Guidance for use of aromatase inhibitors (AI) to optimise linear growth and preserve final height

Authors: Pon R Gokul, Justin H Davies, Helen L Storr

BSPED Growth Disorders SIG:

Helen Storr (Chair)	Peter Clayton	Sally Majid
Justin Davies (Co-Chair)	Mehul Dattani	Rebecca Moon
Michal Ajzensztejn	Renuka Dias	Phil Murray
Karen Blair	Jonathan Fenwick	Reena Perchard
Jeff Bolton	Evelien Gevers	Alan Rice
Gary Butler	Sarah Harrington	Julia Russell
Simon Chapman	Pon Ramya Gokul	Pooja Sachdev
Jenny Child	David Lim	Jarod Wong

Review date: 2029

The aim of this **guidance** is to support clinicians considering using aromatase inhibitors (AI) for growth management in different clinical scenarios by summarising the evidence up to 2025. This is "**guidance**" not a guideline and due to the paucity of studies in this area, evidence-based standards of care cannot be provided. The guidance should be read in conjunction with *"Guidance for use of GnRHa to optimise linear growth and final height",* weblink below.

Background

Height may be optimised for selected growth disorders and endocrine conditions by delaying skeletal maturation using a gonadotropin-releasing hormone analogue (GnRHa) or aromatase inhibitor (AI). Use of GnRHa and AI may allow additional time to promote linear growth by reducing growth plate exposure to oestrogens and delaying epiphyseal fusion. These agents are often used in combination with recombinant human growth hormone (rhGH). The decision to use either GnRHa or AI is individualised. This guidance addresses the use of AI for optimising linear growth.

In males and females, oestrogen mediates epiphyseal fusion and cessation of linear growth. Oestrogen is synthesised by the aromatisation of androgens to oestrogen. AIs block aromatisation and reduce exposure of the epiphyses to oestrogen. AIs may improve linear growth and adult height (AH) by delaying epiphyseal fusion to allow additional time for linear growth. The AIs anastrazole and letrozole have inhibitory potency of 97% and 99% respectively [1].

Studies of AI for growth have been undertaken in pubertal boys. The use of AIs to improve growth in girls has been avoided due to their potential to cause ovarian cysts with associated risk of ovarian torsion. In contrast to boys, use of AIs in girls will delay pubertal progression; and the expected increase in androgens during treatment may cause acne and hirsutism. However, AIs are still recommended in girls for the management of hyperoestrogenism secondary to McCune-Albright syndrome [2].

Although the use of AIs for growth management is off label, in certain situations AIs may still be offered.

We recommend that AIs should be prescribed by clinicians with specialist expertise in growth management and led by a lead specialist centre in paediatric endocrinology.

AIs have been used in two broad clinical scenarios:

1. To optimise linear growth and final adult height in *male* pubertal children and adolescents with short stature and/or constitutional delay of growth and puberty [3,4,5].

2. To preserve linear growth potential in disorders leading to advanced skeletal maturation from hyperandrogenism or hyperoestrogenism.

There are separate BSPED guidance/clinical standards available for:

- Guidance for use of GnRHa to optimise linear growth and final height https://www.bsped.org.uk/media/zimnlizo/gnrha-document-final-280126.pdf
- Shared Care Guidelines: Use of Gonadotrophin Releasing Hormone (GnRH) Agonists https://www.bsped.org.uk/media/1978/gnrh-agonists-shared-care-guidelines-final-version-march-2022.pdf
- Shared care guidelines for GH therapy

https://www.bsped.org.uk/media/alxow2wv/gh-shared-care-guidelines-20240206.pdf

- Standards for GH treatment for GHD https://www.bsped.org.uk/media/iczlv32f/clinical-standards-for-gh-treatment-of-ghd-in-childhood-and-adolescence-v1.pdf
- Standards for GH treatment for other growth disorders excluding GHD https://www.bsped.org.uk/media/kfnh1unq/clinical-standards-for-gh-treatment-of-growth-disorders-excluding-ghd-19122023.pdf

1. Clinical assessment and investigations prior to commencing AI therapy

- History: birth weight, growth trajectory, if features of early puberty establish onset and progress
- Examination: height, weight, BMI, height velocity, pubertal staging, mid-parental height, and target height range
- Investigations:
  - Basal LH, FSH, oestradiol, testosterone, liver profile, fasting lipid profile (including cholesterol and HDL), FBC
  - Bone age
  - DXA and vertebral fracture assessment (VFA)
- Discuss with patient and caregivers:
  - Explanation of off-label use of AI
  - The option of not intervening
  - Evidence base
  - Potential benefits, risks, long-term safety profile unknown, and efficacy of therapy
  - Side effects (see **Appendix 1**)
  - Potential risks of AI which include:
    - Reduced bone mineral density and vertebral fracture
    - Hirsutism, acne (girls)

        - Dyslipidaemia
        - Insulin insensitivity
        - Increased haematocrit
        - Liver dysfunction
        - Possible impact on fertility†
    - Document discussion in the clinical notes
    - Consider capturing outcome data e.g. use of iCAH registry for children with CAH

†Long term follow-up of children treated with AI reported no infertility issues however, extensive long term reproductive safety data are lacking and requires further research [6] .

2. Eligibility considerations

AIs are not recommended for:

- Growth management in girls
- In prepubertal children
- In individuals with:
    - Advanced pubertal development (≥Tanner stage 4)
    - Advanced bone age indicating limited further growth potential
    - Approaching final or near final height (HV <2cm/yr in the preceding 6 months)
- At a chronological age where delaying puberty further would be considered inappropriate considering the length of treatment course needed

3. Dose

- Anastrozole 1 mg orally once daily
- Letrozole 2.5 mg orally once daily

Treatment duration will depend on the clinical indication, response, tolerability, side effects and predicted growth outcome.

4. Monitoring on AI therapy

- 6-monthly:
    - Clinical assessment: height, weight, height velocity, pubertal stage
    - Side effect enquiry including hirsutism*, acne*, nausea, headache, bone pain, abdominal pain, alopecia*
    - Biochemical: LH, FSH, oestradiol*, testosterone*, LFT, lipids, FBC, haematocrit
- Annual:
    - Bone age (BA)
    - DXA and vertebral fracture assessment**

*AIs can cause reduced oestradiol and marked elevation (~50%) in testosterone levels, however, these are usually within the normal range.
** Monitoring recommended as AIs may negatively impact bone health (from lower oestrogen levels) which may lead to lower bone density and potentially (vertebral) fractures. [7,8,9]

5. Discontinuation of AI therapy

AI treatment should be stopped if the patient:

- Reaches predicted adult height (PAH)
- Achieves near adult height with a height velocity <2cm/year
- Side effects not tolerated
- Has a low lumbar z-score (<-2.0 SDS) and/or vertebral fracture [10].

6. Clinical scenarios where AI therapy may be considered to optimise linear growth and final adult height in pubertal *male* children and adolescents with residual height potential

Interpretation of studies using AIs for growth is complicated by selection bias, lack of comparison with untreated controls, use of predicted adult height (PAH) rather than adult height (AH), limited AH data and few studies. Published data report acceptable safety profiles but further longitudinal studies are needed to determine the safety profile of AIs used in this context.

i. Idiopathic short stature (ISS) in pubertal males

A Cochrane review in 2015 [3] found there was insufficient data to conclude that AIs improve AH. However, in selected cases of ISS AIs are sometimes considered.

A randomised control trial (RCT) in peripubertal boys with ISS and 2 years treatment with letrozole vs placebo found an increase of 5.9 cm PAH [11]. However, when participants were followed up no increase in AH was found [12] .

In a pilot study using historical controls, others found a significant increase (~ mean 4.2cm) in near adult height using anastrazole in combination with rhGH when compared to rhGH alone for ISS [13].

Use of AI (anastrazole or letrozole) with/without rhGH for boys in early puberty with ISS showed mean height gains at near adult height (NAH) of 5.2 cm (AI), 7.6 cm (rhGH) and 9.5 cm (rhGH with AI) [14]. Others have found use of letrozole as a monotherapy to improve height in ISS was ineffective [12].

Other studies have assumed the effects on growth of anastrazole and letrozole are similar despite known differences in their relative potencies [14]. One study found greater improvements in PAH with anastrazole compared to letrozole, but AH data was not available [15].

ii. Constitutional delay of growth and puberty (CDGP) in pubertal males

A RCT of letrozole in boys with CDGP suggested an improvement in near adult height (NAH) [16] but AH was not reported. Others found letrozole significantly increased PAH in boys with CDGP [17] or NAH when used in combination with testosterone [18]. AH data was not presented.

iii. Growth hormone deficiency (GHD) in pubertal males

A RCT using anastrazole vs placebo for 3 years in adolescent boys treated with rhGH for GHD, found co-treatment with anastrazole delayed skeletal maturation without affecting pubertal progression [19]. AH was not reported.

Summary recommendations for AI use for growth in pubertal males

- *AI therapy may be considered to improve height outcomes in pubertal boys with residual height potential in:*
    - *ISS – as monotherapy or in combination with rhGH*
    - *CDGP - as monotherapy or in combination with testosterone*
    - *GHD - in combination with rhGH*
- *More data are needed to determine efficacy (AH) and safety profiles*

7. Clinical scenarios where AI therapy may be considered to preserve linear growth potential in disorders leading to advanced skeletal maturation from hyperandrogenism or hyperoestrogenism

i. HYPERANDROGENISM

a. Congenital adrenal hyperplasia (CAH)

- *21-hydroxylase deficiency (21-OHD)*

Combined therapy with GnRHa, rhGH, and anastrozole significantly improved AH in children with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency and gonadotrophin-dependent precocious puberty (GDPP). In seven treated patients, rhGH dose 0.15-0.20 IU/kg/day and anastrozole (1 mg/d) PAH improved from-3.01 SDS to-0.28 SDS, with AH reaching-0.28 SDS, closely matching target height and significantly exceeding initial PAH ($P < 0.001$). The treatment was well tolerated and effective in mitigating bone age advancement and height compromise [20].

Anastrozole therapy in children with CAH due to 21-hydroxylase deficiency and a BA >2 years ahead of chronological age, significantly improved height outcomes over a 6-year period. In 60 patients, bone age Z-scores decreased from 4.2 to 1.3, predicted adult height Z-scores improved from-2.1 to 0.18, and height corrected for bone age improved from-1.7 to 0.18 ($p < .001$). Anastrozole (1 mg/day) was added to each patient's standard hydrocortisone regimen, with fludrocortisone included if salt-wasting was present. Treatment was stopped once bone age reached 14 years in girls and 16 years in boys. Hydrocortisone doses remained unchanged, and elevated androgen

levels were tolerated. PAH Z-score improved from-2.1 to-0.45 at 4 years and 0.18 at 6 years (both p <0.001); corrected height Z-scores improved from-1.7 to-0.33 at 4 years and 0.18 at 6 years (p <0.001) [21].

- *Non-classical CAH (NC-CAH)*

Mild cases of NC-CAH often do not require intervention for growth and there are limited studies of the use of AI for growth. Anastrozole monotherapy was used in three female children with NC-CAH, advanced BA, and early pubarche but normal cortisol response and no genital virilization. Treatment with anastrazole 1mg began at ages 3.7, 3.9, and 6.7 years, with initial bone age Z-scores of 6.4, 1.9, and 2.9, respectively. At therapy completion, bone age Z-scores decreased to-0.75, 0.52, and-0.07, and all patients reached or exceeded their target height. Pubertal progression, ovarian ultrasounds, and bone mineral density remained normal. This case series suggests anastrozole monotherapy may be an option to slow bone maturation and improve height outcomes in children with NC-CAH and normal adrenal function [22].

- *11-beta hydroxylase deficiency (11-BOHD)*

There is anecdotal use of AIs for optimising growth in 11-BOHD as monotherapy (letrozole) [23] or in combination with rhGH (anastrazole) [24].

b. Testotoxicosis

Testotoxicosis is a familial male-limited rare cause of gonadotropin-independent precocious puberty (GIPP) caused by an activating mutation of the luteinising hormone receptor gene. It is characterised by virilisation, rapid linear growth, tall stature for age, significantly advanced skeletal maturation leading to short AH. Combination treatment with anastrozole and bicalutamide has been used to ameliorate the effects of hyperandrogenism and improve growth outcome [25]. AI given in combination with an anti-androgen and a GnRHa have been used for growth management of testotoxicosis [26].

ii. HYPEROESTROGENISM

- McCune-Albright syndrome (MCAS)

Hyperoestrogenism, secondary to functioning ovarian cysts, causes gonadotrophin-independent precocious puberty (GIPP) and is a feature of MCAS. Ovarian surgery in MCAS should be avoided unless there is a significant risk of torsion.

Best practice recommendations are that treatment with letrozole should be offered if there is advanced bone age and recurrent vaginal bleeding [2]. Height outcome is improved only if treatment is started <6 years of age [2]. If letrozole is commenced, monitoring for progression into GDPP is necessary to assess whether GnRHa therapy should be added.

- Other endocrine conditions causing hyperoestrogenism where AIs have been used but with limited evidence:

    a. Aromatase excess syndrome [27.28]
    b. Peutz-Jeghers syndrome [29]
    c. Recurrent functional follicular ovarian cysts [29]

Summary recommendations for AI use in conditions causing sex hormone excess

- *AI therapy may be considered on a case-by-case basis*
- *Data are limited to justify intervention emphasising the requirement for a discussion with caregivers (see Section 1)*
- *More data are needed to determine efficacy of AI and safety profiles for these indications*

References:

1. Wang K, Ye F, Wang DY, Lai PJ, Zhang LQ. Aromatase inhibitors for short stature in male children and adolescents treated with growth hormone: A meta-analysis of randomized controlled trials. BMC Pediatr. 2024;24(1):813.
2. Javaid MK, et al. Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: A consensus statement from the FD/MAS international consortium. Orphanet J Rare Dis. 2019;14(1):139.
3. McGrath N, O'Grady MJ. Aromatase inhibitors for short stature in male children and adolescents. Cochrane Database Syst Rev. 2015;(10):CD010888.
4. Zhang Y, Yuan X, McCormick K, Yang XH, Chen SJ, Chen RM. The efficacy and safety of RhGH treatment combined with Letrozole/GnRHa in adolescent boys. BMC Pediatr. 2025;25(1):59.
5. Hero M. Aromatase inhibitors in the treatment of short stature. Adv Ther Pediatr Endocrinol Diabetol. 2016;30:130–140. doi:10.1159/000439338.
6. Giannopoulou EZ, et al. Long term effects of aromatase inhibitor treatment in patients with aromatase excess syndrome. Front Endocrinol (Lausanne). 2024;15:1487884.
7. UpToDate. Evaluation and management of aromatase inhibitor-induced bone loss. Available from: https://www.uptodate.com/contents/evaluation-and-management-of-aromatase-inhibitor-induced-bone-loss
8. IJCRT Review. Aromatase inhibitor-induced bone loss and its management. Available from: https://ijcrt.org/papers/IJCRT2507712.pdf
9. Wiley MiniReview. The effect of aromatase inhibitors on bone metabolism. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1742-7843.2008.00337.
10. Cui Y, Zhang Q, Hou L, Luo X. The combination of aromatase inhibitors and growth hormone treatment for idiopathic short stature in male adolescents. J Clin Endocrinol Metab. 2025. doi:10.1210/clinem/dgaf271.
11. Hero M, Norjavaara E, Dunkel L. Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: A randomized controlled trial. J Clin Endocrinol Metab. 2005;90:6396–6402.
12. Varimo T, et al. Letrozole monotherapy in pre- and early-pubertal boys does not increase adult height. Front Endocrinol (Lausanne). 2019;10:201. doi:10.3389/fendo.2019.00201.

13. Rothenbuhler A, Linglart A, Bougneres PA. A randomized pilot trial of growth hormone with anastrozole versus growth hormone alone starting at the very end of puberty in adolescents with idiopathic short stature. Int J Pediatr Endocrinol. 2015;2015:4.
14. Mauras N, et al. Randomized trial of aromatase inhibitors, growth hormone, or combination in pubertal boys with idiopathic short stature. J Clin Endocrinol Metab. 2016;101(12):4984–4993.
15. Neely EK, et al. Letrozole vs anastrozole for height augmentation in short pubertal males: First year data. J Clin Endocrinol Metab. 2014;99(11):4086–4093. doi:10.1210/jc.2014-2432.
16. Wickman S, Dunkel L. Novel treatment of delayed male puberty with aromatase inhibitors. Horm Res. 2002;57(Suppl 2):44–52.
17. Salehpour S, et al. A double-blind, placebo-controlled comparison of letrozole to oxandrolone effects upon growth and puberty of children with constitutional delay of puberty and idiopathic short stature. Horm Res Paediatr. 2010;74:428–435.
18. Hero M, Wickman S, Dunkel L. Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. Clin Endocrinol (Oxf). 2006;64(5):510–513.
19. Mauras N, et al. Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: A randomized, placebo-controlled, multicenter trial for one to three years. J Clin Endocrinol Metab. 2008;93(3):823–831. doi:10.1210/jc.2007-1559.
20. Liu X, et al. Combination therapy of GnRHa, RhGH and anastrozole to improve final adult height deficit in CAH children with CPP. BMC Pediatr. 2025;25(1):362. doi:10.1186/s12887-025-05703-8.
21. Al-Rayess H, et al. Anastrozole improves height outcomes in growing children with congenital adrenal hyperplasia due to 21-OHD. J Clin Endocrinol Metab. 2025. [Epub ahead of print]
22. Liu SC, et al. Case report: Anastrozole as a monotherapy for pre-pubertal children with non-classic congenital adrenal hyperplasia. Front Endocrinol. 2023;14:1101843.
23. Atay Z, et al. Restoration of height after 11 years of letrozole treatment in 11β-hydroxylase deficiency. Horm Res Paediatr. 2019;92(3):203–208. doi:10.1159/000501456.
24. Hawton K, et al. Growth hormone with aromatase inhibitor may improve height in CYP11B1 congenital adrenal hyperplasia. Pediatrics. 2017;139(2):e20160730. doi:10.1542/peds.2016-0730.
25. Kreher NC, et al. Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. J Pediatr. 2006;149(3):416–420. doi:10.1016/j.jpeds.2006.04.027.
26. Leschek EW, et al. Effect of antiandrogen, aromatase inhibitor, and gonadotropin-releasing hormone analog on adult height in familial male precocious puberty. J Pediatr. 2017;190:229–235.
27. Binder G, et al. Long-term effect of aromatase inhibition in aromatase excess syndrome. J Clin Endocrinol Metab. 2021;106(5):1491–1500. doi:10.1210/clinem/dgab054.
28. Simões-Pereira J, et al. Prepubertal gynaecomastia in a boy with Peutz-Jeghers syndrome: Managing the aromatase overexpression. J Pediatr Endocrinol Metab. 2018;31(10):1149–1154. doi:10.1515/jpem-2017-0455.
29. Wit JM, Hero M, Nunez SB. Aromatase inhibitors in pediatrics. Nat Rev Endocrinol. 2012;8:135–147. https://doi.org/10.1038/nrendo.2011.161

Appendix 1

Anastrozole – Side Effects in Paediatric Use

Frequent

- Joint pain
- Hot flashes
- Headache
- Nausea and vomiting
- Bone pain
- Insomnia
- Weakened bones (reduced bone mineral density)

Less Frequent

- Increased blood pressure
- Depression
- Rash
- Arthritis

Rare

- Liver enzyme abnormalities
- Severe allergic reactions (e.g., anaphylaxis – very rare)

Letrozole – Side Effects in Paediatric Use:

Frequent

- Fatigue
- Muscle aches
- Headache
- Nausea and vomiting
- Diarrhoea or constipation
- Chest pain
- Decreased bone mineral density (risk of osteoporosis and fractures)

Less Frequent

- Weight gain
- Hair thinning
- Increased cholesterol levels

Rare

- Liver dysfunction
- Severe cardiovascular events (rare but monitored)