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INSL3 and AMH in patients with previously congenital or acquired undescended testes

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ABSTRACT

Background: In previous reports no differences in Leydig and Sertoli cell function were found between congenital undescended testis (CUDT) and acquired UDT (AUDT) on the basis of serum levels of LH, testosterone, FSH or inhibin B. This study tried to detect differences in Leydig and Sertoli cell function between CUDT and AUDT using insulin-like peptide 3 (INSL3) and anti-Müllerian hormone (AMH).
Method: 118 men with a history of UDT (CUDT N = 55 (6/55 bilateral), AUDT N = 63 (15/63 bilateral)) were investigated. Differences between CUDT and AUDT, influence of age at surgery in CUDT, and effect of spontaneous descent or orchiopexy in AUDT were evaluated.
Results: For INSL3, no significant differences were found. AMH levels in bilateral CUDT were significantly lower compared with bilateral AUDT (6.4 (1.7–11.4) vs 13.2 (6.1–30.1) μg/l, $p = 0.02$). AMH levels in unilateral CUDT were significantly higher than in bilateral CUDT (12.1 (2.4–43.7) vs. 6.4 (1.7–11.4) μg/l, $p = 0.02$).
Conclusion: No differences in Leydig cell function on the basis of INSL3 levels between the different UDT groups were found. Sertoli cell function evaluated by AMH, was more negatively affected in bilateral CUDT in comparison with bilateral AUDT and unilateral CUDT.
Level of evidence rating: Level III Treatment Study.

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Undescended testis (UDT) can be of congenital or acquired origin [1–3]. In congenital UDT a stable scrotal position was never reached. Acquired UDT is defined as a palpable UDT that previously had a normal scrotal position. Acquired UDT is seen in 1–3% of boys during childhood [4,5]. The proportion of (pre)pubertal spontaneous descent in boys with acquired UDT is between 57% and 71% [6,7]. It was suggested that men with acquired UDT might have fewer fertility problems than those with congenital UDT, since their testes initially descended and the crucial development of type A spermatogonia had probably already occurred during the first year of life before the testes ascended [8]. However, our previous long-term follow-up study found no statistically significant differences in traditional fertility parameters between congenital and acquired UDT [9]. In that study, we evaluated Leydig cell function by measuring serum levels of luteinizing hormone (LH) and testosterone. Serum follicle stimulating hormone (FSH) and inhibin B (inh B) were used to evaluate Sertoli cell function. In the present study we more extensively evaluated endocrine function (insulin-like peptide 3 (INSL3), anti-Müllerian hormone (AMH), sex hormone binding globulin (SHBG), and estradiol) in the same group of patients to discover whether more subtle differences in Leydig cell and Sertoli cell function between different patient groups with UDT can be found.

INSL3, produced by Leydig cells, is essential for the abdominal part of testicular descent [10–12]. At an adult age, INSL3 has been suggested to be a more sensitive parameter to detect impaired Leydig cell function than testosterone, since men with hypospermatogenesis had normal levels of testosterone and LH but reduced INSL3 levels [13–17]. Although lower serum levels of AMH, which is produced by Sertoli cells, were found in subfertile men in comparison with controls, serum AMH cannot discriminate between fertile and infertile men because of wide overlap of the values and serum AMH does not show a correlation with impaired spermatogenesis [18–20]. However, in contrast with normospermic men, in men with UDT AMH was found to correlate with testicular volume and semen concentrations and therefore was suggested to be a marker for Sertoli cell function in men with UDT

Abbreviations: AMH, anti-Müllerian hormone; AUDT, acquired undescended testis/testes; CUDT, congenital undescended testis/testes; INSL3, insulin-like peptide 3; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin; UDT, undescended testis.

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[21]. In the present study we set out to detect differences in Leydig and Sertoli cell function between congenital and acquired UDT on the basis of INSL3 and AMH serum levels.

1. Materials and methods

1.1. Patients

Men with a history of congenital or acquired UDT who participated in two long term follow-up studies on fertility potential performed at the Erasmus Medical Center were included retrospectively [9,22]. Data on hormone concentrations were prospectively collected between 2005 and 2010. Inclusion and exclusion criteria of participants in these studies were described previously [9,22]. Fig. 1 shows an overview of included men. In the present study only men with two testes at follow-up were included. In short: The *congenital UDT group* (N = 55, of whom 6 bilateral UDT) consisted of men who participated in a study evaluating fertility potential after treatment [22]. Subjects in that study were part of a historical cohort of boys who underwent orchiopexy during childhood at various ages and boys operated on before two years of age [23]. Median age at orchiopexy and follow-up was 3.3 years (range 0.1 to 14.6 years) and 26.1 years (range 20.6 to 35.2 years) respectively. The *acquired UDT group* (N = 63, of whom 15 bilateral UDT) consisted of men who participated in a study evaluating fertility potential in men with previously acquired UDT after follow-up during childhood [9]. Subjects in that study were part of a historical cohort with men with acquired UDT who had annual follow-up examination until puberty [6]. Spontaneous descent was awaited until at least Tanner stage P2G2 and followed by orchiopexy in case of nondescent ('wait-and-see'-protocol). Spontaneous descent had occurred in 32 participants, of whom 8 had had bilateral UDT. Median age at orchiopexy in 31 participants (24 unilateral and 7 bilateral) was 13.3 years (range 4.75 to 17.8 years). Median age at follow-up for the complete acquired group was 27.2 years (range 18.0 to 35.8 years). For both historical cohorts maximum effort was taken to ascertain previous testicular position at inclusion for the initial study [6,23].

1.2. Blood analysis

A venous blood sample was taken, preferably before 10:00 AM and before 11:00 AM at the latest. Serum samples were assayed for INSL3 using radioimmunoassay (Phoenix Pharmaceuticals, Burlingame, CA, USA). AMH was measured using an in-house enzyme immunometric assay (Gen II, Beckman-Coulter, Webster, TX, USA) as previously described [24], LH, FSH and sex hormone binding globulin using fluorescence-based immunometric methods (Immulite 2000, Siemens-DPC, Los Angeles, CA, USA), testosterone and estradiol using coated tube based radioimmunoassays (Siemens-DPC), and inh B using an enzyme-immunometric method (Oxford BioInnovation, Oxford, UK). Reference ranges for all hormone concentrations are given in Table 1. All reference ranges were from the laboratory where the assays were performed, with the exception of those for INSL3, where literature data obtained with the same assay were used [13]. Intraassay and interassay coefficients of variation for the various assays were as follows: INSL3 < 9%, AMH < 5 and <10%, LH < 5 and <11%, FSH <3 and <8%, SHBG <4 and <5%, testosterone <3 and <5%, estradiol <5 and <7%, and inh B < 9 and <15%, respectively. Concentrations of non-SHBG bond testosterone and estradiol were calculated using the method described by de Ronde et al. [25] with a fixed concentration for albumin of 42 g/l.

1.3. Semen analysis

Semen samples were analyzed according to the WHO-manual of 2010 [26].

1.4. Statistics

Differences in hormone levels between different groups were analyzed using the Mann–Whitney U test. Firstly, we compared hormone levels between the congenital UDT group and acquired UDT group. Secondly, we analyzed age at surgery in the congenital group as a continuous variable in linear regression analyses corrected for unilaterality and bilaterality and testicular position at surgery (intraabdominal, inguinal canal, suprainguinal pouch, or at annulus externus). Lastly, in the acquired group we compared men who had spontaneously descended UDT with men who needed orchiopexy. We performed these analyses for unilateral and bilateral UDT separately. Subsequently, we compared hormone levels in the groups with unilateral and bilateral UDT with each other in the congenital and the acquired UDT group. Furthermore, we evaluated correlations between the levels of INSL 3 and AMH and the concentrations of the other hormones, semen parameters, and

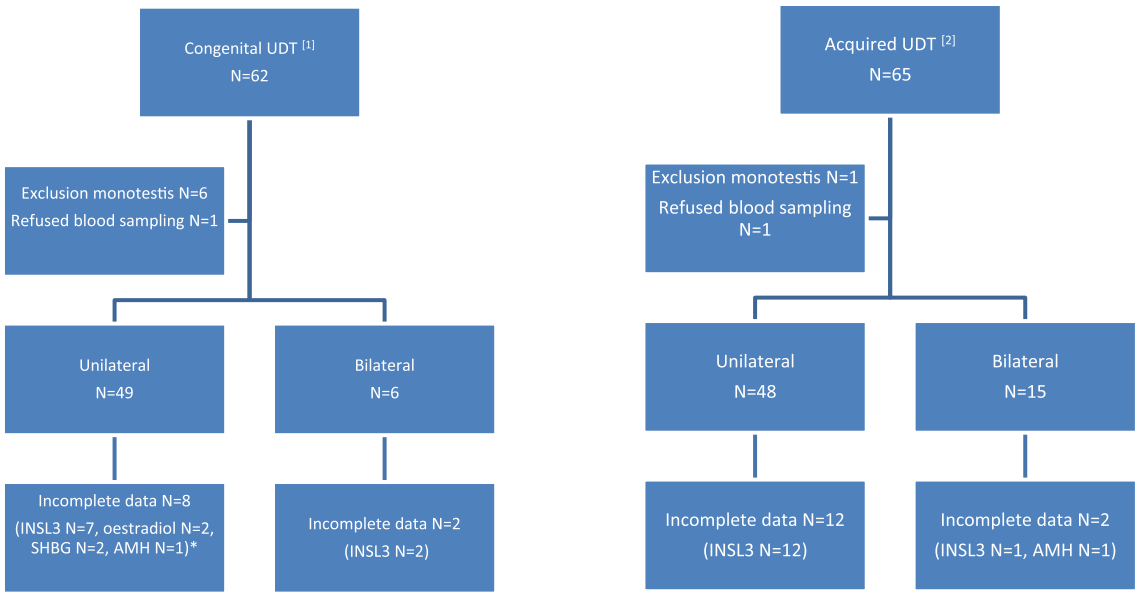

Fig. 1. Overview inclusions and missing data. *Overlapping missing data; N = 6 only missing INSL3, N = 1 missing INSL3, estradiol, SHBG and AMH, N = 1 missing estradiol and SHBG. [1] van Brakel et al [22], [2] van Brakel [9].

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