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1 Management of gonads in adults with androgen insensitivity: an 2 international survey.

3

4 **Short title:** Survey on management of gonads in AIS

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79 **Abstract**

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

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

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

87 **Results:** Data were provided from 22 centres in 16 countries on 166 women (CAIS) and 26 men (PAIS).
88 In CAIS, gonadectomy is recommended in early adulthood in 67% of centres; 19/166 (11.4%) women
89 refused gonadectomy. Out of 142 women who had gonadectomy, or , evidence of germ cell neoplasm
90 in situ (GCNIS), the precursor of GGCC, was reported in two (1.4%). Nine out of 26 men with PAIS
91 (34.6%) had retained gonads; 11% of centres recommend routine gonadectomy in PAIS.

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

95 Introduction

96 Androgen insensitivity syndrome (AIS) is caused by mutations in the *Androgen Receptor (AR)* gene, and
97 results in a partial or complete resistance to androgens. The complete form of AIS (CAIS) occurs in less
98 than 1 per 20.000 of 46,XY individuals, who then develop a female phenotype. In men and women with
99 partial AIS (PAIS), the phenotype is highly variable, depending on the degree of residual androgen
100 activity and other modifying factors [1]. Whereas a likely pathogenic variant in *AR* can be identified in
101 85% of women who have CAIS, this is only the case in less than 30% of individuals who have clinical
102 features suggestive of PAIS, suggesting that other mechanisms affect androgen signalling [2]. Providing
103 care for individuals with AIS is best performed in a multidisciplinary setting and may be challenging [3–
104 6]. Points of uncertainty are whether gonadectomy should be performed and if so, at what age.
105 Gonadectomy in AIS is commonly recommended because of the potential development of gonadal
106 germ cell cancer (GGCC) [1]. This risk to develop GGCC has been related to the presence of *TSPY (testis*
107 *specific protein Y-encoded)* in association with the suboptimal environment of the germ cell niche –
108 due to the lack of androgen signaling - which negatively affects germ cell maturation [7–9]. Both the
109 macro-environment (non-scrotal position of the testis) and micro-environment (in particular Sertoli
110 cells) are affected. The invasive GGCC occurring in AIS, mainly seminoma, belong to the group of the
111 Type II malignant germ cell tumours of the testis and dysgenetic gonad (see [10] for a review), and are
112 for many years preceded by the presence of an *in situ* neoplastic lesion, termed now according to the
113 most recent WHO classification, germ cell neoplasia *in situ* (GCNIS) [11]. An overview of reported cases
114 in children and adults since 2000 is presented in Table 1; before that time, a molecular genetic
115 diagnosis was most often not available and published series mostly reported on a mix of clinical
116 diagnoses, including also many cases with gonadal dysgenesis, who are known to have a much higher
117 risk [12]. Whereas the risk for GGCC has been estimated at less than 1% in childhood, uncertainty
118 prevails concerning this risk in retained gonads after adolescence [13]. Therefore, it has been
119 recommended to perform gonadectomy towards the end of puberty, allowing for spontaneous
120 pubertal (breast) development, through the peripheral conversion of excess testosterone into
121 estradiol [1,14,15]. However, evidence for this recommendation is weak as it is derived from a limited
122 number of small case series. In the series of Deans *et al.* [16], fifteen percent of adult women who have
123 CAIS declined gonadectomy for various reasons, posing challenges to the medical management as no
124 reliable tumour markers or imaging techniques for the detection of early neoplastic lesions in
125 abdominal gonads are currently available [17]. A study from our group in a relatively large sample
126 (n=52) systematically explored the prevalence of GCNIS and even earlier histological changes. This
127 study revealed a prevalence of pre-neoplastic changes, i.e. changes hypothesized to precede the
128 development of GCNIS, of around 10% in young adult women (median age 17.5 years) with CAIS, with

129 no GCNIS or invasive lesions [18]. In countries where the diagnosis of CAIS is rarely made early and/or
130 gonadectomy is not commonly performed due to socio-economic or cultural reasons, invasive or
131 clinically manifest GGCC are seldom reported [19]. In line with this observation, it has been found that
132 only few *in situ* lesions progress to invasiveness in individuals who have AIS [20]. A small number of
133 studies report a positive effect of retained gonads on bone mineral density in women with CAIS, which
134 cannot always be obtained by HRT [21,22]. For men and women with PAIS, recommendations for the
135 management of gonads at risk have been proposed only recently, but the evidence remains weak and
136 partly based on extrapolations from other conditions such as testosterone biosynthesis defects [9].
137 This study aims to explore current attitudes towards gonadectomy in the context of AIS in DSD centres
138 across the world, to estimate the prevalence of (pre)malignant germ cell changes in individuals who
139 have genetically confirmed AIS and have undergone gonadectomy, as well as the occurrence of GCC in
140 retained gonads. Physicians providing care for individuals who have AIS were recruited through the I-
141 DSD Registry (<https://www.i-dsd.org>) [23].
142

143 **Methodology**

144 **Recruitment**

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

150 **Questionnaire**

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

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

158 **Statistics**

159 Statistical analysis was performed using IBM SPSS software package (version 25). A p -value of less than
160 0.05 was considered significant. To test whether centres that do not recommend gonadectomy on a
161 routine basis had more individuals with retained gonads than other centres, a Pearson Chi-Square test
162 and Fisher's Exact test were used for CAIS and PAIS respectively.

163

164 **Results**

165 **General**

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

172

173 **Complete androgen insensitivity syndrome**

174 **General attitudes towards gonadectomy (Table 2).**

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

186

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

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

198

199 **Men who have PAIS (Table 4)**

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

214 Discussion

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

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

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

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

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

252 A low number (34.6%) of men who have PAIS had at least one retained gonad, even in centres that do
253 not perform gonadectomy on a routine basis at any age (55.6% vs. 23.5%). Given the functional
254 importance of the testes and easy accessibility in scrotal position (for some after orchidopexy) for
255 follow-up by self-examination and ultrasound, this finding is surprising. It is possible that the testes
256 were located too high for successful orchidopexy in some men, which could (partially) explain the high
257 gonadectomy rate. Although a higher GGCC risk was initially reported in PAIS as compared to CAIS
258 [7,8], a more recent study did not confirm such findings [18].

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

264
265 Limitations of this study are the small number of participating centres from outside Europe, and the
266 sometimes only partially completed questionnaires. All information, including histology, was as
267 reported by clinicians but was not confirmed by independent analysis. In addition, we had no access
268 to detailed patient data, e.g. regarding hormone levels, type of AR mutation or residual androgen
269 activity. The strength of this study is the inclusion of a large cohort of adult women with CAIS, from
270 whom data were available.

271
272 In conclusion, practices towards gonadectomy in AIS vary around the world and within countries. In
273 CAIS, the majority of centres tend to routinely propose gonadectomy to affected women at the end of
274 puberty, but an estimated 11% of women further postpone this procedure. Main reasons are
275 inconvenient timing, not having come to terms with the diagnosis and concerns about the procedure
276 and about consequences of HRT. In men with PAIS, patient factors such as gonadal function and
277 location seem to influence the decision for gonadectomy. However, the majority of men with PAIS
278 were reported to have undergone bilateral gonadectomy. No invasive GGCC were reported in 166
279 women with CAIS. Of the 142 women with CAIS who had gonadectomy, GCNIS was reported in two,
280 whereas no (pre)malignancies were reported in adult men with PAIS. Taken together, our data
281 highlight the lack of standardization concerning gonadectomy in AIS, and suggest a low incidence of

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

284

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384

385 **Legends:**

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

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

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

400

401

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

402

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.

403

404 **Table 2. Women with CAIS (≥16 years old): approach of centres towards gonadectomy and proportion**
 405 **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%)

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

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

Descriptive statistics	
Number of cases	N = 24
Mean age \pm SD	24.2 \pm 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%)

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

412 **Table 4. Men with PAIS: approach of centres towards gonadectomy, proportion of men with retained**
 413 **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

414 #no gonadectomy/#total: number of men with at least one retained gonads / total number of men with PAIS followed per
 415 center. NA: Not available/missing; Number of patients: number of men who have PAIS (≥16 years of age) followed per centre;
 416 Yes*: choice depends on location of gonads; Yes[#]: choice depends on the function of gonads.
 417

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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