written informed consent was obtained from the parents or legal guardians of underage patients, and from the patients themselves if they were adults.

Statistical Analysis

All statistical analyses were descriptive in nature. Quantitative variables were assessed for distribution; data following a normal distribution were presented as mean values with SD, while non-normally distributed variables were summarized using medians and interquartile ranges. Categorical data were reported as frequencies and percentages. No formal hypothesis testing or inferential statistical procedures were applied due to the small sample size and retrospective design of the study. All analyses were performed using Microsoft Excel for Microsoft 365, Version 2405 (Microsoft Corporation, Redmond, Washington, USA).

Results

Clinical Manifestations

This study included 16 patients: 8 infants, 4 prepubertal children, and 4 pubertal patients. The age at the time of first medical consultation ranged from 5 days to 18 years, with an average age of 5.3 years at the start of diagnostic assessment.

There were four affected families within the studied cohort: in two both offspring were 46,XY diagnosed with CAIS, another two families had both children diagnosed with CAIS, and included a 46,XX *AR* mutation carrier.

The diagnosis of CAIS was established based on a combination of clinical features, hormonal findings, and genetic confirmation. The following clinical indicators prompted further evaluation for CAIS:

Mismatch between prenatal karyotype and phenotype: One case (6.3%) involved a mismatch between a prenatal 46,XY karyotype and a postnatal female phenotype.

Presence of inguinal hernia with testicles: This was the most common initial symptom of CAIS, observed in seven cases (43.7%). The age at surgical intervention for inguinal hernia ranged from 5 days to 4.5 years, with an average age of 1.7 years. During surgery, the presence of gonads was confirmed in four cases, along with the absence of the uterus, fallopian tubes, and ovaries. Gonadal biopsies were performed in three cases, showing microscopic structures corresponding to testicular tissue. In one case, a patient who underwent surgery for an inguinal hernia at 3.5 years of age experienced a recurrence three weeks later. A revision surgery of the inguinal canal unexpectedly revealed a gonad, prompting further investigations (Table 1).

Primary amenorrhea: Primary amenorrhea led to the diagnosis of CAIS in four patients (25%). The age at diagnosis ranged from 13.5 to 16.8 years, with a mean of 15.2 years. All presented with normal breast development but sparse pubic and axillary

Table 1. Clinical and molecular characteristics of CAIS cases

Patient no	Age at diagnosis [years]	Reason for consultation	Base change aminoacid change	Maternal carriers	Other family members affected	Final height* [cm]	Final height [SD] Female/Male	Final length of vagina* [cm]	Location of gonads
1	0.1	Familial *AR* mutation	c.175C>T Gln59Ter	Yes	Sister	NA	NA	NA	Inguinal canal
2	0.5	Inguinal hernia	c.239_240delAA	Yes	No	NA	NA	NA	Inguinal canal
3	3	Inguinal hernia	c.3387C>G p.Leu763Val	Yes	No	NA	NA	NA	Inguinal canal/ Abdomen
4	4.8	Inguinal hernia	c.2513A>T p Glu 838 Val *novel mutation*	Yes	No	NA	NA	NA	Inguinal canal
5	0.2	Familial *AR* mutation	c.175C>T Gln59Ter	Yes	Sister	NA	NA	NA	Inguinal canal
6	0.4	Inguinal hernia	c.175C>T Gln59Ter	Yes	Sister	NA	NA	NA	Inguinal canal
7	4	Inguinal hernia	c.2728G>A Gly910Arg	Yes	No	171.4	1.0/-1.1	3	Inguinal canal
8	0.6	Familial *AR* mutation	N705S	Yes	Sister	183.7	3.0/0.8		Inguinal canal
9	0.1	Karyotype mismatch	c.589C>T p.(Gln197*) *novel mutation*	Yes	No	178.8	2.2/0.1		Abdomen
10	0.6	Inguinal hernia	Deletion after exon 6 – no binding – complete AR defect**	de novo	No	169.1	0.6/-1.5	7	Inguinal canal
11	17	Primary amenorrhea Familial *AR* mutation	c.2599 G>A Val/867 Met	Yes	Sister	169.1	0.6/-1.5	5.6	Inguinal canal
12	17.5	Primary amenorrhea	c.1567G>T *novel mutation*	Yes	No	171.2	0.9/-1.1		Inguinal canal
13	16	Primary amenorrhea	c.2599 G>A Val/867 Met	Yes	Sister	179	2.2/0.1	4.5	Inguinal canal
14	0.4	Familial *AR* mutation	N705S	Yes	Sister	171.4	1.0/-1.1	5.6	Inguinal canal/ Abdomen
15	1.6	Inguinal hernia	N705S	Yes	Sister	172.4	1.3/-1	NA	Inguinal canal/ Abdomen
16	18	Primary amenorrhea	CGA-> CCCGA Arg -> Pro, stop 788	Yes	No	173.5	1.5/-0.9	6.3	Inguinal canal

*Data only shown for those who had achieved final height
NA, not available; CAIS, complete androgen insensitivity syndrome; *AR*, *androgen receptor*; SD, standard deviation

hair. Pelvic US confirmed the absence of a uterus and ovaries, and laboratory evaluation showed markedly elevated T within the male reference range. In two patients, genetic testing was performed promptly after initial hormonal work-up, while in the remaining two, the diagnosis was delayed until further imaging and gonadal biopsy.

Familial presence of *AR* mutation: A family history of CAIS prompted evaluation in four patients (25%). These children were siblings of individuals previously diagnosed at our center. The age at diagnosis ranged from 3 days to 7 years. In two cases, genetic testing was performed shortly after birth due to known maternal carrier status, leading to early confirmation. In the other two, diagnosis followed clinical referral after inguinal hernia repair in an older sibling. All four patients had typical female external genitalia and absent Müllerian structures on imaging.

Physical examinations of the patients revealed typically female external genitalia without any distinctive anomalies. Pubertal patients displayed normally developed breasts but had little to no axillary and pubic hair growth.

The mean final height in patients who reached adult height (n=9/16; 56%) was 171.4 cm (±4.88 cm), which is +0.97 SD according to the standard for Polish women and -1.1 SD compared to the standard for Polish men.

Hormonal and Imaging Evaluation

During the first six months of life, measured gonadotropin and E2 levels in patients fell within the expected mini-puberty ranges (FSH 0.73-4.8 IU/L, LH <0.15-2.17 IU/L, E2 <8.2-17.3 pg/mL), while T varied between 2.5 and 299 ng/dL. In three cases, T was elevated within the typical male range (Table 2).

To further evaluate Leydig cell function, five patients underwent a hCG stimulation test. Post-stimulation, T levels increased significantly, ranging from 209 ng/dL to 884 ng/dL.

AMH levels during minipuberty were consistently above 150 pM in all cases, with a range of 181 pM to over 350 pM. This elevation of AMH, observed across all age groups, indicated normal Sertoli cell function.

During puberty, hormonal analysis showed significantly elevated T levels, ranging from 367 ng/dL to 3460 ng/dL, with a median value of 1361.3 ng/dL. LH levels were also elevated, ranging from 9.6 IU/L to 27.6 IU/L, with a median of 15.7 IU/L.

Pelvic US examinations confirmed the absence of a uterus, fallopian tubes, and ovaries in all patients. Undescended testes were predominantly located in the inguinal region in 10 patients. In one case, the testes were located within the abdominal cavity, while in three cases, the testes were found unilaterally in the inguinal region and unilaterally within the abdominal cavity (Table 1). Assessments of vaginal length revealed a shortened, blind-ending vaginal canal, with post-pubertal lengths ranging from 3 cm to 8.5 cm.

Genetic Testing

In the studied group, chromosomal analysis confirmed a 46,XY karyotype in all patients, as is typical for CAIS. Of note, one patient had a prenatal karyotyping that showed a 46,XY karyotype. This finding, combined with a normal female phenotype observed postnatally, led to an early diagnosis of CAIS.

Genetic testing of the *AR* gene identified various pathogenic mutations (see Table 1). To confirm these findings, Sanger sequencing was performed and successfully verified a hemizygous pathogenic mutation in the *AR* gene in all cases. Variant nomenclature followed the Human Genome Variation Society recommendations, based on the *AR* reference transcript NM_000044.6. Subsequent maternal molecular analysis showed that nearly all mothers (10 out of 11 families) were heterozygous carriers of the mutation. Among the identified variants, 13 had been previously reported, whereas three mutations (c.2513A>T, c.589C>T, c.1567G>T) were novel and have not been described in published databases to date. These novel variants are highlighted in Table 1.

For families with a history of the condition, Sanger sequencing was also extended to the patients' siblings. This analysis identified three families in which the hemizygous variant was inherited from the mother to more than one child. Notably, in one family with four children, three were found to have a 46,XY karyotype and were affected by the mutation, while one subject with a 46,XX karyotype was an asymptomatic carrier of the mutation (Table 1).

Gonadal Biopsy and Gonadectomy

Gonadal biopsy was performed in three cases during inguinal hernia surgery in response to intraoperative findings that suggested the presence of testicular tissue in girls undergoing the procedure. Microscopic examination revealed tissue consistent with testicular structure, showing numerous small tubules lined with immature germinal epithelium, consisting of Sertoli cells and germ cells, while Leydig cells were present in the interstitium (Table 3).

In our cohort, bilateral gonadectomy was performed in five patients (31.3%). The earliest surgery was conducted at nine months of age, while the remaining four patients underwent the procedure post-puberty, between the ages of 14.5 and 18.7 years. In four cases, the surgery was recommended as a prophylactic measure, while in one case, the gonads were removed at the patient's request. Histopathological examination of the gonadal tissue revealed Sertoli and Leydig cell hyperplasia

in two cases (Table 3), with no evidence of malignancy. Tissue analysis from the other three patients revealed testicular tissue predominantly composed of Sertoli cells, with no evidence of mature spermatogenesis or microscopic signs of invasive testicular cancer.-Post-pubertal patients who underwent bilateral gonadectomy required estrogen replacement therapy. Most of these patients were prescribed oral estrogen pills, although one patient opted for a transdermal spray.

Tumour Risk Assessment

In our cohort of patients with CAIS, a tumour surveillance protocol was followed to monitor the risk of gonadal malignancies, which are a recognized concern in this population. Tumour markers, specifically alpha-fetoprotein (AFP) and β-hCG, were measured annually, while routine US examinations were conducted every 2-3 years to detect any potential morphological changes in the gonads.

Table 2. Characteristics of hormonal evaluation in studied cohort of CAIS individuals, considering the age group division

Patient no	LH in mini-puberty [IU/L]	FSH in mini-puberty [IU/L]	E2 in mini-puberty [pg/mL]	Testosterone in mini-puberty [ng/dL]	Testosterone in hCG stimulation test [ng/dL]	AMH [pM/L]	Pubertal LH [IU/L]	Pubertal T [ng/dL]	Pubertal E2 [pg/mL]
1	-	-	-	-	-	>150 (1076)	-	-	-
2	1.6	1.5	17.3	2.5	-	>150	-	-	-
3	-	-	-	-	-	>150	-	-	-
4	-	-	-	-	-	>150	-	-	-
5	0.59	0.73	-	2.5	255.3	>150	-	-	-
6	2.17	4.09	-	13.3	884	>150	-	-	-
7	-	-	-	-	209	>160	12.2	1491	50.1
8	-	-	-	299	-	>150	27.6	1235.8	95.4
9	<0.15	1.52	<8.2	4.3	504.8	>150	9.6	1279	34
10	-	-	-	-	-	>350	-	-	25.9
11	-	-	-	-	-	>150	17.16	3460	68
12	-	-	-	-	-	-	15.8	1688	22.6
13	-	-	-	-	-	-	11	1701.8	53.1
14	0.6	4.8	-	185.3	-	-	10,7	367	14.8
15	-	-	-	-	310.6	>150	17.4	568	34.9
16	-	-	-	-	-	-	18.4	461	20

AMH, Anti-Müllerian hormone; E2, oestradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; -, not available; T, testosterone

Table 3. Gonadal histopathology in study group

Patient no	Type	Age at the time of surgery	Gonadal histopathology
2	Biopsy	6 months	Structure of the testicle Numerous small tubules lined with immature spermatogenic epithelium.
6	Biopsy	8 days	Structure of the testicle Sertoli cells visible in the tubules
15	Biopsy	19 months	Structure of the testicle
10	Gonadectomy	9 months	Structure of the testicle
13	Gonadectomy	17.9 years	Sertoli cell adenoma Few spermatogonia, Leydig cells
14	Gonadectomy	14.5 years	Sertoli cell adenoma Hyperplasia of Leydig cells
15	Gonadectomy	16.75 years	Sertoli cell adenoma Hyperplasia of Leydig cells
16	Gonadectomy	18.7 years	Structure of the testicle Sertoli cell adenoma.

Remarkably, throughout the surveillance period, there were no instances of elevated AFP or β-hCG levels in any of the patients. Furthermore, no US examination revealed any abnormalities suggestive of malignancy.

Psychosexual Care

Sexual identity in all patients was female. Psychological outcomes and quality of life were assessed retrospectively from clinical follow-up notes and patient/parent reports, including emotional well-being, self-acceptance of the CAIS diagnosis, body image perception, and concerns related to fertility and gender identity. No validated psychometric questionnaires were applied. Detailed psychological and psychiatric evaluations were available in 9 out of 16 children (56%), as the remaining patients were too young at the time of assessment to provide reliable psychosexual evaluation. In this subgroup, eight patients demonstrated age-appropriate psychological functioning and good adaptation to the diagnosis. Only one patient was diagnosed with an anxiety disorder requiring psychological follow-up. These findings suggest that, within the limits of the available data, most CAIS patients adapted well psychosocially during childhood and adolescence.

Discussion

Clinical Presentation and Diagnosis

Inguinal hernia was the most common presentation (43.7%), followed by primary amenorrhea (25%) and family history of CAIS (25%), consistent with earlier studies (12,13,14,15). These findings confirm that early diagnosis often results from surgical findings or cascade genetic testing. Prenatal karyotype-phenotype discordance was rare but contributed to early detection in one case (4,5).

Hormonal and Imaging Evaluation

Our hormonal results reflect the characteristic profile of CAIS across developmental stages. During mini-puberty, baseline T ranged from 2.5 to 299 ng/dL, consistent with the transient activation of the hypothalamic-pituitary-gonadal (HPG) axis and variable timing of sampling (16). In contrast to typical 46,XY infants, patients with CAIS do not consistently exhibit a physiological LH-testosterone surge during mini-puberty. This observation aligns with the findings of Bouvattier et al. (17), who demonstrated that activation of the mini-puberty axis required functional androgen receptor signalling, and its absence results in a blunted rise of LH and testosterone despite intact Leydig cell capacity (16).

In our cohort, Leydig cell responsiveness was confirmed by a marked testosterone increase following hCG stimulation, and Sertoli cell function was preserved, as evidenced by uniformly elevated AMH concentrations. Importantly, AMH remains a valuable biomarker to distinguish CAIS from gonadal dysgenesis, where AMH is typically reduced (8,18).

Final height in our cohort averaged 171.4 cm (±4.88), approximately +0.97 SD above the female reference population. This supports previous evidence that delayed bone age and absence of androgen-driven epiphyseal closure contribute to increased adult height in CAIS patients.

Pelvic imaging confirmed the absence of Müllerian structures in all patients, and a shortened, blind-ending vagina (3-8.5 cm) was documented in post-pubertal individuals. These findings reflect the effect of persistent AMH secretion from Sertoli cells, which suppresses Müllerian development during fetal life.

Genetic Testing

Most AR mutations identified in our cohort have been previously described, confirming the heterogeneous but partially recurrent spectrum of pathogenic variants in CAIS. Importantly, three novel *AR* mutations were detected, expanding the mutational landscape and potentially contributing to improved genotype-phenotype interpretation in future cases.

Gonadal Management and Tumor Risk

The timing of gonadectomy remains a key controversy in CAIS management. Historically, early removal of gonads was recommended; however, contemporary studies show malignancy risk in children is low (0.8-2%), increasing gradually to ~14% in adulthood.

In our cohort, 31% (n=5) underwent gonadectomy. Two had benign Sertoli or Leydig cell hyperplasia, and in one case the procedure was patient-driven due to psychological distress. The remaining 11 patients retained their gonads, allowing spontaneous puberty and endogenous estrogen production via aromatization.

Gonadal surveillance included annual AFP and β-hCG testing and US every 2-3 years (median follow-up 7.5 years). No malignant changes were detected. However, consistent with the literature, tumor markers and US have limited sensitivity for early neoplasia, highlighting the need for improved biomarkers.

Our data therefore support the strategy of delaying gonadectomy until after puberty, provided that careful surveillance is in place.

Clinical Decisions and Gonadal Management

Of the five patients who underwent gonadectomy, in four the procedure followed previous standard recommendations, while in one it was performed due to psychological distress. Histology revealed only benign changes (Sertoli cell adenoma and/or Leydig cell hyperplasia).

The remaining 11 patients retained their gonads, which enabled spontaneous puberty and aromatization of testosterone to estrogen, eliminating the need for immediate hormone replacement. Delaying gonadectomy allowed patients to participate in decision-making once mature, which is important given lifelong hormonal consequences and potential psychological impact.

Current Tumor Monitoring Strategies

Tumor surveillance in CAIS most commonly includes serum AFP, β-hCG and lactate dehydrogenase (LDH), although their sensitivity for early malignancy is limited, as elevations may also occur in non-gonadal or benign conditions. Therefore, these markers should not be used as standalone screening tools.

In patients who retain their gonads, recent recommendations suggest a structured surveillance protocol, including clinical self-examination, periodic pelvic/inguinal US, and consideration of targeted gonadal biopsy in late adolescence to detect GCNIS (11,19).

Historically, prophylactic early gonadectomy was advised, but current practice supports delaying removal until after puberty, provided careful follow-up is ensured.

Study Findings Regarding Tumor Surveillance

In our cohort, all patients underwent annual AFP and β-hCG monitoring and US every 2-3 years, and no abnormalities were detected. However, as no routine histological assessment was performed in patients who retained their gonads, subclinical lesions cannot be completely excluded. Isolated reports of germ cell neoplasia *in situ* and Sertoli cell tumors in pediatric CAIS highlight the need for continued surveillance, despite the overall low malignancy risk. Further progress in this area will depend on the development of more sensitive biomarkers and imaging techniques for early detection.

Psychological Aspects of CAIS

All patients were raised as females and identified as such. Although most adapted well, previous studies report that up to 36% may experience reduced certainty of gender identity or femininity. Psychological support is therefore essential, particularly around puberty and disclosure of diagnosis (20,21,22).

Therapeutic Considerations and Long-term Outcomes

HRT remains essential after gonadectomy. In our cohort, some patients required HRT, while others with preserved gonads experienced spontaneous puberty.

Beyond our data, the existing literature explores potential differences between estrogen and T therapy. Auer et al. (23) conducted a randomized, double-blind crossover trial showing comparable metabolic profiles but differential effects on sexual functioning, with T possibly enhancing well-being through neurosteroid activity.

Study Limitations

This study has limitations. Its retrospective design may lead to documentation bias and incomplete data. The small sample size inherent to the rarity of CAIS, limits generalizability and prevents statistical testing. Psychological assessments were based on clinical notes and patient-reported impressions rather than validated psychometric tools. Finally, the long study period (2004-2024) may involve changes in diagnostic and therapeutic practices over time, introducing variability in management.

Conclusion

The management of CAIS remains a subject of ongoing debate, particularly regarding the timing of gonadectomy. Our study supports the importance of an individualized, multidisciplinary approach, balancing the benefits of spontaneous pubertal development and endogenous estrogen production against the potential risk of malignancy. While our findings support delaying gonadectomy in asymptomatic patients under structured surveillance, the lack of sensitive biomarkers for early neoplastic transformation remains a significant limitation. Long-term, standardized follow-up protocols are essential to refine risk stratification and optimize clinical outcomes. Future research should focus on improving tumor surveillance strategies and assessing the long-term impact of gonadal retention on metabolic and bone health.

Ethics

Ethics Committee Approval: The study protocol was approved by the Research Ethics Committee of The Children's Health Memorial, Warsaw, Poland (approval no.: 12/KBE/2024, date: 25.04.2024).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of underage patients, and from the patients themselves if they were adults.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Elzbieta Marczak, Maria Szarras-Czapnik, Concept: Elzbieta Marczak, Maria Szarras-Czapnik, Design: Elzbieta Marczak, Data Collection or Processing: Elzbieta Marczak, Maria Szarras-Czapnik, Agata Skórka, Kinga Kowalczyk, Gabriela Grochowska, Malgorzata Walewska-Wolf, Barbara Antoniak, Katarzyna Bajszczak, Elżbieta Moszczyńska, Analysis or Interpretation: Elzbieta Marczak, Maria Szarras-Czapnik, Agata Skórka, Gabriela Grochowska, Barbara Antoniak, Literature Search: Elzbieta Marczak, Elżbieta Moszczyńska, Writing: Elzbieta Marczak, Maria Szarras-Czapnik, Katarzyna Bajszczak, Elżbieta Moszczyńska.

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