

**Eunice Kennedy Shriver National Institute of Child Health
and Human Development (NICHD)
Obstetric and Pediatric Pharmacology Branch (OPPB)
Best Pharmaceuticals for Children Act (BPCA)**

Selected Citations—Aromatase Inhibitors

1. Ambler, G.R. "Androgen therapy for delayed male puberty." *Current Opinion in Endocrinology, Diabetes and Obesity* 16.3 (2009): 232-239.

Abstract

PURPOSE OF REVIEW: Delayed puberty in men is a commonly presenting problem to paediatricians and an understanding of the available evidence on cause, treatments and outcomes is important to guide practice.

RECENT FINDINGS: Understanding of the regulation of the onset of puberty is gradually unfolding, although the genetic factors that dictate the timing of puberty in individuals and families remain poorly elucidated. Mutations and polymorphisms in candidate genes are being actively studied and it is likely that there is significant overlap between traditional diagnostic categories. Also, environmental endocrine disruptors may interact with the genetic regulation of puberty. Delayed puberty may not always be a benign condition, with increased risks of failing to achieve target height, adverse psychological and educational consequences, delayed sexual and psychosocial integration into society and effects on skeletal proportions and bone mass reported. Appropriate evaluation and follow-up is needed to guide clinical practice, particularly to distinguish constitutional delay in growth and puberty from that associated with other medical disease or permanent disorders.

SUMMARY: In milder cases of delayed puberty, treatment is often not required; however, considerable evidence exists for the efficacy and safety of short courses of low-dose testosterone therapy for appropriately selected individuals. This treatment is associated with high levels of patient satisfaction. There is not yet sufficient evidence for the routine use of other therapies (e.g. growth hormone, aromatase inhibitors) for constitutional delay in growth and puberty and better characterization of cause may lead to more targeted individual therapy.

2. Artini, P.G., O.M. Di Berardino, G. Simi, F. Papini, M. Ruggiero, P. Monteleone, and V. Cela. "Best methods for identification and treatment of PCOS." *Minerva Ginecologica* 62.1 (2010): 33-48.

Abstract

The polycystic ovarian syndrome (PCOS) includes a wide spectrum of clinical symptoms and signs. Three different diagnostic classifications have been proposed to define this disease. The first one, published in 1990, known as the "NIH criteria" requires the simultaneous presence of hyperandrogenism and menstrual dysfunction in order to diagnose PCOS. Later on, in 2003, an expert panel met in Rotterdam and added to the previous criteria the presence of polycystic ovarian morphology detected by transvaginal ultrasonography. The later classification broadened the spectrum of PCOS and also included women with oligomenorrhea and PCO without hyperandrogenism or hyperandrogenism and PCO without menstrual dysfunction. Finally, the Androgen Excess Society, published in 2006 new diagnostic criteria which required the presence of clinical or biochemical hyperandrogenism, with either PCO or menstrual dysfunction to diagnose PCOS. This review focuses on the diagnostic techniques and methods of treatment for PCOS patients. Special attention is given to the role of insulin resistance and the potential utility of insulin sensitizers in management of the syndrome. The benefit and utmost importance of lifestyle modification for the long-term health of these women is stressed as well. It is hoped that some clarity in this regard will allow more women to not only be diagnosed and managed properly for their presenting symptoms (hirsutism, irregular menses, etc.), but also to be educated and managed for the continuing health risk of insulin resistance throughout their lives.

3. **Bedognetti, D., A. Rubagotti, G. Zoppoli, and F. Boccardo. "Gynaecomastia: the anastrozole paradox." *Journal of Pediatric Endocrinology & Metabolism* 23.1-2 (2010): 205-206.**
(No Abstract Available)
4. **Cernich, J., J.D. Jacobson, W.V. Moore, and J. Popovic. "Use of aromatase inhibitors in children with short stature." *Pediatric Endocrinology Reviews* 2.1 (2004): 2-7.**

Abstract

Estrogen has been shown to have an important role in skeletal maturation in both males and females. The use of aromatase inhibitors may provide a means to delay skeletal maturation and increase final height in children with short stature. These medications have been used primarily in women with breast carcinoma and also in children with autonomous estrogen production, such as patients with McCune-Albright Syndrome. Several studies have evaluated the safety and metabolic effects in adults. A few studies in children have evaluated the efficacy and safety of these medications. These studies demonstrate a beneficial effect on bone age advancement and predicted adult height. Other studies have evaluated the effects on bone mineral density, lipid metabolism and adrenal function in children. This review summarizes the studies in the pediatric population and some of the metabolic effects in adults.

5. **Chagin, A.S., and L. Säwendahl. "Oestrogen receptors and linear bone growth." *Acta Paediatrica* 96.9 (2007): 1275-1279.**

Abstract

In this review we summarize available data regarding linear growth in oestrogen receptor alpha (ERalpha)- and oestrogen receptor beta (ERbeta)-deficient mice. We discuss these findings in relation to known oestrogenic effects in humans and the possibility of applying this knowledge for the therapeutic modulation of longitudinal bone growth employing selective oestrogen receptor modulators (SERMs). We conclude that SERMs potentially could offer new possibilities to modulate bone growth by specifically targeting different oestrogen receptors within the growth plate.

6. **Damiani, D. "Pharmacological management of children with short stature: the role of aromatase inhibitors." *Jornal de Pediatria* 83.5 Supplement (2007): S172-177.**

Abstract

OBJECTIVE: To review the use of aromatase inhibitors, a novel treatment strategy for patients with short stature, which aims at delaying bone age advancement. Skeletal maturation is estrogen-dependent even in male children.

SOURCES: We performed a MEDLINE search of studies published in the last 10 years, including aromatase, short stature, and early puberty as keywords. The most informative articles on indications, dosages, treatment schedules, and side effects of aromatase inhibitors were included in the review.

SUMMARY OF THE FINDINGS: It has become increasingly clear that bone age advancement depends on the production of estrogen and its effect on the growth plate. In boys, testosterone is converted to estradiol by the cytochrome P450 enzyme aromatase. The use of aromatase inhibitors has been shown to be effective in prolonging the length of the growth phase in children with idiopathic short stature, constitutional growth delay, delayed puberty, as well as in children with growth hormone deficiency, in which bone age advancement jeopardizes the results of hormonal replacement therapy with growth hormones. As yet, significant adverse effects have not been reported, and results are encouraging in terms of effective increase in height, whenever the indication for the drug is appropriate.

CONCLUSIONS: Among the pharmacological treatments for short stature, aromatase inhibitors are indicated in cases in which bone age advancement may constitute an obstacle for reaching a final height that is in keeping with the family's target height.

7. Diaz-Thomas, A., and D. Shulman. "Use of aromatase inhibitors in children and adolescents: what's new?." *Current Opinion in Pediatrics* 22.4 (2010): 501-507.

Abstract

PURPOSE OF REVIEW: Aromatase inhibitors have been reported to increase height prediction in boys with short stature, and in boys and girls with gonadotropin-independent precocious puberty. The following review discusses data published since 2008 regarding the safety and efficacy of aromatase inhibitors in pediatric patients.

RECENT FINDINGS: Third-generation aromatase inhibitors in combination with antiandrogens appear effective in preventing bone age advancement and virilization in boys with familial male-limited precocious puberty (FMPP). Letrozole, but not anastrozole, decreased bleeding episodes and bone age advancement in girls with McCune-Albright syndrome (MAS), despite ovarian enlargement. Letrozole-treated boys with idiopathic short stature (ISS) had no loss of bone density but were noted to have more vertebral abnormalities than a placebo group. Two years of letrozole therapy did not increase predicted adult height in pre and peripubertal boys with ISS when re-assessed 4 years after the treatment period.

SUMMARY: Aromatase inhibitors together with an antiandrogen appear to be a very promising treatment for FMPP. Further longer-term studies with letrozole are needed in MAS. The prevalence of vertebral deformities should be evaluated prospectively in patients treated with aromatase inhibitors. Adult height data are still lacking in pediatric patients treated with aromatase inhibitors. Two years of therapy in pre and peripubertal short boys does not appear to increase adult height. Hemogram, lipids, and bone density should be periodically assessed in treated patients. Further controlled studies are needed to demonstrate safety and efficacy of aromatase inhibitors in pediatric patients.

8. Dunkel, L. "Update on the role of aromatase inhibitors in growth disorders." *Hormone Research in Paediatrics* 71. Supplement 1 (2009): 57-63.

Abstract

Background: Without oestrogen action, the fusion of the growth plates is postponed and longitudinal growth continues for an exceptionally long period of time. Aromatase inhibitors that block oestrogen biosynthesis have therefore emerged as a new potential treatment option for children with short stature. Results from three prospective randomised controlled trials using potent third-generation aromatase inhibitors have recently been published. These studies all show that treatment with the aromatase inhibitors letrozole and anastrozole effectively delays bone maturation and increases predicted adult height in boys with constitutional delay of growth and puberty (CDGP), idiopathic short stature and growth hormone deficiency. Long-term follow-up data from the study in which boys with CDGP were treated with letrozole for 1 year during adolescence suggest that the achieved gain in predicted adult height also results in taller final adult height. Conclusions: Until the safety profile of aromatase inhibitors, particularly their qualitative effects on bone development, is established, use of these agents must be considered experimental in treating short stature.

9. Dunkel, L. "Use of aromatase inhibitors to increase final height." *Molecular and Cellular Endocrinology* 25 (2006): 254-255;207-216.

Abstract

During puberty in both sexes, the mechanism involved in epiphyseal fusion is mediated by the action of estrogen through a cascade of events including proliferation, differentiation, and apoptosis of chondrocytes. The enzyme P450 aromatase catalyzes the aromatization of C19 androgens (androstenedione and testosterone) to C18 estrogens (estrone and estradiol). Inhibition of estrogen action by aromatase inhibitors (AIs) appears to decelerate the process of growth plate fusion, and thus AIs may be used therapeutically to increase adult height. The clinical experience with AIs in the pediatric setting is limited to testolactone, fadrozole, letrozole, and anastrozole. Testolactone, a nonselective steroidal AI, has been used successfully as an adjunct to antiandrogen and gonadotropin-releasing hormone analogue (GnRHa), therapy for children with familial male-limited precocious puberty (FMPP) and congenital adrenal hyperplasia (CAH), and with some success in girls with McCune-Albright syndrome. The limitations of testolactone include its relatively low potency

and the need for frequent dosing. Results of a randomized placebo-controlled trial in boys with delayed puberty treated with letrozole, a selective nonsteroidal AI, found that boys treated with letrozole + testosterone experienced delayed bone maturation and good growth response and achieved an increase in predicted adult height. In this study, only minor differences in bone density were seen between the placebo and letrozole treatment groups, both of which were receiving concomitant testosterone therapy. No adverse effects on testis size or inhibin B concentration were noted. The therapeutic value of AIs in growth promotion now remains to be substantiated in future controlled clinical trials.

10. Dunkel, L., and S. Wickman. "Novel treatment of short stature with aromatase inhibitors." *The Journal of Steroid Biochemistry and Molecular Biology* 86.3-5 (2003): 345-356.

Abstract

Estrogens have an essential role in the regulation of bone maturation and importantly in the closure of growth plates in both sexes. This prospective, randomized, placebo-controlled study was undertaken to evaluate whether suppression of estrogen synthesis in pubertal boys delays bone maturation and ultimately results in increased adult height. A total of 23 boys with constitutional delay of puberty (CDP) received a conventional, low-dose testosterone treatment for inducing progression of puberty. Eleven of these 23 boys were randomized to receive a specific and potent P450-aromatase inhibitor, letrozole, for suppression of estrogen action, and 12 boys were randomized to receive placebo. Estradiol concentrations in the letrozole-treated boys remained at the pretreatment level during the administration of letrozole, whereas the concentrations increased during the treatment with testosterone alone and during spontaneous progression of puberty. Testosterone concentrations increased in all groups, but during the letrozole treatment, the increase was more than fivefold higher than in the group treated with testosterone alone. The inhibition of estrogen synthesis delayed bone maturation. The slower bone maturation in the boys treated with testosterone and letrozole, despite higher androgen concentrations, than in the boys treated with testosterone indicate that estrogens are more important than androgens in regulation of bone maturation in pubertal boys. During the 18 months follow-up, an increase of 5.1 cm in predicted adult height was observed in the boys who received testosterone and letrozole, but no change was seen in the boys who received testosterone alone or in the untreated boys. This finding indicates that an increase in adult height can be attained in growing adolescent boys by inhibiting of estrogen action.

11. Eugster, E.A. "Aromatase inhibitors in precocious puberty: rationale and experience to date." *Treatments in Endocrinology* 3.3 (2004): 141-151.

Abstract

Aromatase inhibitors have been used in the treatment of selective forms of precocious puberty since the mid-1980s. The primary aim of therapy is attenuation of the effects of estrogen on growth, skeletal maturation, and secondary sexual development. The first-generation agent, testolactone, has been demonstrated to be tolerable and effective in the treatment of familial male precocious puberty, while mixed results with testolactone have been achieved in girls with McCune-Albright syndrome. A favorable outcome with the use of testolactone in conjunction with conventional therapy in children with congenital adrenal hyperplasia has also been suggested. Although a few anecdotal reports of the use of newer generation aromatase inhibitors in precocious puberty exist, the extreme rarity of the relevant disorders remains a limiting factor in clinical investigation. In this review, the pathophysiology, presentation, and treatment of precocious puberty are described. Particular attention is devoted to the specific disorders in which aromatase inhibitors have been utilized, which are forms of peripheral (gonadotropin-independent) precocious puberty. The impact of untreated precocious puberty on growth and adult stature is discussed, and the actions of estrogen in the human skeleton are summarized. Finally, a detailed description of the existing literature pertaining to aromatase inhibitors in the pediatric population is provided. Emerging potential new indications are discussed. In conclusion, aromatase inhibitors, particularly testolactone, have a proven track record in the treatment of a few forms of precocious puberty. Continued exploration with new generation aromatase inhibitors in these disorders is ongoing. The wider application of aromatase inhibitors for

the purposes of delaying skeletal maturation and increasing adult height in several conditions leading to short stature is currently a subject of intense investigation.

12. Eyssette-Guerreau, S., G. Pinto, A. Sultan, M. Le Merrer, C. Sultan, and M. Polak. "Effectiveness of anastrozole and cyproterone acetate in two brothers with familial male precocious puberty." *Journal of Pediatric Endocrinology & Metabolism* 21.10 (2008): 995-1002.

Abstract

Testotoxicosis is a rare form of precocious puberty caused by a constitutively activating mutation in the luteinizing hormone receptor (LHR) gene. Symptoms include rapid virilization, accelerated growth and reduced adult height. We describe a rare association of testotoxicosis with a metaphyseal chondrodysplasia called cartilage-hair hypoplasia (CHH) and report two brothers with testotoxicosis after 4 years of treatment. The brothers had a T577I mutation in the LHR gene. One brother also presented CHH. The older brother was treated with ketoconazole, then with the aromatase inhibitor anastrozole and the anti-androgen cyproterone acetate. The younger brother received this combination as first-line therapy. Clinical improvements included reductions in growth velocity and bone maturation rate, which should result in taller adult stature. Tolerance was good. CONCLUSION: Combined treatment with anastrozole and cyproterone acetate is effective in improving the prognosis of adult height in testotoxicosis.

13. Faglia, G., M. Arosio, and S. Porretti. "Delayed closure of epiphyseal cartilages induced by the aromatase inhibitor anastrozole. Would it help short children grow up?." *Journal of Endocrinological Investigation* 23.11 (2000): 721-723.

Abstract

Estrogens locally generated from androgen precursors due to the action of aromatase play a main role in epiphyseal cartilage fusion. Treatment with an aromatase inhibitor (anastrozole, 1 mg/day for 3 yr) in a boy previously operated on for a hamartoma causing precocious puberty and presenting with advanced bone maturation and nearly fused epiphyseal cartilages, slowed cartilage fusion consenting a higher final stature than expected (164.4 cm vs 158.4 cm). It is suggested that treatment with aromatase inhibitors, alone or in combination with rh-GH, may also be useful in children with constitutional short stature in order to delay epiphyseal closure and improve the final height.

14. Feuillan, P.P., C.M. Foster, O.H. Pescovitz, K.D. Hench, T. Shawker, A. Dwyer, J.D. Malley, K. Barnes, D.L. Loriaux, and G.B. Cutler, Jr. "Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testolactone." *New England Journal of Medicine* 315.18 (1986): 1115-1119.

Abstract

The McCune-Albright syndrome is characterized by café au lait spots, fibrous dysplasia of bones, and sexual precocity. Girls with precocious puberty due to this syndrome have episodic increases in serum estrogen levels together with the formation of large ovarian cysts. The serum gonadotropin levels are typically suppressed, and the precocious puberty has not responded to treatment with long-acting analogues of luteinizing hormone-releasing hormone (LHRH). Encouraged by our initial success in a pilot study of one patient, we have now treated five girls with the McCune-Albright syndrome with the aromatase inhibitor testolactone, which blocks the synthesis of estrogens. Testolactone decreased the levels of circulating estradiol (P less than 0.05) and the ovarian volume (P less than 0.05), and there was a return to pretreatment levels after testolactone was stopped. During treatment, the peak responses of luteinizing hormone and follicle-stimulating hormone to stimulation by LHRH rose above suppressed pretreatment levels--significantly above pretreatment levels for follicle-stimulating hormone (P less than 0.02)--and then returned to pretreatment levels after testolactone was discontinued. Growth rates fell in three patients during treatment but could not be assessed in the other two because of bone deformities. The mean rate of bone maturation decreased and menses stopped in three of the four girls who were menstruating regularly. We

conclude that testolactone is an effective treatment of precocious puberty in the McCune-Albright syndrome.

15. Geffner, M.E. "For debate: Aromatase inhibitors to augment height: have we lost our inhibitions?." *Pediatric Endocrinology Reviews* 5.3 (2008): 756-759.
(No Abstract Available)
16. Haddad, N., and E. Eugster. "An update on the treatment of precocious puberty in McCune-Albright syndrome and testotoxicosis." *Journal of Pediatric Endocrinology & Metabolism* 20.6 (2007): 653-661.

Abstract

McCune-Albright syndrome and testotoxicosis are rare forms of peripheral precocious puberty. Our understanding of the pathophysiology and mechanism of these diseases has significantly increased following identification of their underlying molecular etiology. However, their treatment remains challenging. We provide a review of the various treatment modalities used in both conditions with an update on recent trials using novel and promising pharmacological agents.

17. Hero, M., O. Mäkitie, H. Kröger, E. Nousiainen, S. Toiviainen-Salo, and L. Dunkel. "Impact of aromatase inhibitor therapy on bone turnover, cortical bone growth and vertebral morphology in pre- and peripubertal boys with idiopathic short stature." *Hormone Research in Paediatrics* 71.5 (2009): 290-297.

Abstract

In this randomized placebo-controlled study we examined the influence of aromatase inhibition on bone turnover, cortical bone growth, and vertebral body morphology in peripubertal boys. Thirty peripubertal boys with idiopathic short stature were treated with the aromatase inhibitor letrozole or placebo for 2 years. During treatment and posttreatment follow-up, dual-energy X-ray absorptiometry (DXA)-assessed bone mineral density, metacarpal index (MCI), and markers of bone turnover were examined. Vertebral morphology was examined by DXA after cessation of treatment. In letrozole-treated boys, the concentrations of the bone resorption marker urine aminoterminal telopeptide of type I collagen initially increased and thereafter slowly declined while the concentrations of the bone formation markers serum aminoterminal propeptide of type I collagen and serum alkaline phosphatase remained unchanged or slightly increased, respectively. In placebo-treated boys, all markers of bone turnover increased significantly during treatment. Among those who progressed into puberty, metacarpal index (MCI) increased more in the letrozole-treated than in the placebo-treated boys during treatment (25 vs. 9%, $p = 0.007$). The change in MCI correlated with the testosterone-to-estradiol ratio ($r = 0.59$, $p = 0.02$). Vertebral deformities were detected in 6 out of 13 boys receiving letrozole and in 4 out of 11 receiving placebo ($p = 0.70$). Aromatase inhibition suppresses bone turnover, possibly through an androgen-mediated effect. In pubertal boys, treatment stimulates cortical bone growth by increasing the testosterone-to-estradiol ratio.

18. Hero, M., S. Maury, E. Luotoniemi, E. Service, and L. Dunkel. "Cognitive effects of aromatase inhibitor therapy in peripubertal boys." *European Journal of Endocrinology* 163.1 (2010): 149-155.

Abstract

OBJECTIVE: Aromatase inhibitors, blockers of oestrogen biosynthesis, have emerged as a new potential treatment modality for boys with short stature. The cognitive effects of such therapy are unknown. In this study, we explored the effects of aromatase inhibition on cognitive performance in peripubertal boys.

DESIGN: Prospective, double-blind, randomised, placebo-controlled clinical study.

METHODS: Twenty-eight boys, aged 9.0-14.5 years, with idiopathic short stature were treated with the aromatase inhibitor letrozole (2.5 mg/day) or placebo, for 2 years. During the treatment, the progression of physical signs of puberty and the concentrations of sex hormones were followed up. A selection of cognitive tests, focusing on memory function, was administered to the participants at entry, at 12 months and at 24 months after the start of the treatment.

RESULTS: Letrozole effectively inhibited the conversion of androgen to oestrogen, as indicated by high serum testosterone and low serum oestradiol concentrations in letrozole-treated boys who progressed into puberty. In both the groups, there was a gain in performance during the follow-up period in tests of verbal performance, in most of the tests of visuospatial performance and in some tests of verbal memory. No significant differences between the letrozole- and placebo-treated boys in development of cognitive performance were found in any of the tests during the follow-up period.

CONCLUSIONS: Our results suggest that blockade of oestrogen biosynthesis with an aromatase inhibitor does not influence cognitive performance in peripubertal males.

- 19. Hero, M., S. Toiviainen-Salo, S. Wickman, O. Mäkitie, and L. Dunkel. "Vertebral morphology in aromatase inhibitor-treated males with idiopathic short stature or constitutional delay of puberty." *Journal of Bone and Mineral Research* 25.7 (2010): 1536-1543.**

Abstract

Aromatase inhibitors (AIs), blockers of estrogen biosynthesis, delay bone maturation and therefore are used increasingly to promote growth in children and adolescents with growth disorders. The effects of treatment on skeletal health are largely unknown. Since estrogen deficiency is associated with various detrimental skeletal effects, we evaluated in this cross-sectional posttreatment study vertebral body morphology, dimensions and endplates, and intervertebral disks by the use of magnetic resonance imaging (MRI) in two cohorts of males previously treated with the AI letrozole or placebo. Males with idiopathic short stature received treatment with letrozole or placebo for 2 years during prepuberty or early puberty; males with constitutional delay of puberty received letrozole or placebo in combination with low-dose testosterone for 1 year during early or midpuberty. In males with idiopathic short stature, mild vertebral body deformities were found in 5 of 11 (45%) letrozole-treated subjects, whereas in the placebo group no deformities were detected ($p = .01$). In the cohort of males with constitutional delay of puberty, a high prevalence of endplate and intervertebral disk abnormalities was observed in both the letrozole- and the placebo-treated groups. We conclude that AI therapy during prepuberty or early puberty may predispose to vertebral deformities, which probably reflect impaired vertebral body growth rather than impaired bone quality and compression fractures. If AIs are used in growth indications, follow-up of vertebral morphology is indicated. (c) 2010 American Society for Bone and Mineral Research.

- 20. Hero, M., S. Wickman, and L. Dunkel. "Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty." *Clinical Endocrinology* 64.5 (2006): 510-513.**

Abstract

OBJECTIVE: We investigated whether inhibition of oestrogen biosynthesis with the aromatase inhibitor, letrozole, during adolescence improves near-final height in boys with constitutional delay of puberty.

PATIENTS AND METHODS: Seventeen boys with constitutional delay of puberty were randomized to receive testosterone (T) enanthate (1 mg/kg i.m.) every 4 weeks for 6 months in combination with placebo (PI, $n = 8$), or the aromatase inhibitor letrozole (Lz, 2.5 mg/day orally) ($n = 9$), for 12 months. After treatment, patients were followed up until near-final height. Height discrepancy was calculated as near-final height minus mid-parental target height.

MEASUREMENTS: The primary end point was the difference in near-final height between the groups treated either with T + PI or T + Lz. Secondly, height discrepancy and gain in height standard deviation score (SDS) were analysed in both groups.

RESULTS: Boys treated with T + Lz reached a higher mean near-final height than did boys on T + PI (175.8 vs. 169.1 cm, respectively, $P = 0.04$). In T + Lz-treated boys, mean near-final height did not differ from their mid-parental target height (175.8 vs. 177.1 cm, $P = 0.38$), whereas in T + PI-treated boys, mean near-final height was lower than mid-parental target height (169.1 vs. 173.9 cm, $P = 0.007$). T + Lz-treated boys had a greater increment in height SDS over the pretreatment height SDS than T + PI-treated boys (+1.4 SDS vs. +0.8 SDS, $P = 0.03$).

CONCLUSIONS: Our findings indicate that in adolescent boys an increase in adult height can be attained by use of aromatase inhibitors.

21. Karmazin, A., W.V. Moore, J. Popovic, and J.D. Jacobson. "The effect of letrozole on bone age progression, predicted adult height, and adrenal gland function." *Journal of Pediatric Endocrinology & Metabolism* 18.3 (2005): 285-293.

Abstract

A common problem in pediatric endocrinology is limited growth potential resulting from advancing skeletal maturation. We determined the efficacy of letrozole, an aromatase inhibitor, on delaying bone age advancement in adolescent males with limited growth potential. Twenty-four patients met the study inclusion criteria. Six patients treated with androgen were analyzed separately. Low-dose ACTH stimulation tests were performed to ascertain the effect of letrozole on adrenal gland function. In patients not on androgen, bone age progression decelerated from 1.51+/-0.57 (deltabone age/deltachronological age) before treatment to 0.68+/-0.66 on therapy (mean duration 12.4 months; $p < 0.0005$). Predicted adult height standard deviation scores (SDS) increased from -1.41+/-0.54 to -0.64+/-0.65 on treatment ($p < 0.0005$). Similar results were noted in androgen-treated patients. Approximately one-fourth of patients displayed subnormal responsiveness to ACTH. In summary: 1) letrozole decelerates skeletal maturation, resulting in significant increases in predicted adult height, and 2) letrozole causes mild adrenal suppression.

22. Kreher, N.C., O.H. Pescovitz, P. Delameter, A. Tiulpakov, and Z. Hochberg. "Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole." *The Journal of Pediatrics* 149.3 (2006): 416-420.

Abstract

This report describes the use of bicalutamide and anastrozole in two subjects with familial male-limited precocious puberty. Clinical improvements include decreased facial acne and pubic hair. Most importantly, a marked decrease in growth velocity and skeletal advancement has been achieved.

23. Lee, P.A. "The effects of manipulation of puberty on growth." *Hormone Research in Paediatrics* 60.Supplement 1 (2003): 60-67.

Abstract

Short stature in adulthood can be considered as a disability because it can be associated with many difficulties including those of a psychological and social nature. Many factors can influence final adult height such as genetics, the magnitude of growth hormone (GH) secretion, height before puberty, and the onset and duration of puberty. A crucial factor affecting final adult height, however, is the total height achieved during puberty. The combination of GH and gonadotropin-releasing hormone analogues greatly enhances growth and their separate and combined use for the treatment of GH deficiency, central precocious puberty and other diagnoses in children and adolescents is discussed in this article.

24. Ma, N.S., and M.E. Geffner. "Gynecomastia in prepubertal and pubertal men." *Current Opinion in Pediatrics* 20.4 (2008): 465-470.

Abstract

PURPOSE OF REVIEW: Gynecomastia is often benign, but it can be the sign of serious endocrine disease and the source of significant embarrassment and psychological stress. Understanding its pathogenesis is crucial to distinguish a normal developmental variant from pathological causes. RECENT FINDINGS: There is a growing list of potential causes of gynecomastia. Rare and unique case reports continue to supplement the literature to augment our understanding of this common physical finding. However, the exact basis for the pathogenesis of gynecomastia remains unknown. There appears to be a local imbalance between estrogen stimulation and the inhibitory action of androgens on breast tissue proliferation. Gynecomastia in a prepubertal boy is rare and should

prompt an immediate evaluation for possible endocrine disorder. Pubertal gynecomastia, on the contrary, is common and usually physiological, with sympathetic reassurance and watchful waiting the mainstays of treatment. There is some evidence that early pharmacological intervention with antiestrogens may diminish persistent pubertal gynecomastia, but treatment with an aromatase inhibitor has not been shown to be more effective than placebo.

SUMMARY: Treatment of gynecomastia is geared toward its specific cause. Currently, there are insufficient data to recommend medical therapy in children with idiopathic gynecomastia.

25. Mauras, N. "Strategies for maximizing growth in puberty in children with short stature." *Endocrinology and Metabolism Clinics of North America* 38.3 (2009): 613-624.

Abstract

The approach to the child with growth retardation who is in puberty remains an important clinical challenge. The use of high-dose growth hormone (GH), suppression of puberty with GnRH analogs in combination with GH, and the use of selective inhibitors of the aromatase enzyme with aromatase inhibitors (also in combination with GH) are all therapeutic choices that have been studied.

Aromatase blockade effectively blocks estrogen production in males with a reciprocal increase in testosterone, and a new generation of aromatase inhibitors, including anastrozole, letrozole and exemestane, is under investigation in adolescent subjects with severe growth retardation. This class of drugs, if judiciously used for a window of time, offers promise as an adjunct treatment of growth delay in pubertal patients with GH deficiency, idiopathic short stature, testotoxicosis, and other disorders of growth. These evolving uses of aromatase inhibitors, however, represent off-label use of the product, and definitive data on their efficacy are not available for each of the conditions mentioned. Safety issues regarding bone health also require further study.

26. Mauras, N., V. Hayes, and K.O. O'Brien. "Estrogen treatment and estrogen suppression: metabolic effects in adolescence." *Journal of Pediatric Endocrinology & Metabolism* 13.Supplement 6 (2000): 1431-1437.

Abstract

The metabolic consequences of reaching full reproductive maturity in humans involve not only growth hormone (GH) and insulin-like growth factor-I, but also the collaborative interaction of the gonadal sex steroids. Estrogen is critical for completing linear growth. It also inhibits bone resorption, decreases plasma lipid levels and serves as an antiatherosclerotic agent. Our studies show that, in low doses, estrogen increases GH production, increases calcium absorption and decreases bone turnover; however, unlike testosterone, estrogen has no effects as a protein-anabolic agent, at least at the whole body level. Studies of selective estrogen suppression, achieved using a potent aromatase inhibitor, show that estrogen is the main regulator of the gonadotropin axis. In boys, selective aromatase blockade may have a role in delaying epiphyseal fusion. Large placebo-controlled trials will be required to study this effect further.

27. Mieszczak, J., and E.A. Eugster. "Treatment of precocious puberty in McCune-Albright syndrome." *Pediatric Endocrinology Reviews* 4.Supplement 4 (2007): 419-422.

Abstract

McCune-Albright syndrome (MAS) is typically defined as a triad of precocious puberty (PP), café au lait spots and fibrous dysplasia of bone. PP is the most common endocrinological manifestation of this rare disease and is much more common in girls than in boys. The treatment options for PP associated with MAS have evolved over the last twenty plus years. Therapy in girls typically includes the use of an anti-estrogen, while treatment options in boys include an antiandrogen in combination with an aromatase inhibitor (AI). This article will briefly review the older therapies and explain why they have largely been supplanted by newer approaches. We will discuss current pharmacotherapy options for the treatment of PP in MAS and finally describe potential novel therapies that will hopefully enable optimal care for affected patients.

28. Rudd, B.T. "Precocious and delayed sexual development in children." *Acta endocrinologica* 288 (1988): 66-76.

Abstract

A review is presented of tests used to diagnose either isosexual precocity or delayed pubertal development in children. The importance of auxological measurements is emphasised. Attention is drawn to the limitations of measuring basal or stimulated levels of LH, FSH and the sex steroids for the diagnosis of these conditions. The value of gonadotropin profiles is discussed for either diagnosis or for assessing the response to GnRH therapy in patients with either isosexual precocity or isolated gonadotropin deficiency. Examples are given of new therapeutic agents and procedures that are used to treat these two groups of patients. These include GnRH agonists for treatment of children with isosexual precocity either alone, or in combination with inhibitors of aromatase or C17-20 lyase enzyme activity in the biosynthesis of the sex steroids and pulsatile GnRH for the treatment of adolescents with gonadotropin deficiency.

29. Sawathiparnich, P., P. Osuwanaratana, J. Santiprabhob, and S. Likitmaskul. "Tamoxifen improved final height prediction in a girl with McCune-Albright syndrome: patient report and literature review." *Journal of Pediatric Endocrinology & Metabolism* 19.1 (2006): 81-86.

Abstract

McCune-Albright syndrome (MAS) is characterized by gonadotropin-independent precocious puberty, café-au-lait spots on the skin and polyostotic fibrous dysplasia of bones. Treatment of precocious puberty (PP) in MAS should be considered in patients with poor predicted adult height (PAH). Treatment of gonadotropin-independent PP in MAS with ketoconazole, cyproterone acetate or testolactone, an aromatase inhibitor, does not appear to be always effective in slowing bone maturation. We report here a Thai girl with MAS who received tamoxifen, one of the selective estrogen receptor modulators, for the management of advanced puberty and rapid bone maturation. Her pubertal progression, vaginal bleeding, growth rate and PAH improved during treatment with tamoxifen despite persistently elevated serum estradiol levels and an enlarged ovarian cyst.

30. Wickman, S., I. Sipilä, C. Ankarberg-Lindgren, E. Norjavaara, and L. Dunkel. "A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomised controlled trial." *The Lancet* 357.9270 (2001): 1743-1748.

Abstract

BACKGROUND: The role of oestrogens in the closure of growth plates in both sexes is unequivocal. We postulated that inhibition of oestrogen synthesis in boys with delayed puberty would delay maturation of the growth plates and ultimately result in increased adult height.

METHODS: We did a randomised, double-blind, placebo-controlled study in which we treated boys with constitutional delay of puberty with testosterone and placebo, or testosterone and letrozole. Boys who decided to wait for the spontaneous progression of puberty without medical intervention composed the untreated group.

FINDINGS: Letrozole effectively inhibited oestrogen synthesis and delayed bone maturation. Progression of bone maturation was slower in the letrozole group than in the placebo group. In 18 months, bone age had advanced 1.1 (SD 0.8) years in the untreated group and 1.7 (0.9) years in the group treated with testosterone and placebo, but only 0.9 (0.6) years in the letrozole group ($p=0.03$ between the treatment groups). Predicted adult height did not change significantly in the untreated group and in the placebo group, whereas in the group treated with letrozole the increase was 5.1 (3.7) cm ($p=0.004$).

INTERPRETATIONS: Our findings suggest that if oestrogen action is inhibited in growing adolescents, adult height will increase. This finding provides a rationale for studies that aim to delay bone maturation in several growth disorders.