



RESEARCH

Clinical Efficacy of Letrozole in the Management of Pediatric Micropenis

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Abstract

Background Micropenis is a condition characterized by an abnormally small penis, defined as a stretched penile length (SPL) more than 2.5 standard deviations below the mean for age—typically less than 2.5 cm in newborns and less than 5 cm in pubertal boys—which may lead to low self-esteem and sexual dysfunction. Although testosterone therapy is an available option for hypogonadism to stimulate penile growth, its effect on final adult penile size remains uncertain. Patients with hypogonadism-related micropenis are prone to obesity, which increases aromatase activity, converting testosterone to estradiol. Though not approved for pediatric use, aromatase inhibitors (AIs) like Letrozole (LTZ) may help by targeting this conversion process, potentially offering therapeutic benefits in managing micropenis associated with hormonal imbalances.

Method A total of 56 boys aged 10 to 16 years with micropenis (defined as SPL < 5 cm) and a pubertal stage above Tanner G2 were evaluated for the efficacy of LTZ treatment, compared With 54 patients in the placebo group.

Results After treatment, the mean penile length was 5.6 cm in the LTZ group and 4.45 cm in the placebo group, with a significant difference between the groups ($P < 0.001$). Mild side effects in the letrozole group included testicular pain, dysuria, and severe acne, with no serious adverse events reported.

Conclusion LTZ has been observed to have a significant effect on penile size in children, most of whom were overweight, particularly at Tanner stage G3.

Keywords Micropenis · Letrozole · Aromatase inhibitor · Penile growth · Pediatric hypogonadism

Introduction

Micropenis is a condition characterized by an abnormally small penis, often defined as a SPL more than 2.5 standard deviations below the mean for age- and pubertal stage-matched peers, in the absence of other penile abnormalities. While this definition is somewhat arbitrary—since length exists along a continuum—it is widely accepted in clinical practice [1]. The masculinization of the genitalia is driven by testosterone and dihydrotestosterone (DHT), secreted by Leydig cells in the testes. During the first 3 months of fetal development, this process is mediated by human chorionic gonadotropin from the placenta, leading to the initial differentiation of the penis. From the fourth month onward, fetal testicular stimulation is mediated by luteinizing hormone

and follicle-stimulating hormone secreted by the pituitary gland, enabling continued penile growth [2]. Micropenis is defined as a SPL that is 2.5 standard deviations below the mean for age- and pubertal stage-matched peers, in the absence of other syndromic or genital abnormalities such as hypospadias or cryptorchidism. The etiology may lie in the testes (hypergonadotropic hypogonadism), the pituitary/hypothalamus (hypogonadotropic hypogonadism), or remain idiopathic [2, 3]. SPL is measured from the pubic bone to the distal tip of the glans under maximal extension, approximating erect penile length [3, 4]. Accurate measurement at any age allows for comparison with normative data to diagnose micropenis. The next step is determining the underlying cause [3]. Treatment is important regardless of etiology, as micropenis can lead to parental anxiety as well as psychological distress, low self-esteem, sexual dysfunction, and dissatisfaction in affected individuals [5, 6]. Exogenous testosterone is known as a possible treatment option for micropenis. Alternatives include transdermal testosterone or DHT [7]. Surgical therapy [8] may be considered if endocrine

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treatment does not produce satisfactory results, but it is not part of standard practice and lacks robust evidence.

Most boys with micropenis exhibit hypogonadism, which leads to reduced testosterone levels and contributes to increased fat accumulation and altered body composition [2, 9]. Obesity is associated with elevated aromatase activity in adipocytes, resulting in peripheral conversion of testosterone to estradiol. Increased estradiol further suppresses gonadotropin-releasing hormone via negative feedback on the hypothalamic-pituitary-gonadal axis and directly inhibits 17α -hydroxylase activity in Leydig cells, further reducing endogenous testosterone production [9, 10]. These hormonal changes lead to decreased muscle mass, gynecomastia, and a more feminized body habitus, including increased gluteal and subcutaneous (gynoid-pattern) fat, where aromatase activity is at least ten times higher than in visceral adipose tissue [11, 12]. This creates a self-reinforcing “hypogonadal-obesity cycle,” in which declining testosterone promotes fat accumulation, which increases estrogen production and further suppresses testosterone [9]. In obese boys with micropenis, standard testosterone therapy may be less effective because the administered hormone is readily aromatized into estradiol, potentially perpetuating the cycle rather than resolving it. Studies indicate that higher levels of obesity correspond to reduced efficacy of testosterone treatment, with severely obese boys often showing minimal improvement in androgen-responsive outcomes [13]. Consequently, therapeutic strategies targeting the underlying hormonal dysregulation may be more effective in this population.

AIs prevent the conversion of androgens to estrogens. Although not approved for pediatric use, they have been used off-label to treat hyperestrogenism, hyperandrogenism, pubertal gynecomastia, short stature, and delayed puberty [14]. Despite potential benefits, the primary concern is safety in children. By increasing gonadotropin levels, AIs may lead to testicular enlargement, though they do not adversely affect testicular function, sperm quality, or sperm count. In fact, their gonadotropin-stimulating effects have been used to treat male infertility. While prostate hyperplasia has been observed in animal models, neither this nor prostate cancer has been reported in human pediatric populations [14, 15]. Long-term estrogen deprivation may impair bone health, as observed in males with aromatase deficiency or estrogen resistance. However, studies have shown that LTZ does not negatively affect bone mineral density (BMD), likely due to the bone-protective role of androgens. In contrast to women, who may experience increased bone turnover and fracture risk on AIs, boys have shown decreased bone turnover—possibly due to androgen-mediated inhibition of bone resorption [14, 16].

A key concern remains the risk of vertebral deformities. A 2010 study by Hero et al. reported mild vertebral body deformities in 5 of 11 boys treated With LTZ for 2 years.

These deformities likely resulted from impaired vertebral growth rather than reduced bone quality, as BMD remained unaffected. However, boys With constitutional delay of puberty treated with a shorter course and at a later age did not develop such deformities. A follow-up study by Hero et al. in 2020 concluded that short-term LTZ therapy (6 months) does not cause significant skeletal harm [15, 17]. AIs can also alter body proportions, decreasing trunk length and increasing leg length, as seen in the 2010 Hero study. Since pubertal growth hormone (GH) secretion is estrogen-dependent, aromatase inhibition lowers estradiol and, consequently, GH-IGF-1 levels. Nonetheless, height velocity during AI therapy tends to increase, suggesting that androgens may independently promote pubertal growth. Despite lower GH/IGF-1, the combination of high testosterone and low estradiol may yield neutral or even positive effects on insulin sensitivity. However, AIs may slightly reduce HDL cholesterol. Patients receiving LTZ should have hemoglobin levels monitored due to the risk of erythrocytosis from elevated testosterone, which may increase thrombotic risk [14]. Our group conducted this study to investigate LTZ's efficacy as a potent treatment for micropenis.

Material and Methods

The present study is a randomized, double-blind clinical trial involving boys aged 10 to 16 years with micropenis (SPL less than 5 cm) [18]. Between 2016 and 2022, these boys were either referred to or presented at the endocrinology clinic of Ali Asghar Children's Hospital for ongoing evaluation of micropenis. The primary hypothesis was that LTZ would be more effective than a placebo in increasing penile length in children with micropenis. Children with other diseases, chromosomal abnormalities, or who were undergoing treatment with glucocorticoids, GH, or testosterone were excluded ($n = 50$). A total of 160 eligible boys were to be enrolled in either the intervention or placebo group. Patients in the intervention group received LTZ (from a single manufacturer) at a dose of 2.5 mg once daily for 6 months, while the placebo group received an identically appearing placebo from the same manufacturer, matching in taste, color, and appearance. Written informed consent was obtained from the parents prior to participation. Drug envelopes, sealed and coded to indicate whether they contained LTZ or placebo, were randomly distributed by a secretary not involved in assigning intervention types.

All participants, both in the case and control groups, underwent complete blood count, lateral spinal X-rays, lipid profile, and liver enzyme tests before enrollment. Throughout the study, patients were followed up every 2 months during the 6-month treatment period. Initially, researchers contacted the participants by phone to provide medication

instructions and assess any side effects. Follow-up clinic visits were scheduled at 4 and 6 months after treatment initiation, during which a designated investigator recorded all relevant clinical information and laboratory results on standardized forms. These forms were developed in accordance with the ethical principles outlined in the Declaration of Helsinki and were approved by the Hospital Review Board and Ethics Committee. Data were entered into SPSS software and analyzed primarily using paired and independent *t*-tests. A *P*-value of less than 0.05 was considered statistically significant.

Results

Of 160 enrolled participants, 50 discontinued due to loss to follow-up, consent withdrawal, unrelated health issues, non-compliance, or side effects. The study involved an analysis of two groups: the LTZ group and the placebo group. Ultimately, 56 patients in the LTZ group and 54 patients in the placebo group remained for post-trial analysis (Table 1). The mean age in the LTZ group was 12 years and 6 months, while in the placebo group, it was 12 years and 3 months. However, the age difference between the two groups was not statistically significant (*P*=0.26).

The mean height in the LTZ and placebo groups was 152.67 cm and 152.85 cm, respectively (*P*=0.93). Similarly, the mean weight in the LTZ group was 56.33 kg, compared to 59.19 kg in the placebo group (*P*=0.39). The mean body mass index (BMI) was 24.2 in the LTZ group and 25.4 in the

placebo group. Both values fall between the 85th and 95th BMI percentiles, classifying the participants in both groups as overweight.

Letrozole was generally well tolerated. However, several side effects were reported, including macroorchidism-related pain (*n*=5), dysuria (*n*=2), and severe acne (*n*=1), the latter requiring dermatologic treatment. Some parents also reported voice deepening and increased irritability in their children. No patients reported back pain, and physical examinations revealed no scoliosis or vertebral deformities during the study period. Given concerns from prior studies about potential skeletal effects, further long-term monitoring of bone health is warranted. Penile size was systematically evaluated and compared before and after treatment, providing an objective measure of therapeutic response and demonstrating the efficacy of the intervention (Fig. 1).

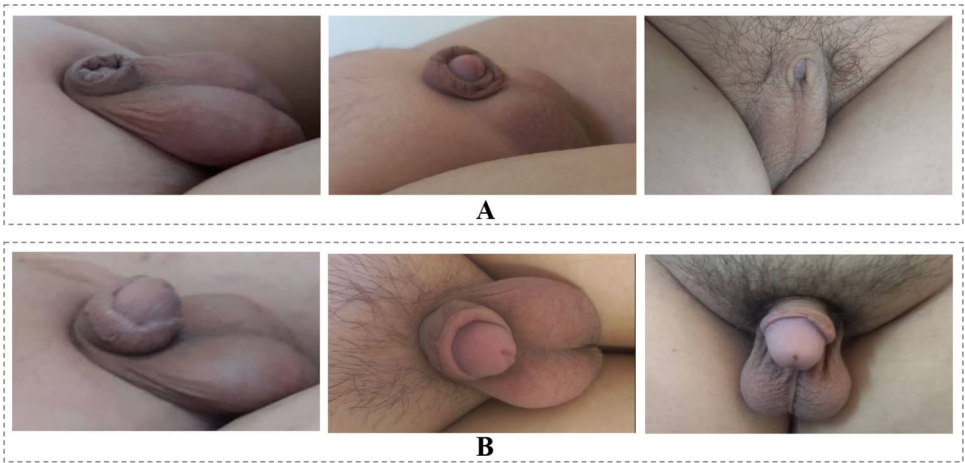
Before treatment, the mean penis size was 4.01 cm in the LTZ group and 3.79 cm in the placebo group. This difference was not statistically significant (*P*=0.11). However, after treatment, significant differences were observed within both groups (*P*<0.001, Fig. 2). The mean penis size after treatment was 5.6 cm in the LTZ group and 4.45 cm in the placebo group, indicating a significant difference between the two groups (*P*<0.001). The mean difference in penis size between the placebo and LTZ groups was −1.155 cm, With a 95% confidence interval ranging from −1.565 to −0.746.

The study further found no correlation between height, weight, or age and penis size or treatment response in either group. However, a correlation was observed between Tanner stages and penis size in both groups, suggesting that patients at Tanner stage G3 exhibited a better response to LTZ treatment. The distribution of penis size and Tanner stages in the studied groups was analyzed and is illustrated in Fig. 3. This figure presents penis size across different stages of pubertal development, enabling a comparison between the LTZ and placebo groups based on Tanner stages.

Table 1 Demographic features of participants

Group	Age (year)	BMI	Weight (kg)	Height (cm)
Placebo	12.3	25.4	59.19	152.85
LTZ	12.6	24.2	56.33	152.67

Fig. 1 Three patients treated with LTZ are shown as examples: A before and B after treatment



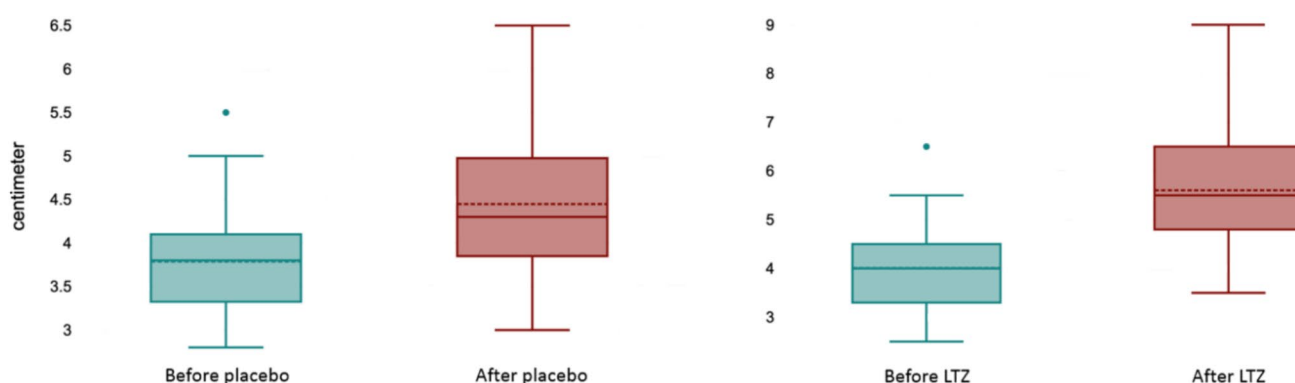


Fig. 2 Penis size in the studied groups before and after the intervention

Discussion

In this randomized, double-blind trial, LTZ treatment produced greater increases in SPL compared with placebo, with the largest apparent gains observed around Tanner stage G3; however, subgroup sizes limited statistical power for some stage-specific comparisons. The observed pattern of response is biologically plausible. In boys with hypogonadism or excess adiposity, increased peripheral aromatase activity promotes the conversion of testosterone to estradiol, which can suppress hypothalamic–pituitary–gonadal signaling and reduce endogenous androgen availability during the pubertal window when penile growth occurs. Aromatase inhibition with LTZ may therefore increase the relative availability of androgens at a critical time for penile development, potentially explaining the greater gains seen at mid-pubertal stages in our study.

Our results are broadly consistent with prior reports indicating that aromatase inhibitors can alter androgen/estrogen

balance and influence androgen-responsive outcomes during adolescence [19, 20]. Unlike studies that focus on bone or linear growth outcomes [21, 22], our trial specifically evaluated penile length in adolescents with micropenis and provides preliminary evidence that aromatase inhibition may have a measurable effect in selected patients. Nonetheless, direct comparisons are limited by differences in study populations, dosing regimens, and outcome measures across the literature.

An important limitation is that boys at Tanner stage G5P5, and even those at G4, are already near the completion of penile growth. Therefore, treatment effects at these later stages are likely to be minimal, reflecting the limited remaining growth potential. This factor should be considered when interpreting results across Tanner stages, particularly since our subgroup analyses included individuals at or near this plateau phase.

Safety observations in this study were generally reassuring over the treatment period, and specific adverse events are reported in the Results. While most events were transient

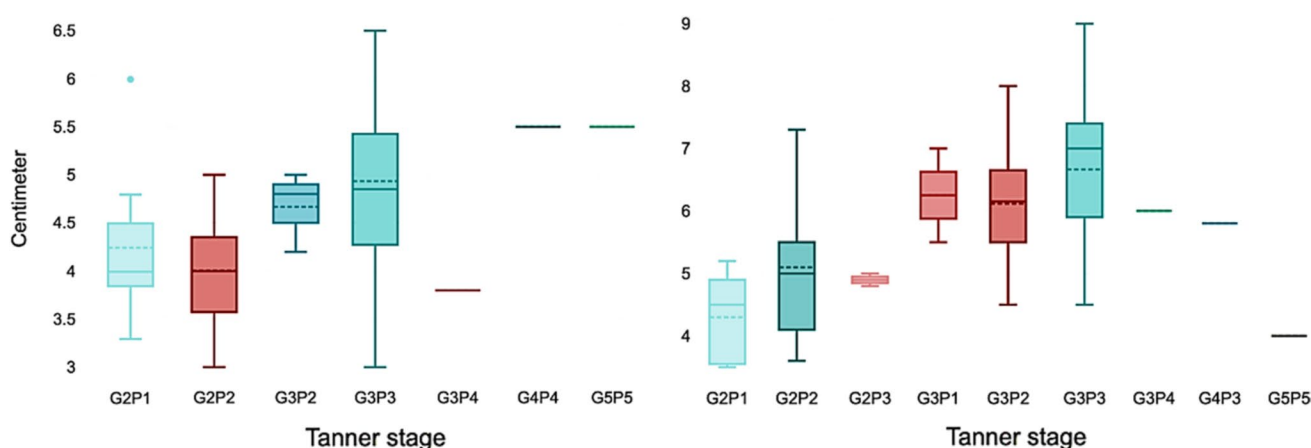


Fig. 3 Distribution of Tanner stages in the studied groups. The left panel corresponds to the placebo-treated group, and the right panel represents the LTZ-treated group

or manageable, the possibility of treatment-related effects on behavior, voice, and dermatologic status underscores the importance of close monitoring. Given prior concerns about potential skeletal effects with aromatase inhibition, long-term assessment of bone health remains important.

Limitations

Despite careful study design, several limitations should be acknowledged:

- I. Blinding integrity: although the study was double-blinded, some patients receiving letrozole exhibited known side effects—such as acne, macroorchidism, and voice deepening—which may have compromised blinding for investigators or parents.
- II. Measurement variability: accurate measurement of stretched penile length can be challenging in overweight children due to suprapubic fat, potentially introducing variability and affecting the precision of our results. Additionally, changes in penile diameter were not recorded, although anecdotal observations suggested that some cases experienced greater improvement in diameter than in length.
- III. Lack of hormonal monitoring during treatment: baseline hormone levels and serial monitoring during and after treatment were not performed, limiting our ability to directly correlate hormonal changes with treatment response.
- IV. Other developmental parameters: while pubertal progression was monitored, formal assessments of testicular volume, psychosocial outcomes, bone age, growth hormone–IGF-1 axis function, and growth charts were not included. Likewise, no long-term follow-up was conducted to assess final adult height, sexual function, or fertility.

Future Directions

These findings suggest that aromatase inhibition may be a therapeutic consideration for select adolescents with micropenis, particularly when hypogonadism and adiposity contribute to an unfavorable androgen-to-estrogen ratio. However, given the limitations above, LTZ should be considered investigational for this indication until larger, longer, and mechanistically detailed studies confirm efficacy and safety. Future research should:

- I. Include long-term follow-up to evaluate final adult penile size and reproductive outcomes.

- II. Compare LTZ with other treatment modalities, such as testosterone and DHT.
- III. Stratify patients by BMI and pubertal stage to better identify responders.
- IV. Incorporate serial hormone monitoring (testosterone, estradiol, DHT, LH, FSH) and assess the effects on bone age and body composition.
- V. Evaluate behavioral and psychosocial outcomes, which may be influenced by hormonal changes during puberty.

Conclusion

Our investigation revealed that letrozole significantly increased penile length in boys with micropenis, particularly in those in mid-puberty. The treatment was generally well tolerated, with only mild to moderate side effects observed. Although these results are promising, they should be interpreted cautiously due to measurement challenges, small subgroup sizes, and the lack of long-term follow-up. AIs may offer a viable alternative treatment, especially for patients with obesity-associated hypogonadism. Further research is needed to confirm long-term efficacy, safety, and the optimal timing of treatment.

Abbreviations AIs: Aromatase inhibitors; BMI: Body mass index; BMD: Bone mineral density; DHT: Dihydrotestosterone; GH: Growth hormone; LTZ: Letrozole; SPL: Stretched penile lengths

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Author Contribution M.V and E.Z: study concept and design, data acquisition, data analysis, data interpretation, and manuscript writing. M.V and M.M: study concept and design and manuscript revision. All authors have read and agreed to the published version of the manuscript.

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Data Availability No datasets were generated or analyzed during the current study.

Code Availability Not applicable.

Declarations

Ethics Approval This study was conducted with full regard for the rights and welfare of all participants and in accordance with ethical standards. The protocol was reviewed and approved by the Medical Ethics Committee of Ali-Asghar Children's Hospital.

Consent to Participate Informed consent was obtained from the parents or legal guardians of all participants included in this study. Prior to enrollment, detailed information regarding the study's objectives, procedures, potential risks, and benefits was provided. Participation was

voluntary, and parents/legal guardians had the right to withdraw their child from the study at any time without consequences. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Ali-Asghar Children's Hospital.

Consent for Publication Written informed consent for publication of anonymized clinical data was obtained from the parents or legal guardians of all participants. All identifying information has been removed to ensure confidentiality.

Conflict of interest The authors declare no competing interests.

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