

ORIGINAL ARTICLE

Timing of gonadectomy in adult women with complete androgen insensitivity syndrome (CAIS): patient preferences and clinical evidence

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Abstract

Objective Adult women with complete androgen insensitivity syndrome (CAIS) are increasingly likely to defer or decline gonadectomy despite counselling about malignancy risk. The objectives of this study were to review the evidence on the risk of gonadal malignancy in adult women with CAIS and to explore women's reasons for deferring gonadectomy.

Study Design A case series and literature review.

Patients Sixteen women with CAIS over the age of 18 years who have elected to defer gonadectomy.

Results Sixty-two relevant papers were identified. Of these, 14 confirmed that tumours had been reported in 98 adults. Taking into account the limitations of combining historic case series, this review estimates a risk of gonadal malignancy of 14% (range 0% and 22%) in adults with CAIS. The most common reasons women offered for deferring gonadectomy included inconvenience of surgery, concern about surgical risk and reluctance to take hormone replacement therapy.

Conclusions Perceived benefits for retaining gonads in women with CAIS are prompting more women to keep their gonads in situ. An accurate estimate for adult malignancy risk is unavailable, and the risks currently quoted may be falsely reassuring.

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Introduction

Risk of gonadal tumours is a recognized aspect of clinical management of complete androgen insensitivity syndrome (CAIS). It has been a standard practice to advocate prophylactic removal of the

gonads as soon as the diagnosis is confirmed. Since the original description of the condition by Morris in 1955¹ however, reports of the estimated risk of gonadal malignancy have varied from as high as 22% to as low as 0.8%.² As a consequence, some specialists and advocacy groups suggest leaving the gonads in situ through puberty to allow spontaneous pubertal development.³

At our national centre of referral for disorders of sexual development (DSD), an increasing number of adult women with CAIS are opting to retain their gonads indefinitely. This has prompted the current study, which aimed to explore more systematically the reasons why individual women elected to defer gonadectomy and to review the evidence on risk of malignancy in adult women with CAIS, on which advocacy for prophylactic gonadectomy had been based. The review was carried out to ensure that adults with CAIS received the best possible clinical advice available.

Methods

The study took place at a tertiary referral DSD centre. Ethical approval was obtained from the NRES Committee London-Chelsea 11/LO/0519. The centre offers multidisciplinary care for children, adolescents and adults with CAIS and other DSDs. Current practice is to recommend gonadectomy after the completion of puberty. Women who chose not to undergo gonadectomy are counselled about potential malignant changes in the testes. A clinical protocol based on robust evidence is currently unavailable. Our interim strategy for monitoring has been to offer annual reviews focusing on the following observations: (i) clinical history including unusual abdominal symptoms such as pain or development of a mass; (ii) clinical examination for abdominal and groin tenderness or swelling; (iii) pelvic magnetic resonance imaging (MRI) by a radiologist experienced in MRI of DSD; and (iv) tumour markers including alpha fetoprotein, beta-human chorionic gonadotrophin, Ca 125 and lactose dehydrogenase.

The current report is based on two strands of review:

- Case notes review

The case notes of all women over the age of 18 years with CAIS who have chosen to retain their gonads were reviewed. Information recorded included the reasons for declining gonadectomy, clinical

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features, demographic data and details of the diagnosis of CAIS based on clinical findings and genetic data if available.

• Literature review

A review of the literature was performed to examine the evidence for malignancy risk in the gonads of adult patients with CAIS. Electronic resources including Medline, PubMed, Current Contents and EMBASE were searched using the MeSH terms including all subheadings and keywords 'testicular feminisation', 'androgen insensitivity syndrome', 'gonad', 'malignancy risk', 'disorders of sex development', 'XY female' and 'surgery'. The reference lists of identified papers were also searched and reviewed. Cases were only included in our analysis if there was a clear clinical description consistent with CAIS excluding cases, which did not meet the diagnostic criteria for the clinical diagnosis for CAIS, that is, nonvirilized female with an XY karyotype and absent uterus. Cases of carcinoma in situ and intratesticular germ cell neoplasia were also excluded. As the aim of our review was to advise adult women and their doctors, we further excluded papers where all patients had undergone gonadectomy under the age of 20 years or where the age of subjects in the study was not specified. The remaining papers were reviewed in detail by the multidisciplinary team.

Results

Case notes review

Of the 104 adult women with CAIS under review in the clinic, 16 (15%) have chosen to defer or decline gonadectomy. The mean (range) age of the women was 28 years (18–51). Fifteen women had been seen within the previous 1 year, and at that time, all tumour markers were negative. MRI and ultrasound had shown no frankly suspicious findings. One patient had not attended clinic for over 2 years and had failed to respond to appointments or correspondence. The reasons for deferring gonadectomy are given in Table 1.

Literature review

A total of 62 papers were identified and reviewed containing cases of CAIS. The majority of papers included a range of diagnoses under the descriptive umbrella of 'CAIS' such as partial androgen insensitivity syndrome and gonadal dysgenesis (Swyer syndrome). The vast majority of evidence in the literature was case reports and reviews of these reports including some case reports of tumours^{4–6} or small case series of women with CAIS reporting no tumours.^{7,8} Case series with apparently limited ascertainment bias were found in 16 papers that included patients who met the criteria for a diagnosis of CAIS. In four of these, we identified a repetition of cases^{1,9–15} and only additional cases from these papers were included in our summary. Of the 12 papers remaining, we excluded 6 where either the age was not given^{16,17} or where the upper age limit of cases included was under 20 years.^{18–21} One paper was excluded as although age distribution was given, the cases were combination of a case series and a literature review of case reports and these could not be separated.¹⁷ One study was excluded as although an age range was given, there was no information on the

proportion or of the number of adult patients who had undergone gonadectomy.²²

At the end of this process, four papers with usable data were identified covering women above age 20 years.^{1,13,15,23} Although these four papers contained a total of 396 cases of CAIS, the series were mixtures of paediatric and adult cases. Only 97 patients were confirmed as over 20 years. All were retrospective or cross-sectional reviews or a combination of both. A flowchart of the literature review process is given in Fig. 1.

The adult data obtained from each of the four papers included were as follows:

Morris 1953¹

This paper reported 181 cases of CAIS in whom 14 malignant tumours were reported. The age of the patients was given, and the group was divided into under and over 30 years of age. In the under 30 group ($n = 131$), three tumours were reported giving a risk of 0.02%. In the over 30 group ($n = 50$), 11 tumours were reported giving a risk of 22%. However, the paper states that 'considerably more than half' of the patients had already undergone gonadectomy. There was no information as to the age at gonadectomy and how many of the over 30 group had already had gonadectomy. If a significant number of the over-30s had undergone gonadectomy, this would imply the 22% risk was an underestimate. The risk in adult women in this series is 11 of 50 cases.

Dewhurst 1971²³

This paper reports 82 cases with CAIS, but no tumours were found at any age. Age ranges were given, and 17 patients (30%) were over the age of 20 years; 41/82 had undergone gonadectomy, and this was performed over the age of 30 years in nine patients. There is no information on what proportion of adult patients had gonads in situ at the time of the study. The adult risk in this series is 0 in 17 cases.

Table 1. Reasons given for deferring or declining gonadectomy (patients may give more than one)

Reason given	Number of women
Concern about the risks of the procedure	8
Surgery was not convenient because of academic commitments, secondary and tertiary education examinations	6
Did not want to take hormone replacement throughout adult life either because of inconvenience, concern about risks and side effects or worries that it might not work	6
Felt unable to make this decision as they had not yet come to terms with their diagnosis of complete androgen insensitivity syndrome	5
Hoped their testes could be used for future fertility if gametes were viable	3
Under follow-up at another unit and chose to retain her gonads as she was unaware of any malignancy risk	1
Believed she had undergone a bilateral gonadectomy in adolescence but in fact had undergone a unilateral gonadectomy with a hernia repair and replacement of gonad into the abdominal cavity on the other side	1

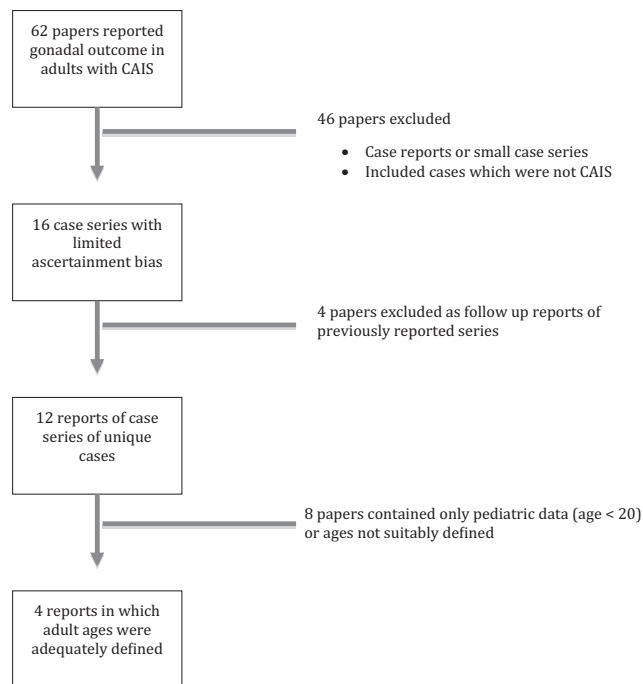


Fig. 1 Flow Chart of criteria assessment for the risk of gonadal malignancy in adult women with complete androgen insensitivity syndrome.

Rutgers 1991¹³

This report of 40 women is likely to include the same patients reported in a previous paper by this group in 1987.¹⁴ Three tumours were reported in patients aged 35, 51 and 71. The mean age in the study was 27 years (range 16–83). This report is a histology paper so by definition all subjects had undergone gonadectomy. Taking the older half of subjects in this study, that is, 20 women over the age of 27 years, the malignancy risk is 15% (3/20). The adult risk in this series is three in 20 patients.

Ahmed 2005¹⁵

This group of 105 patients included subjects from a later histology paper by the same team.¹⁰ This is essentially a paediatric study with a median age of 13.2 years. The age for 90th centile is 26.8, meaning that 10 or 11 patients are over 26.8. Whilst no tumours in adult patients are reported by Ahmed, Hannema does report two cases of carcinoma *in situ* – one in a 17-year-old patient and one in a 53-year-old patient; 77% of patients have had their gonads removed, and in 66% of cases, this was performed before puberty. It is not possible in this paper to ascertain the number of patients over 26.8 years who have already had gonadal removal. The adult risk in this series is 0 in 11 patients.

In summary, there are therefore 14 confirmed tumours in 98 adult patients. With the limitations combining historic case series in mind, this review suggests an estimated risk of gonadal malignancy of 14% (range 0% and 22%) in adults with CAIS.

Discussion

This report demonstrated a very limited evidence based on which clinicians can advise asymptomatic adult women with CAIS about

the pros and cons of gonadectomy. In the few studies where adult data can be extracted, malignant testicular tumours occurred in 16% of adult patients. This contrasts starkly with data arising from studies based on a paediatric population where malignancy rates are low ranging 0.8%² to 2.0%.³ This review highlights a neglect in seeking reliable evidence on the adult CAIS population. The observation that malignancy risk increases with age has been inferred before,¹⁷ but no prospective data exist to confirm this.

Factors that are likely to inflate the estimated risk for gonadal malignancy include: (i) the high number of case reports; (ii) gonadal malignancy index cases that might have triggered the creation of a small series; (iii) referral bias of gonadal malignancies; (iv) the practice of nondisclosure where some women with CAIS may be unaware of their diagnosis; and (v) inclusion of cases carrying higher risks, such as Swyer syndrome.

Factors that are likely to reduce the estimated risk of malignancy in adults with CAIS include (i) basing risk estimates for adult women on studies where only a paediatric population are included and (ii) inclusion of cases that are no longer at risk because they have already undergone gonadectomy.

The majority of papers did not give sufficiently detailed information on age of their subjects. Those that did give age data had low mean or median ages, suggesting that the data were not normally distributed and that most data had been drawn from paediatric settings. Until recently, the standard practice has been to perform a gonadectomy either during childhood or early adolescence just after puberty. In all papers, detailed data on the timing of gonadectomy were lacking. Adult patients who have had gonadectomy in childhood will have no risk of developing a testicular tumour but remain included in follow-up studies. This means that large case series giving low malignancy rates are likely to underestimate the risk. In the current series, the malignancy risk appears to increase with age up to 16%. Thus, if the gonads are removed immediately postpuberty, the malignancy risk is low. However, if gonadectomy is not performed immediately postpuberty, the malignancy risk will increase with age. The difficulty with conserving gonads is that there are no available reliable screening tests that detect early malignant change. The testes are usually intra-abdominal and so are impalpable. Neither ultrasound nor MRI can reliably detect premalignant changes, and tumour markers are unspecific. This means that presentation with a gonadal malignancy is often late and with clinical symptoms.

Psychological factors are strongly implicated in patients' intentions in relation to prophylactic surgery.²⁴ This study briefly explored patients' reasons for deferring gonadectomy. Where an individual is in good health, there is an understandable reluctance to undergo a procedure, which will certainly make them feel less well in the short term and perhaps even indefinitely. Furthermore, the initial presentation of CAIS is often in mid- or late adolescence, at a time when patients are busy with academic commitments. There is an understandable reluctance to be absent from school or college. Clinicians need to appreciate these barriers and be able to explore them with patients to facilitate informed consent.

An important observation was concerns about surgical risk in half of our sample. A gonadectomy can be performed with laparoscopic or open surgical techniques. The type of operation required

depends on the site of the testes, and this is determined with magnetic resonance scanning. Testes in CAIS may be sited anywhere along the line of foetal testicular descent from high in the abdomen next to the internal iliac vessels or low down in the groin and labia. Testes sited in the abdomen are usually removed laparoscopically and those in the groins and labia require exploration of the inguinal canal. Although the advent of laparoscopic surgery has reduced the morbidity of the procedure, no operation is without risk. In terms of laparoscopic removal, there are no specific figures available for gonadectomy in CAIS. However, there are data available for laparoscopic entry to the abdomen. It has been estimated that diagnostic laparoscopy alone carries an estimated risk of death of 0.1/1000 and the risk of injury to bowel, bladder or blood vessel of 2.4%, of whom two-thirds will require a laparotomy.^{25,26} Groin exploration entails risks of infection, bleeding and damage to the ilioinguinal nerve.

Preservation of fertility potential was another reason for declining gonadectomy. Spermatogonia were reported found in resected testes in several series.^{10,13,21} However, these germ cells pose an uncertain fertility potential. Hannema found germ cells in 95% of cases and most were spermatogonia. Although the occasional meiotic spermatocyte was noted, there was no evidence of spermatogenesis. Cools *et al.*²¹ reported that germ cells could be identified in 28/30 cases. However, only in two cases of partial androgen insensitivity syndrome were spermatocytes and spermatids seen. In no cases were spermatozoa identified. These papers were however in both paediatric cases series, and the majority of gonads studied were prepubertal. In both these series, the presence of multinucleated germ cells was reported and the numbers of germ cells decreased with age. Nevertheless, the possibility may 1 day exist for maturation to spermatozoa or spermatids, and subsequent fertilization of an oocyte using assisted reproductive technologies. This was certainly the reason cited from a number of patients in this study, and it is uncertain how to advise such patients as to the future development in reproductive technologies. The ethical issues surrounding this also remain unexplored.

After gonadectomy, women would be required to take oestrogen replacement until the age of 50 years or so to maintain general and bone health. Young patients may be reluctant to consider daily medication for a seemingly interminable time. Adult women have been concerned about finding an appropriate hormone replacement in terms of both side effects of treatment and in efficacy particularly in terms of libido. Some women may be aware of the negative press that hormone replacement has attracted because the Women's Health Initiative data were published in 2002²⁷ and will require reassurance that health data for young women remain reassuring.

Prophylactic organ removal surgery has been recommended for a number of conditions, and useful parallels may be drawn between prophylactic gonadectomy in CAIS and other clinical contexts. Some of the most common clinical contexts are prophylactic mastectomy and oophorectomy for carriers of the BRCA mutations, and colectomy for familial adenomatous polyposis. In these groups, the risks of developing malignancy may be as high as 85%.²⁸ Even so, elective surgery is a difficult decision and is not without potential physical and psychological harm.²⁹ Despite

proven risk reduction with prophylactic oophorectomy and mastectomy in women with BRCA 1 and 2 mutations, surgical uptake is reported to be generally low.³⁰ For example, in asymptomatic women with BRCA mutations, between 13% and 51% opted for prophylactic mastectomy and 13–64% for oophorectomy.³¹

Perceptions of risks and benefits, beliefs about how other people are choosing, levels of trust in the accuracy of detection technology, history of malignancies within the family, obligations towards others, concerns about fertility and menopause, and fear of surgical complications^{32,33} and many more factors may affect patient choice. Furthermore, these drivers may vary across social groups. The medical and psychological aspects of prophylactic gonadectomy in CAIS warrant further research. Whilst this study has its limitations, it has been important to confirm that the available information on the topic is unreliable and to point towards a need for collaborative, multicentre, longitudinal research. It further signposts a need for detailed qualitative analysis of one-to-one interviews and focus groups to make sense of user's perspectives on prophylactic surgery.

Conclusions

The perceived benefits for retaining gonads in women with CAIS are prompting more women to keep their gonads in situ. A figure for adult malignancy risk is unavailable, and the low malignancy risks currently quoted by clinicians are likely to be falsely reassuring. Effective malignancy detection techniques are currently unavailable. This issue poses a dilemma for care providers. Thus far, the recommendation for postpubertal gonadectomy would still seem prudent. Women who choose to defer gonadectomy must be counselled on what little is known and the many unknowns relating to potential risks and effective monitoring.

Conflict of interest and financial disclosure

Nothing to declare.

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