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*Lancet Diabetes Endocrinol.* 2018 Jul 31. pii: S2213-8587(18)30197-9. doi: 10.1016/S2213-8587(18)30197-9. [Epub ahead of print]

## Oestrogen versus androgen in hormone-replacement therapy for complete androgen insensitivity syndrome: a multicentre, randomised, double-dummy, double-blind crossover trial.

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### Abstract

**BACKGROUND:** Women with complete androgen insensitivity syndrome (CAIS) after gonadectomy have complained about reduced psychological wellbeing and sexual satisfaction. The aim of this study was to compare the effectiveness of hormone-replacement therapy with either androgen or oestrogen in women with 46,XY karyotype and CAIS after gonadectomy.

**METHODS:** This national, multicentre, double-blind, randomised crossover trial was performed at three university medical centres and three specialised treatment institutions in Germany. Eligible participants were women aged 18-54 years with 46,XY karyotype, genetically diagnosed CAIS, and removed gonads. Participants were randomly assigned (14:12) by a central computer-based minimisation method to either oestradiol 1·5 mg/day for 6 months followed by crossover to testosterone 50 mg/day for 6 months (sequence A) or to testosterone 50 mg/day for 6 months followed by crossover to oestradiol 1·5 mg/day for 6 months (sequence B). Participants also received oestradiol or testosterone dummy to avoid identification of the active substance. All participants received oestradiol 1·5 mg/day during a 2 months' run-in phase. The primary outcome was mental health-related quality of life, as measured with the standardised German version of the SF-36 questionnaire. Secondary outcomes were psychological wellbeing, as measured with the Brief Symptom Inventory (BSI), sexual function, as measured with the Female Sexual Function Index (FSFI), and somatic effects, such as signs of virilisation and effects on metabolic blood values. The primary analysis included all patients who were available at least until visit 5, even if protocol violations occurred. The safety analysis included all patients who received at least oestradiol during the run-in phase. This trial is registered with the German Clinical Trials Register, number DRKS00003136, and with the European Clinical Trials Database, number 2010-021790-37.

**FINDINGS:** We enrolled 26 patients into the study, with the first patient enrolled on Nov 7, 2011, and the last patient leaving the study on Jan 23, 2016. 14 patients were assigned to sequence A and 12 were assigned to sequence B. Ten participants were withdrawn from the study, two of whom attended at least five visits and so could be included in the primary analysis. Mental health-related quality of life did not differ between treatment groups (linear mixed model,  $p=0\cdot794$ ), nor did BSI scores for psychological wellbeing (global severity index,  $p=0\cdot638$ ; positive symptom distress index,  $p=0\cdot378$ ; positive symptom total,  $p=0\cdot570$ ). For the FSFI, testosterone was

superior to oestradiol only in improving sexual desire (linear mixed model,  $p=0.018$ ). No virilisation was observed, and gonadotrophin concentrations remained stable in both treatment groups. Oestradiol and testosterone concentrations changed substantially during the study in both treatment groups. 28 adverse events were reported for patients receiving oestradiol (23 grade 1 and five grade 2), and 38 adverse events were reported for patients receiving testosterone (34 grade 1, three grade 2, and one grade 3). One serious adverse event (fibrous mastopathy) and 20 adverse events (16 grade 1 and four grade 2) were reported during the run-in phase, and 12 adverse events during follow-up (nine grade 1 and three grade 2).

**INTERPRETATION:** Testosterone was well tolerated and as safe as oestrogen for hormone-replacement therapy. Testosterone can be an alternative hormone substitution in CAIS, especially for women with reduced sexual functioning.

**FUNDING:** German Federal Ministry of Education and Research.

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PMID: 30075954 DOI: [10.1016/S2213-8587\(18\)30197-9](https://doi.org/10.1016/S2213-8587(18)30197-9)

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