Management of gonads in adults with androgen insensitivity: an international survey.

Short title: Survey on management of gonads in AIS

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Abstract

Background: Complete and partial androgen insensitivity syndrome (CAIS, PAIS) are associated with an increased risk of gonadal germ cell cancer (GGCC). Recent guidelines recommend gonadectomy in women with CAIS in late adolescence. Nevertheless, many adult women prefer to retain their gonads.

Aims: To explore attitudes towards gonadectomy in AIS in centres around the world, estimate the proportion of adults with retained gonads and/or who developed GGCC, and explore reasons for declining gonadectomy.

Methods: Survey among health care professionals who use the International DSD Registry (I-DSD).

Results: Data were provided from 22 centres in 16 countries on 166 women (CAIS) and 26 men (PAIS). In CAIS, gonadectomy is recommended in early adulthood in 67% of centres; 19/166 (11.4%) women refused gonadectomy. Out of 142 women who had gonadectomy~~;~~ : or , evidence of germ cell neoplasm in situ (GCNIS), the precursor of GGCC, was reported in two (1.4%). Nine out of 26 men with PAIS (34.6%) had retained gonads; 11% of centres recommend routine gonadectomy in PAIS.

Conclusion: Although development of GGCC seems rare, gonadectomy after puberty is broadly recommended in CAIS; in PAIS this is more variable. Overall, our data reflect the need for evidence-based guidelines regarding prophylactic gonadectomy in AIS.

Introduction

Androgen insensitivity syndrome (AIS) is caused by mutations in the *Androgen Receptor (AR)* gene, and results in a partial or complete resistance to androgens. The complete form of AIS (CAIS) occurs in less than 1 per 20.000 of 46,XY individuals, who then develop a female phenotype. In men and women with partial AIS (PAIS), the phenotype is highly variable, depending on the degree of residual androgen activity and other modifying factors [1]. Whereas a likely pathogenic variant in *AR* can be identified in 85% of women who have CAIS, this is only the case in less than 30% of individuals who have clinical features suggestive of PAIS, suggesting that other mechanisms affect androgen signalling [2]. Providing care for individuals with AIS is best performed in a multidisciplinary setting and may be challenging [3–6]. Points of uncertainty are whether gonadectomy should be performed and if so, at what age. Gonadectomy in AIS is commonly recommended because of the potential development of gonadal germ cell cancer (GGCC) [1]. This risk to develop GGCC has been related to the presence of *TSPY (testis specific protein Y-encoded)* in association with the suboptimal environment of the germ cell niche – due to the lack of androgen signaling - which negatively affects germ cell maturation [7–9]. Both the macro-environment (non-scrotal position of the testis) and micro-environment (in particular Sertoli cells) are affected. The invasive GGCC occurring in AIS, mainly seminoma, belong to the group of the Type II malignant germ cell tumours of the testis and dysgenetic gonad (see [10] for a review), and are for many years preceded by the presence of an *in situ* neoplastic lesion, termed now according to the most recent WHO classification, germ cell neoplasia *in situ* (GCNIS) [11]. An overview of reported cases in children and adults since 2000 is presented in Table 1; before that time, a molecular genetic diagnosis was most often not available and published series mostly reported on a mix of clinical diagnoses, including also many cases with gonadal dysgenesis, who are known to have a much higher risk [12]. Whereas the risk for GGCC has been estimated at less than 1% in childhood, uncertainty prevails concerning this risk in retained gonads after adolescence [13]. Therefore, it has been recommended to perform gonadectomy towards the end of puberty, allowing for spontaneous pubertal (breast) development, through the peripheral conversion of excess testosterone into estradiol [1,14,15]. However, evidence for this recommendation is weak as it is derived from a limited number of small case series. In the series of Deans *et al.* [16], fifteen percent of adult women who have CAIS declined gonadectomy for various reasons, posing challenges to the medical management as no reliable tumour markers or imaging techniques for the detection of early neoplastic lesions in abdominal gonads are currently available [17]. A study from our group in a relatively large sample (n=52) systematically explored the prevalence of GCNIS and even earlier histological changes. This study revealed a prevalence of pre-neoplastic changes, i.e. changes hypothesized to precede the development of GCNIS, of around 10% in young adult women (median age 17.5 years) with CAIS, with

no GCNIS or invasive lesions [18]. In countries where the diagnosis of CAIS is rarely made early and/or gonadectomy is not commonly performed due to socio-economic or cultural reasons, invasive or clinically manifest GGCC are seldom reported [19]. In line with this observation, it has been found that only few *in situ* lesions progress to invasiveness in individuals who have AIS [20]. A small number of studies report a positive effect of retained gonads on bone mineral density in women with CAIS, which cannot always be obtained by HRT [21,22]. For men and women with PAIS, recommendations for the management of gonads at risk have been proposed only recently, but the evidence remains weak and partly based on extrapolations from other conditions such as testosterone biosynthesis defects [9].

This study aims to explore current attitudes towards gonadectomy in the context of AIS in DSD centres across the world, to estimate the prevalence of (pre)malignant germ cell changes in individuals who have genetically confirmed AIS and have undergone gonadectomy, as well as the occurrence of GCC in retained gonads. Physicians providing care for individuals who have AIS were recruited through the I-DSD Registry (https://www.i-dsd.org) [23].

Methodology

Recruitment

An international survey was performed among health care professionals working in DSD centres around the world between 2015 and 2017. Contact details of clinicians were retrieved through the I-DSD Registry. A total of 41 centres (28 European and 13 non-European) were contacted by e-mail, with three reminders sent to centres that did not reply. The questionnaires were attached to these e-mails and centres were asked to return the completed forms electronically.

Questionnaire

The first section of the questionnaire concerned adult women (≥16 years) who have CAIS and was divided in two parts. The first part asked about the number of individuals with CAIS known to the centre and general attitudes of the centre towards gonadectomy **(Table 1)**. Part two explored individuals who had not undergone gonadectomy in more detail, focussing on reasons for declining gonadectomy and if there had ever been any suspicion of tumour development **(Table 2)**.

The second section of the survey explored adult men (≥16 years) who have PAIS and followed the same structure as the previous section **(Table 3)**.

Statistics

Statistical analysis was performed using IBM SPSS software package (version 25). A *p*-value of less than 0.05 was considered significant. To test whether centres that do not recommend gonadectomy on a routine basis had more individuals with retained gonads than other centres, a Pearson Chi-Square test and Fisher's Exact test were used for CAIS and PAIS respectively.

Results

General

Twenty-two out of 41 contacted centres (53.7%) replied to the survey. Of these, there were eighteen European and four non-European centres (18.2%) (USA, Sudan, Israel and Turkey). However, not all questionnaires were fully completed, mostly because patient data were unavailable after transition to an adult department. This led to missing data for 10 centres (45.5%). A total of 160 emails were sent to the centre leads of all centres combined (including reminders). In total, data were collected on 175 women with CAIS and 26 men with PAIS.

Complete androgen insensitivity syndrome

General attitudes towards gonadectomy (Table 2).

Of 166 women, 24 (14.5%) had retained gonads at the time of the survey. Gonadectomy was performed on a routine basis during childhood in four out of the 21 centres (19%), whereas it was routinely proposed after puberty in 12 of 18 centres (67%) that replied to this question (Fig 1A, B). Six centres reported not to propose gonadectomy on a routine basis at any age but to perform the procedure according to patients' preferences. In these centres, nine out of forty-four women (20.5%) had retained gonads at the time of the survey as compared to fifteen of the 122 women (12.3%) at all other centres (p=0.187). Centre-specific gonadectomy rates varied from 0% to 100%. Two of 142 women (1.4%) who had gonadectomy were diagnosed with GCNIS, according to the clinicians' information, no invasive GGCC were reported. No data are available about the age of these women at the time of the procedure or about the medical indication (e.g. presence of complaints or symptoms, tumour suspicion on imaging studies) for gonadectomy.

Women older than 16 years with CAIS and who have retained gonads (Table 3)

Twenty-four women were reported to have retained gonads, of which 50% had abdominal and 25% had inguinal gonads; the gonadal location was unknown in the remaining 25%. Median age of these women was 20 years (range: 16-48 years). Out of these 24 women, 19 (79.2%) preferred not to have gonadectomy, one had never been advised to have gonadectomy and for the four remaining cases, no further information was available. For 13 out of the 19 women who declined gonadectomy, a specific reason was reported. Multiple reasons were given in eight women (61.5%). Concerns about the procedure was the most frequently reported reason (8/13 women), followed by inconvenience to plan surgery when it was proposed (6/13 women), not wanting hormone replacement therapy (5/13 women) and not having come to terms with the diagnosis yet (4/13). In addition, clinicians reported that two of those thirteen women were unaware of or did not understand the cancer risk.

Men who have PAIS (Table 4)

Eighteen out of 22 centres provided information on whether they recommend routine gonadectomy to their male patients who have PAIS. One (5.6%) centre reported to routinely perform gonadectomy during childhood in boys who have PAIS; in four other centres, the decision depends on the gonadal location. Two centres perform gonadectomy as a standard procedure during adolescence/adulthood, whereas in four centres (22.2%), the decision was made on a case by case basis, taking into account gonadal function and location of the gonads (Fig 1C,D). Five out of nine men (55.6%) followed in centres that do not perform gonadectomy on a routine basis at any age had retained at least one gonad compared to four out of the seventeen men (23.5%) of the remaining centres (p=0.194). Information was available on twenty-six men with PAIS older than 16 years. Only nine men (34.6%) were reported to have at least one retained gonad at the time of the survey. In 11 men, this information was unavailable. Of the nine men who had at least one retained gonad, seven had scrotal testes, one had bilateral inguinal testes and one had an abdominal testis. The latter was reported to have undergone unilateral gonadectomy at the age of 55 years for suspicion of GGCC. However, no malignancy was found, the final diagnosis being Leydig cell hyperplasia.

Discussion

This study tries to capture attitudes towards gonadectomy for AIS in DSD centres around the world. Through the I-DSD Registry, information was obtained from 22 centres, jointly following a reasonably large cohort of individuals with AIS, mainly women with CAIS. In addition, we have tried to collect information on the natural evolution of retained gonads in this condition, with respect to development of a GGCC. Eventually underlying motivating factors in affected individuals for declining gonadectomy were also explored.

The response rate of our survey was 53.7%, which we consider reasonably high for a time-consuming survey. Since only four of the 13 (30.8%) approached centres from outside Europe participated, our study mainly reflects practices within European centres. Differences in timing of gonadectomy were seen on an international level, as well as within countries, suggesting that recently issued recommendations to postpone gonadectomy until adulthood are not generally implemented [1,15]. Insufficiently convincing evidence due to small sample sizes as well as sociocultural reasons may partly account for this variation in practice [14].

Nevertheless, from our survey it is clear that currently, most clinicians from participating centres prefer to postpone gonadectomy until after puberty so that secondary sex characteristics can develop optimally [24,25]. Eleven percent of the women with CAIS in our study had declined a gonadectomy and the main reasons for declining were concerns about the procedure, inconvenience of planning surgery, not wanting HRT and not having adjusted to the diagnosis. These results are in line with the study of Deans *et al.* [16].

Recent data and a meta-analysis of historical series suggest a risk for *in situ* lesions and preneoplastic changes of the germ cells of 10-15% in retained gonads, mainly in women with CAIS. However, it is unclear to what extent these lesions will show invasive progression later in life [16,18–20,26–28]. To our best knowledge, no invasive GGCC had occurred so far in the 166 adult women included in our survey. However, in two out of 142 women (1.4%) who had gonadectomy, a histological diagnosis of GCNIS was established according to the case files. This number has to be interpreted with caution as detailed histopathological findings of the gonadal tissue were only provided for eight women including the two who had GCNIS, but it is in line with recently reported data [18,19]. Although the risk of GGCC may be small, monitoring abdominal gonads for early neoplastic changes in those who decline gonadectomy is challenging. Relocation of the gonads to a more superficial region may be an alternative [29]. To date, little evidence-based data exist that guides clinicians in when to propose a gonadectomy in AIS. Based on the findings of this and our previous studies, we propose the clinical algorithm presented in figure 2 and 3. In addition, when discussing the pros and cons of gonadectomy, the agency of an individual should be taken into account. However, this is currently poorly identified.

Developing a validated questionnaire or checklist can help clinicians assess their patient's understanding of the complex medical information they receive and their correct appraisal of the consequences of a decision in favour or against gonadectomy [30,31]. Important questions and factors that should be included in this questionnaire are represented in table 5.

A low number (34.6%) of men who have PAIS had at least one retained gonad, even in centres that do not perform gonadectomy on a routine basis at any age (55.6% *vs.* 23.5%). Given the functional importance of the testes and easy accessibility in scrotal position (for some after orchidopexy) for follow-up by self-examination and ultrasound, this finding is surprising. It is possible that the testes were located too high for successful orchidopexy in some men, which could (partially) explain the high gonadectomy rate. Although a higher GGCC risk was initially reported in PAIS as compared to CAIS [7,8], a more recent study did not confirm such findings [18].

Increasingly it is felt that the testes can be safely preserved in most men with PAIS, especially in the case of a scrotal position, under the condition that a strict surveillance protocol is insured. This surveillance should consist of regular follow-up by self-examination and ultrasound, as well as a testis biopsy in early adulthood which is then evaluated for the presence of GCNIS in an experienced pathology service, as proposed by van der Zwan *et al.* [9].

Limitations of this study are the small number of participating centres from outside Europe, and the sometimes only partially completed questionnaires. All information, including histology, was as reported by clinicians but was not confirmed by independent analysis. In addition, we had no access to detailed patient data, e.g. regarding hormone levels, type of *AR* mutation or residual androgen activity. The strength of this study is the inclusion of a large cohort of adult women with CAIS, from whom data were available.

In conclusion, practices towards gonadectomy in AIS vary around the world and within countries. In CAIS, the majority of centres tend to routinely propose gonadectomy to affected women at the end of puberty, but an estimated 11% of women further postpone this procedure. Main reasons are inconvenient timing, not having come to terms with the diagnosis and concerns about the procedure and about consequences of HRT. In men with PAIS, patient factors such as gonadal function and location seem to influence the decision for gonadectomy. However, the majority of men with PAIS were reported to have undergone bilateral gonadectomy. No invasive GGCC were reported in 166 women with CAIS. Of the 142 women with CAIS who had gonadectomy, GCNIS was reported in two, whereas no (pre)malignancies were reported in adult men with PAIS. Taken together, our data highlight the lack of standardization concerning gonadectomy in AIS, and suggest a low incidence of

invasive GGCC in AIS during adulthood. Therefore, individualised decision-making, taking also into account patient preferences and agency, rather than chronological age, seems appropriate.

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References

1 Hughes IA, Davies JD, Bunch TI, Pasterski V, Mastroyannopoulou K, MacDougall J: Androgen insensitivity syndrome. Lancet 2012;380:1419–1428.

2 Hornig NC, Ukat M, Schweikert HU, Hiort O, Werner R, Drop SLS, et al.: Identification of an AR Mutation-Negative Class of Androgen Insensitivity by Determining Endogenous AR Activity. J Clin Endocrinol Metab 2016;101:4468–4477.

3 Beale JM, Creighton SM: Long-term health issues related to disorders or differences in sex development/intersex. Maturitas 2016;94:143–148.

4 Hiort O, Birnbaum W, Marshall L, Wünsch L, Werner R, Schröder T, et al.: Management of disorders of sex development. Nat Rev Endocrinol 2014;10:520–529.

5 Hughes IA: Consensus statement on management of intersex disorders. Arch Dis Child 2005;91:554–563.

6 Cools M, Nordenström A, Robeva R, Hall J, Westerveld P, Flück C, et al.: Caring for individuals with a difference of sex development (DSD): a Consensus Statement. Nat Rev Endocrinol 2018;14:415–429.

7 Cools M, van Aerde K, Kersemaekers A-M, Boter M, Drop SLSS, Wolffenbuttel KP, et al.: Morphological and immunohistochemical differences between gonadal maturation delay and early germ cell neoplasia in patients with undervirilization syndromes. J Clin Endocrinol Metab 2005;90:5295–303.

8 Cools M, Drop SLSS, Wolffenbuttel KP, Oosterhuis JW, Looijenga LHJJ: Germ Cell Tumors in the Intersex Gonad: Old Paths, New Directions, Moving Frontiers. Endocr Rev 2006;27:468–484.

9 van der Zwan YG, Biermann K, Wolffenbuttel KP, Cools M, Looijenga LHJ: Gonadal Maldevelopment as Risk Factor for Germ Cell Cancer: Towards a Clinical Decision Model. Eur Urol 2015;67:692–701.

10 Oosterhuis JW, Looijenga LHJ: Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer 2005;5:210–222.
11 Idrees MT, Ulbright TM, Oliva E, Young RH, Montironi R, Egevad L, et al.: The World Health Organization 2016 classification of testicular non-germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel. Histopathology 2017;70:513–521.
12 Cools M, Wolffenbuttel KP, Drop SLS, Oosterhuis JW, Looijenga LHJ: Gonadal development and tumor formation at the crossroads of male and female sex determination. Sex Dev 2011;5:167–80.
13 Cools M, Looijenga L: Update on the Pathophysiology and Risk Factors for the Development of Malignant Testicular Germ Cell Tumors in Complete Androgen Insensitivity Syndrome. Sex Dev 2017; DOI: 10.1159/000477921
14 Bertelloni S: Gonadal Surgery in Complete Androgen Insensitivity Syndrome: A Debate. Sex Dev 2017; DOI: 10.1159/000475907
15 Lee PA, Nordenström A, Houk CP, Ahmed SF, Auchus R, Baratz A, et al.: Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. Horm Res Paediatr 2016;85:158–180.
16 Deans R, Creighton SM, Liao L-M, Conway GS: Timing of gonadectomy in adult women with complete androgen insensitivity syndrome (CAIS): patient preferences and clinical evidence. Clin Endocrinol (Oxf) 2012;76:894–898.
17 Cools M, Looijenga LHJ, Wolffenbuttel KP, T'Sjoen G: Managing the Risk of Germ Cell Tumourigenesis in Disorders of Sex Development Patients; in : Endocrine development. 2014, pp 185–196.
18 Cools M, Wolffenbuttel KP, Hersmus R, Mendonca BB, Kaprová J, Drop SLS, et al.: Malignant testicular germ cell tumors in postpubertal individuals with androgen insensitivity: prevalence, pathology and relevance of single nucleotide polymorphism-based susceptibility profiling. Hum Reprod 2017;32:2561–2573.
19 Chaudhry S, Tadokoro-Cuccaro R, Hannema SE, Acerini CL, Hughes IA: Frequency of gonadal tumours in complete androgen insensitivity syndrome (CAIS): A retrospective case-series analysis. J Pediatr Urol 2017;13:498.e1-498.e6.
20 Kaprova-Pleskacova J, Stoop H, Brüggenwirth H, Cools M, Wolffenbuttel KP, Drop SLS, et al.: Complete androgen insensitivity syndrome: factors influencing gonadal histology including germ cell pathology. Mod Pathol 2014;27:721–30.
21 Bertelloni S, Meriggiola MC, Dati E, Balsamo A, Baroncelli GI: Bone Mineral Density in Women Living with Complete Androgen Insensitivity Syndrome and Intact Testes or Removed Gonads.

Sex Dev 2017;11:182–189.
22 Döhnert U, Wünsch L, Hiort O: Gonadectomy in Complete Androgen Insensitivity Syndrome: Why and When? Sex Dev 2017;11:171–174.
23 Ahmed SF, Rodie M, Jiang J, Sinnott RO: The European Disorder of Sex Development Registry: A Virtual Research Environment. Sex Dev 2010;4:192–198.
24 Kathrins M, Kolon TF: Malignancy in disorders of sex development. Transl Androl Urol 2016;5:794–798.
25 Patel V, Casey RK, Gomez-Lobo V: Timing of Gonadectomy in Patients with Complete Androgen Insensitivity Syndrome–Current Recommendations and Future Directions. J Pediatr Adolesc Gynecol 2016;29:320–325.
26 Nakhal R.S., Hall-Craggs M., Freeman A., Kirkham A., Conway G.S., Arora R., et al.: Evaluation of retained testes in adolescent girls and women with complete androgen insensitivity syndrome. Radiology 2013;268:153–160.
27 Cheikhelard A, Morel Y, Thibaud E, Lortat-Jacob S, Jaubert F, Polak M, et al.: Long-Term Followup and Comparison Between Genotype and Phenotype in 29 Cases of Complete Androgen Insensitivity Syndrome. J Urol 2008;180:1496–1501.
28 Audi L, Fernández-Cancio M, Carrascosa A, Andaluz P, Torán N, Piró C, et al.: Novel (60%) and recurrent (40%) androgen receptor gene mutations in a series of 59 patients with a 46,XY disorder of sex development. J Clin Endocrinol Metab 2010;95:1876–1888.
29 Wolffenbuttel KP, Hersmus R, Stoop H, Biermann K, Hoebeke P, Cools M, et al.: Gonadal dysgenesis in disorders of sex development: Diagnosis and surgical management. J Pediatr Urol 2016;12:411–416.
30 Hullmann SE, Chalmers LJ, Wisniewski AB: Transition from pediatric to adult care for adolescents and young adults with a disorder of sex development. J Pediatr Adolesc Gynecol 2012;25:155–7.
31 McCracken KA, Fallat ME: Transition from pediatric to adult surgery care for patients with disorders of sexual development. Semin Pediatr Surg 2015;24:88–92.
32 Ahmed SF, Cheng A, Dovey L, Hawkins JR, Martin H, Rowland J, et al.: Phenotypic features, androgen receptor binding, and mutational analysis in 278 clinical cases reported as androgen insensitivity syndrome. J Clin Endocrinol Metab 2000;85:658–65.
33 Hannema SE, Scott IS, Rajpert-De Meyts E, Skakkebæk NE, Coleman N, Hughes IA: Testicular development in the complete androgen insensitivity syndrome. J Pathol 2006;208:518–527.

Legends:

Figure 1: Preferences of centres regarding gonadectomy. A: Preferences of centres regarding gonadectomy in women with CAIS before puberty; B: Preferences of centres regarding gonadectomy in women with CAIS after puberty; C: Preferences of centres regarding gonadectomy in men with PAIS before puberty; D: Preferences of centres regarding gonadectomy in men with PAIS after puberty. Proportion of centres that recommend routine gonadectomy (light grey), solely on indication (dark grey), based on gonadal location (horizontal stripes), based on gonadal function (vertical stripes).

Figure 2. Clinical algorithm for considering gonadectomy in CAIS. GCNIS: germ cell neoplasm in situ, GGCC: gonadal germ cell cancer; HRT: hormone replacement therapy; US: ultrasound; MRI: magnetic resonance imaging; alphaFP: alpha fetoprotein; betaHCG: beta human chorionic gonadotropin; miR: novel serum microRNA.

Figure 3. Clinical algorithm for considering gonadectomy in PAIS. GCNIS: germ cell neoplasm in situ, GGCC: gonadal germ cell cancer; HRT: hormone replacement therapy; US: ultrasound; MRI: magnetic resonance imaging; alphaFP: alpha fetoprotein; betaHCG: beta human chorionic gonadotropin; miR: novel serum microRNA; DHT: dihydrotestosterone.

Table 1. Overview of reported germ cell cancers in androgen insensitivity syndrome since 2000.

Author	Year	Reported gonadal tumors
Ahmed [32]	2000	CAIS: - GCNIS/GGCC: 0/65 PAIS: - GCNIS/GGCC: 0/56
Hannema [33]	2006	CAIS (mostly prepubertal cases): - GCNIS: 2/44 (4.5%), age: 17 and 53 years - GGCC: 0/44
Cheikhelard [27]	2008	CAIS: - GCNIS: 1/29 (3.4%), age: 14 years
Audi [28]	2010	CAIS/PAIS: - GCNIS/GGCC: 0/13 (CAIS & PAIS)
Nakhal [26]	2013	CAIS (>16 years old): - GCNIS: 3/25 (12%), age: 19, 20 and 38 years
Chaudhry [19]	2017	CAIS: - GCNIS: 7/133 (5.3%), age: 1.6, 2.8, 16, 17, 17, 20 and 53 years - GGCC: 2/133 (1.5%), age: 30 and 68 years
Cools [18]	2017	CAIS: - Pre-GCNIS: 6/42 (14.3%), age: 14, 15, 15, 18, 21 and 22 years - GCNIS/GGCC: 0/42 PAIS: - Pre-GCNIS: 1/10 (10%), age: 15 years - GCNIS/GGCC: 0/10

CAIS: complete androgen insensitivity syndrome; PAIS: partial androgen insensitivity syndrome; GGCC: gonadal germ cell cancer; GCNIS: germ cell neoplasm *in situ*; Age: age of individual(s) with reported (pre-)GCNIS/GGCC.

Table 2. Women with CAIS (≥16 years old): approach of centres towards gonadectomy and proportion of women with retained gonads.

Centre	Number of patients	Gonadectomy in childhood	Gonadectomy in adolescence or adulthood	No gonadectomy
1	25	No	Yes	2/25 (8.0%)
2	16	No	NA	3/16 (18.8%)
3	12	No	No	1/12 (8.3%)
4	0	No	No	0/0
5	3	No	Yes	3/3 (100%)
6	5	Yes	Yes	0/5 (0%)
7	5	Yes	Yes	1/5 (20%)
8	3	No	Yes	1/3 (33.3%)
9	9	No	No	1/9 (11.1%)
10	11	No	Yes	1/11 (9.1%)
11	1	No	No	1/1 (100%)
12	5	No	Yes	0/5 (0%)
13	NA	No	No	NA
14	2	NA	NA	1/2 (50%)
15	2	Yes	NA	1/2 (50%)
16	17	No	Yes	0/17 (0%)
17	0	No	Yes	0/0
18	3	No	Yes	0/3 (0%)
19	1	Yes	Yes	1/1 (100%)[+]
20	22	No	No	6/22 (27.3%)
21	0	No	NA	0/0
22	24	No	Yes	1/24 (4.2%)
Total	**166**	**4/21 (19%)**	**12/18 (66.7%)**	**24/166 (14.5%)**

NA: Not available/missing; Number of patients: number of patients with CAIS, ≥16 years of age followed per centre; [+]:Died of an unrelated condition before the (recommended) gonadectomy procedure had been performed

Table 3. Summary of women who have CAIS (≥16 years old) with retained gonads: descriptive statistics, gonadal location and reasons for declining gonadectomy.

Descriptive statistics	
Number of cases	N = 24
Mean age ± SD	24.2 ± 8.12
Declined gonadectomy	19/24 (79.2%)
Gonadectomy had not been proposed	1/24 (4.2%)
Missing/lost to follow-up	4/24 (16.7%)
Gonadal location	
Missing	12/24
Abdominal	6/12 (50%)
Inguinal	3/12 (25%)
Unknown	3/12 (25%)
Reasons for declining	
Not specified	6/19 (31.6%)
Concerns about the procedure	8/13 (61.5%)
Inconvenient to plan surgery	6/13 (46.2%)
Concerns about HRT	5/13 (38.5%)
Had not come to terms with diagnosis yet	4/13 (30.8%)
Unaware of malignancy risk or doesn't understand the malignancy risk	2/13 (15.4%)

Not specified: No specific reason was given as to why gonadectomy was refused, including wanting to wait to make the decision; SD: standard deviation; HRT: hormone replacement therapy.

Table 4. Men with PAIS: approach of centres towards gonadectomy, proportion of men with retained gonads and gonadal location of retained gonads

Centre	Gonadectomy: childhood	Gonadectomy: Adolescence or Adulthood	#no gonadectomy / #total	Location gonads
1	Yes*	Yes*	NA	
2	No	No	0/0	
3	No	No	2/2	Both scrotal
4	No	No	1/1	Scrotal
5	Yes	No	0/0	
6	Yes*	No	1/2	Scrotal
7	NA	NA	0/0	
8	No	Case specific	0/0	
9	No	No	1/1	Abdominal
10	No	Yes	0/12	
11	No	No	0/0	
12	No	Yes[#]	NA/10	
13	NA	NA	NA	
14	NA	NA	NA	
15	Yes*	Yes	1/1	Inguinal
16	No	No	1/1	Scrotal
17	No	No	NA/1	
18	No	Yes[#]	2/2	Both Scrotal
19	NA	NA	NA	
20	No	No	0/4	
21	Yes*	Yes*	0/0	
22	No	No	0/0	
Total	**Yes: 1/18 (5.6%)** **Yes*: 4/18 (22.2%)**	**Yes: 2/18 (11.1%)** **Yes*: 2/18 (11.1%)** **Yes[#]: 2/18 (11.1%)**	**9/26 (34.6%)**	**7 scrotal, 1 inguinal, 1 abdominal**

#no gonadectomy/#total: number of men with at least one retained gonads / total number of men with PAIS followed per center. NA: Not available/missing; Number of patients: number of men who have PAIS (≥16 years of age) followed per centre; Yes*: choice depends on location of gonads; Yes[#]: choice depends on the function of gonads.

418 **Table 5.** Assessing agency and readiness for gonadectomy in AIS (modified from [30,31]).

Key Questions
Does the individual know his/her health history?
Does the individual understand the diagnosis of AIS?
Can the individual ask relevant and insightful questions to the involved health care providers regarding AIS?
Can the individual weigh the risks and benefits specific of his/her own situation, regarding (postponing) gonadectomy?
Is the patient capable of finding useful information on AIS and gonadectomy? (internet, support groups,…)
Is there sufficient social support to make important health-related decisions?
Has the individual come to terms with the diagnosis?
Important factors to be weighed in
Independence and willingness to make and attend own appointments with health care providers
Willingness to take hormone replacement therapy
Ability to perform gonadal exams and (if applicable) self-exams
The current social, educational and / or professional context of the individual

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