Effect of Anastrozole Treatment on Predicted Adult Height in Prepubertal Boys with Idiopathic Short Stature

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Abstract: Objective: To investigate the effect of blocking estrogen biosynthesis with anastrozole,a potent aromatase inhibitor on growth and consequently predicted adult height in boys and adolescents with high estrogen level. Secondarily, the effects of aromatase inhibition on gonadotropin secretion in boys during prepubertal phase. **Study design:** A retrospective, double-blind, randomized, placebo(Pl)-controlled study was done. Forty boys, aged 9.0–14.5 yr, diagnosed with idiopathic short stature were enrolled into the study. The children were classified into two groups (20 children each). The control group received starch tablet daily for one year. The second group received anastrozole tablet 1mg orally/day for one year .Laboratory investigations were estimated: serum estradiol, testosterone, follicle stimulating hormone, luteinizing hormone, and insulin-like growth factor type 1 levels. Height estimation is also included. **Results:** Serum testosterone levels were significantly increased, while serum estrogen levels were significantly decreased after anastrozole treatment. However, the levels of serum luteinizing hormone, follicle stimulating hormone and insulin-like growth factor type 1 did not change significantly in anastrozole group. On the other hand, the levels of height were significantly increased in anastrozole group whereas showed no changes occurred in the respective measures in control boys. **Conclusion:** Anastrozole delays bone maturation and improves PAH in boys with ISS.

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Key words: growth hormone, testosterone, estradiol, aromatase inhibitor. PAH**,** predicted adult height, ISS, idiopathic short stature, AIs, aromatase inhibitors.

1. Introduction

Idiopathic short stature or non-GH-deficient short stature is a condition of a decreased childhood growth without any cause. These children have a height that is below normal, and others have growth failure similar to that of GH deficiency [1, 2].These families of such children seek medical intervention such as GH treatment. So, thousands of children with idiopathic short stature receive GH therapy [3, 4].

Estrogen is responsible for the development of secondary sexual characteristics and plays a major role in reproductive function in women. There is a close relationship between estrogen and GH in the regulation of growth and development in puberty [5]. Estrogen promotes GH secretion by stimulating growth hormone (GHR) release. This is responsible for the adolescent growth spurt. Estrogen derived by aromatization of adrenal androgen in both sexes (adrenarche) [6].

The role of estrogen in the regulation of growth has been identified during the past decade. The action of estrogen involves other hormones and factors such as GH, IGFs and their binding proteins, thyroid hormone, vitamin D, retinoids, PTH and PTH-related peptide, cytokines, and their receptors[7]. Estrogen plays a major role in the pubertal growth spurt, skeletal maturation, and the accrual and maintenance of bone mass in both females and males. Estrogen affects pubertal skeletal growth as it initiates the pubertal growth spurt and stimulates skeletal growth[8].

Testosterone plays a major role in the pubertal growth spurt in boys. Testosterone is the most important androgen of men, and it is secreted by testis. A large amount of weakly active androgens is secreted by adrenal cortex.[9].

Testosterone is important for differentiation of male gonadal structures before birth. In adulthood, it is important for sexual maturation during puberty and for maintenance of male secondary sexual characteristics, genital function and spermatogenesis. Men have a larger skeletons and greater muscle mass than women. So, they have high androgen levels[10].

Testosterone is also has a major role on bone mass accrual. AIs are used to decrease estrogen and

increase androgen levels for extending the period of growth of short boys inprepubertal period [11].

There are some disorders such as estrogen-responsive breast cancer, endometriosis, peripheral precocious puberty, congenital adrenal hyperplasia (CAH), short stature, and gynecomastiain children and adolescents that the use of AIs has been reported to treat it. [12].

AI is used to improve the final adult height in short prepubertal boys. The mechanism of action is suppressing estrogen formation after the onset of puberty. The result is delaying the closure of the epiphyses, and allowing for a long period of growth without affecting the progress of androgen development. Adverse effects of AIs, are reduced bone mineral density (BMD), metabolic effects including a propensity for insulin resistance and dyslipidemia, and impairment of the hypothalamic-pituitary-gonadal axis [13].

Therefore, the current study was aimed to investigate the effect of blocking estrogen biosynthesis with an aromatase inhibitor on growth and consequently predicted adult height in boys and adolescents with high estrogen level. Secondarily, the effects of aromatase inhibition on gonadotropin secretion in boys during prepubertal phase.

2. Patients and methods

Patients

The study was carried on 40 boys with high estrogen level aged from nine to fourteen years who attended at the outpatients Clinic of urology, Tanta University Hospital.

Inclusion Criteria:

The boys had no signs of underlying disease accounting for the short Stature. They were identified through a systematic review of growth charts and medical records. They had no signs of chronic or endocrine illness in medical history, clinical examination, and routine laboratory tests and were eligible for recruitment. Calendar age of 9.0 –14.5 yr and height at least 2 SD below the mean for age or at least 2 SD below midparental target height. None of the boys had any treatment known to affect growth or bone maturation.

Exclusion criteria:

Chronic illness. a known genetic syndrome. Previous treatment with GH, estrogen or androgen. Current treatment with other drugs likely to affect growth including methylphenidate or similar stimulants.

Assessment:

(1)-Family history:

(a)-Maternal pregnancy history, medical illnesses and medication use.

(b)-Birth weight and length, and estimate of gestational age are important because premature infants with appropriate small weight tend to have a normal growth potential, whereas infants with intrauterine growth retardation who are inappropriately small for gestational age may not have catch-up growth.

(c)-Complete review of systems:

1-Renal, polyuria and polydipsia for hypothalamic and/or pituitary disorders.

2-Cardiac peripheral edema, murmurs, and cyanosis

3-Gastrointestinal, diarrhea, flatulence (malabsorption), vomiting, and/or abdominal pain.

4-Pulmonary sleep apnea, asthma, or symptoms suggestive of cystic fibrosis.

5-Neurological, visual field defects suggesting pituitary neoplasms.

(d)-Growth history close review of symptoms from growth charts for various disease states)

(e)-Family history adult height and growth and pubertal patterns of his sibling.

(f)-Dietary history.

(g)-Review of the growth chart.

(2)-Physical Examination (clinical examination):

A complete physical examination is the next step in the evaluation and should include:

1-Height and weight.

2-Arm span and upper-to-lower (U/L) body-segment ratio.

(3)-Investigations (Laboratory Evaluation):

Routine Laboratory Screening: Includes complete blood cell (CBC) count, sedimentation rate, urinalysis, chemistry profile including serum creatinine and liver enzymes.

(4)-Management:

The study will be carried on 40 boys with high estrogen level aged from nine to fourteen years. They will identify through a systematic review of growth charts and medical records. Boys will be with no signs of chronic or endocrine illness in medical history, clinical examination, and routine laboratory tests. They will consider having short stature and will eligible for recruitment.

The children will be classified into two groups:

The first group (20 children) will receive Anastrozole tablet (Arimidex®), 1mg daily for one year.

The second group (20 children) will be served as a control group and will be received starch tablet daily for one year.

Methods

The following were being investigated for the patient:

(1)- Height measurements were being obtained every one month for 12 months by wall mounted

stadimetre (The Seca 222 wall mounted stadiometre, USA) with sensitivity of 0.1 cm .The growth of the children was followed every one month for 12 months after starting the study. Children should be measured while they are standing with stadiometre mounted on the wall for stability.

(2)- Laboratory investigations were included:

(a) – Serum estradiol (E2).

(b) – Serum testosterone (T).

(c) - Serum follicle stimulating hormone (FSH).

(d) – Serum leutinizing hormone (LH).

(e) – Serum insulin-like growth factor type 1 (IGF-1).

These tests were being done at the beginning of the treatment, and every four months in the two groups by the suitable available techniques (ELISA, chemiluminescence's technique, or radioimmunoassay)

Biochemical measurements

Venous blood samples were drawn. Concentrations of serum testosterone (T), estradiol, FSH, LH and IGF-I were determined every four months for twelve months. Serum and concentrations were measured in sera stored at _20 C until required. Serum T concentrations were determined by Chemiluminescence Immunoassay. The normal values were expected between 2.41 to 8.28 ng/ml[(14)].Serum estradiol (E2) concentrations were quantified with chemiluminescence enzyme immunoassay with a detection limit of 1.2 pg/ml[(15)].Serum FSH levels were measured by chemiluminescence enzyme immunoassay with a detection limit of 1.4 to 18.1 mIU[(16)].LH levels were measured by chemiluminescence enzyme immunoassay with a detection limit of0.1 to 6 mIU[(16)].Serum IGF-I concentrations weredetermined by Enzyme Amplified Sensitive Immunoassay (EASIA) with a detection limit of4.9 ng/ml[(17)].

Height measurements

Height measurements should be obtained every one month for 12 months by wall mounted stadiometre[(18)] with sensitivity of 0.1 cm .The growth of the children was followed every one month for 12 months after starting the study. Children should be measured while they are standing with stadiometre mounted on the wall for stability.

3. Results:

Determination of serum hormonal levels in ISS patients

1. Determination of serum testosterone levels before and after treatment with anastrozole

This study showed that serum testosterone levels after treatment with anastrozole (in a dose of 1mg/ day /4 months) was found to be significantly higher than those of placebo or test I.S.S groups (Fig.1).

After treatment with anastrozole (in a dose of 1mg/ day / 8 months), serum testosterone levels was found to be significantly higher than those of the treated group with the same drug for 4 months, compared with test or placebo I.S.S groups (Fig.1).

After treatment with anastrozole (in a dose of 1mg/ day / 12 months), serum testosterone levels was found to be significantly higher than those of the treated group with the same drug for 4 months, and 8 months, compared with test or placebo I.S.S groups (Fig.1).

2. Determination of serum estrogen levels before and after treatment with anastrozole

This study showed that serum estrogen levels after treatment with anastrozole (in a dose of 1mg/ day / 4 months) were found to be significantly lower than those of placebo or test I.S.S groups (Fig.2).

After treatment with anastrozole (in a dose of 1mg/ day / 8 months), serum estrogen levels were found to be significantly lower than those of the treated group with the same drug for 4 months, compared with test or placebo I.S.S groups (Fig.2).

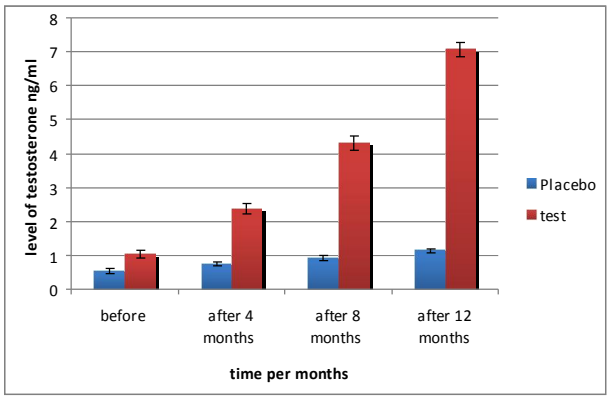

Fig 1. Study of serum testosterone levels before & after treatment with anastrozole as compared with placebo and test idiopathic short stature patients.

Each bar represents the mean of 20 patients with vertical lines indicating SEM Each value represents the mean ± SEM (n= 20) a = significantly different from both placebo & test at $P \leq 0.05$ b = significantly different from Anastrozole treated group value / 4 months c = significantly different from Anastrozole treated group value / 8 months

Placebo: means ISS patients which are given tablets containing starch. Test: means ISS patients which are given anastrozole.

After treatment with anastrozole (in a dose of 1mg/ day / 12 months), serum estrogen levels were found to be significantly lower than those of the treated group with the same drug for 4 months, and 8 months, compared with test or placebo I.S.S groups (Fig.2).

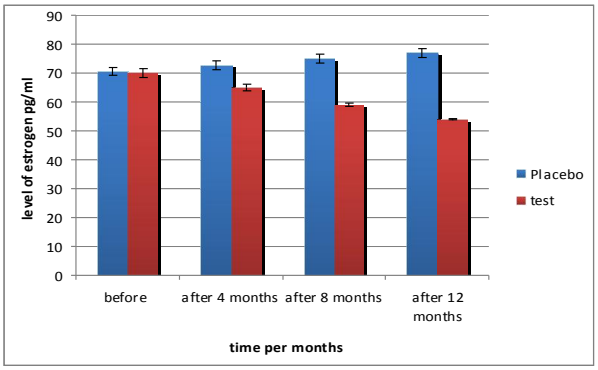

Fig 2. Study of serum estrogen levels before & after treatment with anastrozole as compared with placebo and test idiopathic short stature patients.

Each bar represents the mean of 20 patients with vertical lines indicating SEM.

Each value represents the mean ± SEM (n= 20) a = significantly different from both placebo & test at P ≤ 0.05 b = significantly different from Anastrozole treated group value / 4 months c = significantly different from Anastrozole treated group value / 8 months.

Placebo: means ISS patients which are given tablets containing starch. Test: means ISS patients which are given anastrozole.

3. Determination of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), insulin like growth factor-1(IGF-1) levels before and after treatment with anastrozole

This study revealed that serum luteinizing hormone(LH), follicle stimulating hormone (FSH) and insulin like growth factor-1(IGF-1) levels after treatment with anastrozole (in a dose of 1mg/ day / 4 months, 8 months and 12 months respectively) did not significantly change in all groups compared with either placebo or test groups (Fig.3, Fig.4 and Fig.5 respectively).

Determination of height levels before and after treatment with anastrozole

This study showed that height levels after treatment with anastrozole (in a dose of 1mg/ day / 4 months) was found to be significantly higher than those of placebo or test I.S.S groups (Fig.6).

After treatment with anastrozole (in a dose of 1mg/ day / 8 months), height levels was found to be significantly higher than those of the treated group with the same drug for 4 months, compared with test or placebo I.S.S groups (Fig.6).

After treatment with anastrozole (in a dose of 1mg/ day / 12 months), height levels was found to be significantly higher than those of the treated group with the same drug for 4 months, and 8 months, compared with test or placebo I.S.S groups (Fig.6).

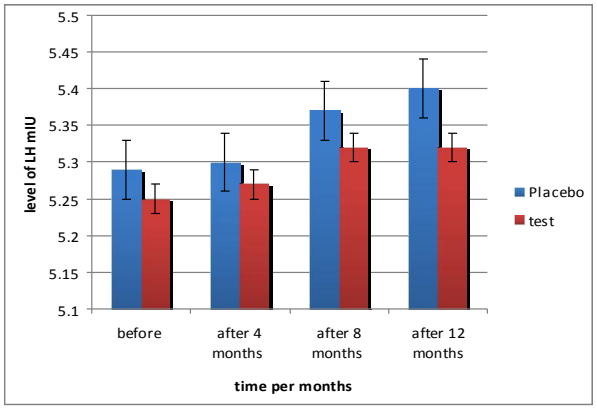

Fig 3. Study of serum luteinizing hormone (LH) levels before & after treatment with anastrozole as compared with placebo and test idiopathic short stature patients

Each bar represents the mean of 20 patients with vertical lines indicating SEM.

Placebo: means ISS patients which are given tablets containing starch. Test: means ISS patients which are given anastrozole.

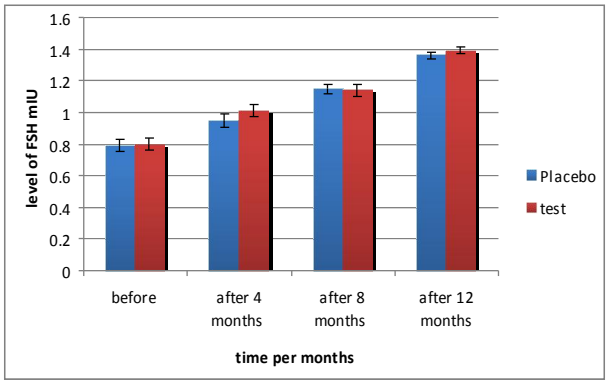

Fig 4. Study of serum follicle stimulating hormone (FSH) levels before & after treatment with anastrozole as compared with placebo and test idiopathic short stature patients

Each bar represents the mean of 20 patients with vertical lines indicating SEM Placebo: means ISS patients which are given tablets containing starch. Test: means ISS patients which are given anastrozole.

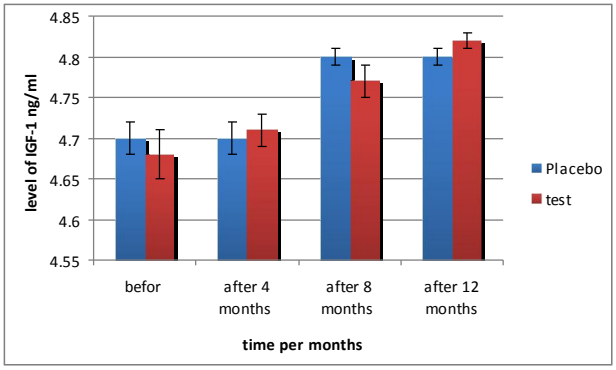

Fig 5. Study of serum insulin like growth factor-1(IGF-1) levels before & after treatment with anastrozole as compared with placebo and test idiopathic short stature patients

Each bar represents the mean of 20 patients with vertical lines indicating SEM.

Placebo: means ISS patients which are given tablets containing starch.

Test: means ISS patients which are given anastrozole.

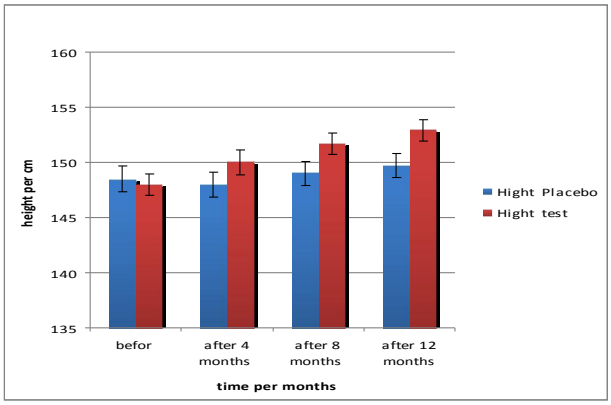

Fig 6. Study of height levels before & after treatment with anastrozole as compared with placebo and test idiopathic short stature patients

Each bar represents the mean of 20 patients with vertical lines indicating SEM Each value represents the mean ± SEM (n= 20) a = significantly different from both placebo & test at P ≤ 0.05 b = significantly different from Anastrozole treated group value / 4 months c = significantly different from Anastrozole treated group value / 8 months

Placebo: means ISS patients which are given tablets containing starch.

Test: means ISS patients which are given anastrozole.

Statistical analysis

All values in this work are expressed as mean ±SEM of the mean (SEM). The results were analyzed by unpaired student's (t) test to determine the differences between two means before and after a given treatment. *P*-value of < 0.05 was considered to be statistically significant.

4. Discussion

The approach to children with growth retardation in puberty stage remains an important clinical challenge. In most children with decreased childhood growth, a specific etiology cannot be identified, a condition termed idiopathic short stature (ISS) or non-growth hormone-deficient short stature. Most such children have height which is only below normal, but others have growth failure similar to that of GH deficiency. Many families of such children seek medical intervention [19,20].

Current strategies for increasing adult height include growth hormone treatment alone or together with Gonadotropin-releasing hormone analog (GnRHa) therapy to suppress pubertal development in boys and girls [21,22,23].

GH doses may increase risk of supraphysiological insulin like growth-1(IGF-I) concentration [24], carbohydrate abnormalities [25,26,27]. and development of acromegalic features [24].Detrimental effects of GnRHa may occur on body composition, muscle strength, and protein, lipid, and calcium metabolism, GnRHa may alsoinhibitvirilization in males [28, 29,30]. These effects make the use of GH and GnRHa unsuitable in the long term if the sole purpose of treatment is to increase final height.

A study by [31] reported that "treatment with luteinizing hormone-releasing hormone (LHRH) agonist for 3.5 years increased adult height by 0.6 SD in adolescents with very short stature but substantially decreased bone mineral density. Such treatment cannot be routinely recommended to augment height in adolescents with normally timed puberty.

Androgens have direct growth stimulating effects in the growth plate since androgens receptors have indeed been located in human growth plates. In males, testosterone was the principal sex hormone responsible for the pubertal growth spurt, skeletal maturation, accrual of bone mineral, and maintenance of skeleton [30].

The role of estrogen in the regulation of growth has been clarified considerably during the past decade. Estrogen has an important critical role (presumably in both sexes) in gaining and maintaining bone mass, closing of the epiphyses and regulation of gonadotropin through the feedback on gonadotropin secretion. Case reports of patients with estrogen insensitivity [32] or estrogen deficiency [33, 34, 35] have substantiated the fact that in the absence of an estrogen effect on the growth plate, epiphyses remain open, and

longitudinal growth continues for an exceptionally long period of time. Because ultimate fusion of the growth plates is estrogen-dependent in both boys and girls, aromatase inhibitors administration may help to slow down epiphysial maturation and allow for greater height potential. On the basis of these observations, it has become possible to postulate that longitudinal growth can be modulated by blocking estrogen biosynthesis with aromatase inhibitors, which inhibit aromatization of C19 androgens [mainly androstenedione and testosterone (T)] to C18 estrogens [36].

Aromatase inhibitors have been reported to increase height prediction in boys with short stature, and in boys and girls with gonadotropin-independent precocious puberty. They may be an attractive alternative for traditional testosterone substitution in elderly men because these compounds can be administered orally once daily and may result in physiological 24 h testosterone profiles.

Additionally, misuse of aromatase inhibitors is unlikely since testosterone levels will not be stimulated to vastly supraphysiological levels [37]. The clinical features of patients with defects in CYP19A1, the gene encoding aromatase, have revealed a major role for this enzyme in epiphyseal plate closure, which has promoted interest in the use of inhibitors of aromatase to improve adult height [38].

Aromatase inhibitors are classified as either steroidal or nonsteroidal, or as first, second or third generation. Steroidal inhibitors such as formestane and exemestane inhibit aromatase activity by mimicking the substrate androstenedione. The third-generation nonsteroidal enzyme inhibitors such as anastrozole and letrozole inhibit enzyme activity by binding with the heme iron of the enzyme (active site of P450 aromatase) through interaction of a heterocyclic nitrogen that is critical for their markedly increased activity [39].

Third generation aromatase inhibitors are now available and offer significant advantages over weak aromatase inhibitor in terms of potency, safety, and tolerability. Thus, the use of a potent selective aromatase blocker, anastrozole, offers the advantage of continued virilization and maintenance of pubertal body composition in boys while potentially delaying skeletal maturation. Therefore the use of an AI with or without GH is a better option for enhancing the growth potential of short pubertal boys [40,41,42].

Biochemical markers of puberty including serum testosterone, gonadotropins, and changes in the estradiol to-testosterone ratio showed the expected effects of relative estrogen suppression, and the hormone levels eventually remained in the normal range for the pubertal stage [38].

The current study was conducted to determine whether the aromatase inhibitor anastrozolecould play a role on growth and consequently predicted adult height in boys with high estrogen level. Also, the study was aimed to investigate the effects of aromatase inhibition on gonadotropin secretion in boys during prepubertal phase.

Results of the present study showed a significant increase in serum testosterone levels and a significant decline in serum estrogen levels in boys with ISS treated with anastrozole 1 mg taken orally / day / 4, or 8 and 12 months respectively as compared to placebo subjects. These results are in consistent with other trials which revealed that estrogen levels were substantially decreased, whereas testosterone levels were significantly increased in those who received anastrozole treatment compared with control subjects [43]. It was reported that aromatase blockade effectively blocks estrogen production in males with a reciprocal increase in testosterone [38].

It is well known from experimental evidence and from clinical observations that estradiol has powerful effects on gonadotropin release in men. Modulation of plasma estradiol levels within the male physiological range is associated with strong effects on plasma levels of LH through an effect at the level of the pituitary gland [44].Although FSH release is primarily under the control of inhibin, circulating estradiol has a substantial effect on FSH levels in men [45]. Aromatase inhibition results in a three-fold increase in levels of FSH in eugonadal men and may potentially stimulate sperm production [45, 46]. Due to their mode of action the use of aromatase inhibitors is limited to men with at least some residual function of the hypothalamo-pituitary- gonadal axis.

Lowering estradiol levels, by administering an aromatase inhibitor, is associated with an increase in levels of LH, follicle-stimulating hormone (FSH) and testosterone. [45,46].These results are in discrepancy with the present study which revealed no significant change in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels that appeared between treatment groups at the beginning of the study. After four, eight, and twelve months of treatment serum levels of LH and FSH in anastrozole group (in a dose of 1mg/ day for twelve months) did not significantly change compared to the placebo group or within the anastrozole group by elongation the duration of therapy (four, eight, and twelve months). These findings were in agreement with the concept that the control of gonadotropin secretion before the onset of puberty is mediated via the central nervous system rather than by sex steroids. In accord with the previous findings a study by Hero et al., 2005 reported no changes in boys who remained prepubertal throughout the study in FSH and LH levels between

treatment group of AI and placebo group. Simultaneously, the respective values in the pubertal boys changed significantly in both AI and placebo groups. In the placebo-pubertal boys, LH and FSH levels gradually increased significantly. On the other hand, in the respective AI group, LH and FSH levels increased more rapidly and remained higher than that in the placebo-treated pubertal boys during the treatment period. Hero et al., 2005 concluded that the suppression of estrogen biosynthesis by AI decreases the negative feedback control of gonadotropin secretion and raises serum FSH and LH levels after the onset of puberty. This increase in gonadotropin secretion resulted in a supraphysiological rise in T concentrations and rapid testicular growth.

Growth hormone and IGF-1 levels were positively correlated with estradiol levels [(47).] In anastrozole-treated boys in whom treatment started at the beginning of puberty, IGF-I levels were lower than in placebo-treated control [(48).] As expected, GH-deficient boys treated with GH and anastrozole showed a larger increase in height than their GH only-treated control [(49).] Results of the current study revealed no significant changes in serum IGF-I levels were observed between the different groups before treatment. After 12 months of treatment the serum IGF-1 levels in anastrozole group (1mg oral dose/ day) did not significantly change compared to the placebo group or within the anastrozole group during the therapy (four, eight, and 12 months).

Our explanation of this finding is that the puberty is associated with stimulation of the GH-IGF-I axis, which is normally mediated by estrogen. Estrogen was inhibited in boys treated with anastrozole, as evidenced by no significant change in IGF-I levels in the treatment groups. On contrast to the present results Hero et al., 2005 reported that serum IGF-I levels were significantly higher in the pubertal placebo-treated boys at 18 and 24 months after the start of treatment compared to AI group.

The observed growth velocity in the anastrozole group in the current study strongly suggests that in the prepubertal stage, the low estradiol and IGF-I levels and the high androgen levels may be able to enhance growth velocity.

The present study compared the effect of aromatase inhibitor, anastrozole, on predicted adult height (PAH) in boys with ISS. At entry, no significant change in the mean levels of height between treatment groups. After four, eight, and 12 months of treatment, the mean levels of height were significantly increased in anastrozole group compared to placebo group. Also there were a significant increase in the mean levels of height within anastrozole group by elongation the duration of therapy (eight, and 12 months compared to four months).

Clinically, after one year of treatment the mean level of height was improved as much as (4.9 cm) in anastrozole group which was significantly higher than the increase in the mean level of height in control group (1.2 cm) after one year of placebo treatment.

In contrast with the previous findings, a study of 12-month treatment with the aromatase inhibitor (anastrozole) in adolescent boys with GH deficiency, failed to find an effect of anastrozole on PAH. This is potentially explained by the short duration of treatment of the study where the patients were pubertal before the start of anastrozle and may be due to GH deficiency [(50).]

Although the overall results of treatment with AIs are encouraging and their use seems to be rapidly expanding, we agree with the recommendation by several of the studies that endocrinologists should be cautious and that AIs should preferentially be used within carefully controlled clinical trials. More data on adult heights are needed. If AIs are shown to increase adult height, then questions that will still need to be addressed include the optimal agent, dosage, duration of therapy, and whether the intervention is equally efficacious regardless of underlying diagnosis (e.g. do patients with idiopathic short stature, constitutional delay of growth and maturation, and growth hormone deficiency all gain similarly?). What is the average and range of the gain in adult (not predicted adult) height?

In conclusion: Anastrozole treatment in idiopathic short stature boys offers promise and may be a useful choice in the approach to the growth-retarded boys in puberty. Long-term follow-up to final adult height is still needed to fully characterize the safety and efficacy of this approach.

Conflict of interest

The authors declare that there are no conflicts of interest.

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