THE AUSTRALASIAN PAEDIATRIC ENDOCRINE GROUP: TOP FIVE RECOMMENDATIONS ON LOW VALUE PRACTICES

The Australasian Paediatric Endocrine Group (APEG) is the premier professional body representing paediatric endocrinology in Australasia. APEG is committed to high standards of clinical care, advocacy, education, stakeholder relationships, and research in paediatric endocrinology. It is a specialty society affiliated with the Royal Australasian College of Physicians.

1. Do not rely on random measures of circadian hormones for diagnostic purposes

Numerous hormones, such as growth hormone and testosterone, are subject to circadian rhythms. Relying on random measures of these hormones is therefore of limited diagnostic utility as their levels may peak and plateau at particular times throughout the day. Unless adjustments are made to take account of these circadian rhythms then random readings will not be sufficiently informative.

Supporting Evidence

- Ayling J. More guidance on growth hormone deficiency. *J Clin Pathol.* 2004; 57(2): 123–125.
- Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The Effect of Diurnal Variation on Clinical Measurement of Serum Testosterone and Other Sex Hormone Levels in Men. *The Journal of Clinical Endocrinology and Metabolism.* 2009; 94(3):907–913.
- Hawkes C, Grimberg A. Measuring Growth Hormone and Insulin-like Growth Factor-I in Infants: What is Normal? *Pediatr Endocrinol Rev.* 2013; 11(2): 126–146.

2. Do not rely solely on bone age measurement for assessing growth in young children with short stature under 2 years of age

There is no consensus protocol on bone-age assessment of younger children and infants, particularly those under the age of two. Skeletal growth and maturation is most rapid in infants and toddlers, so accurate bone-age assessment in these children is challenging.

Of the bone-age measurement techniques available, there is a major inadequacy with one of the most used methods: the limited change in the appearance of the ossification centres of the hand/wrist change in the first months of life. A recent survey found much lower rates of confidence in the accuracy of this technique when applied to the one-to-three-year-old group. Although a recently reported and validated bone-age measurement technique based on fibular shaft length was found to outperform other methods, it still yielded significant errors when applied to infants (i.e. under one year).

Supporting Evidence

- Breen, M.A., Tsai, A., Stamm, A. et al. Bone age assessment practices in infants and older children among Society for Pediatric Radiology members. *Pediatr Radiol* (2016) 46: 1269.
- Tsai A, Stamoulis C, Bixby SD, et al. Infant bone age estimation based on fibular shaft length: model development and clinical validation. *Pediatr Radiol* (2016) 46:342–356.

3. Do not routinely measure insulin-like growth factor binding protein 3 (IGFBP-3) for workup and diagnosis of childhood short stature

Particularly given its low sensitivity, insulin-like growth factor binding protein 3 (IGFBP-3) does not significantly contribute to the diagnosis of childhood short stature resulting from growth-hormone deficiency (GHD), which can lead to the under identification of GHD. It should therefore not be used as a routine measure for the workup and diagnosis of children with short stature. However, IGFBP-3 testing may have a role, along with IGF-1 testing, as an auxiliary diagnostic index for provocative testing.

Supporting Evidence

- Boquete HR, Sobrado PG, Fideleff HL, et al. Evaluation of diagnostic accuracy of insulin-like growth factor (IGF)-I and IGF-binding protein-3 in growth hormone-deficient children and adults using ROCplot analysis. *J Clin Endocrinol Meta* 2003; 88:4702–8
- Cianfarani S, Liguori A, Boemi S, Maghnie M, et al. Inaccuracy of insulin-like growth factor (IGF) binding protein (IGFBP)-3 assessment in the diagnosis of growth hormone (GH) deficiency from childhood to young adulthood: association to low GH dependency of IGF-II and presence of circulating IGFBP-3 18-kilodalton fragment. *J Clin Endocrinol Metab.* 2005;90(11):6028–34.
- Shen Y, Zhang J, Zhao Y, et al. Diagnostic value of serum IGF-1 and IGFBP-3 in growth hormone deficiency: a systematic review with meta-analysis. *Eur J Pediatr.* 2015;174(4):419–27.

4. Do not initiate gonadotropin-releasing hormone (GnRH) analogue treatment in children outside of central precocious puberty, for the target outcome of delaying puberty and improving final adult height

While there is some evidence that the use of GnRH agonists can achieve improvements in height in females with early puberty, it is also associated with the development of polycystic ovary syndrome (PCOS) in adolescence and risks compromising bone health. Its use outside of clinical trials is not recommended. Given that the treatment duration must also be lengthy for its benefits to be manifested, its use is not recommended to augment height in adolescents with short stature and normally timed puberty.

Supporting evidence

- Chiavaroli V, Liberati M, D'Antonio F, et al. GnRH analog therapy in girls with early puberty is associated with the achievement of predicted final height but also with increased risk of polycystic ovary syndrome. *Eur J Endocrinol.* 2010;163(1):55–62.
- Dunkel L, Treatment of idiopathic short stature: effects of gonadotropin-releasing hormone analogs, aromatase inhibitors and anabolic steroids, *Horm Res Paediatr.* 2011;76 Suppl 3:27–9.
- Wit M, Visser-van Balen H, Kamp GA, Oostdijk W. Benefit of postponing normal puberty for improving final height. *European Journal of Endocrinology* 2004;151:S41–S45
- Yanovski JA, Rose SR, Municchi G, et al. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med.* 2003; 348(10):908–17.

5. Do not routinely prescribe aromatase inhibitors to promote growth in children with short stature

Aromatase inhibitors are used as adjuvant therapy for breast cancer. There is growing acceptance of their use to increase the adult height of children with short stature and some evidence that aromatase inhibitors can at least improve short-term growth outcomes. One recent clinical trial of aromatase inhibitors used in paediatric patients found them to be safe and effective. Even so, there is still little evidence overall that this treatment improves final adult height or is sufficiently safe. A 2015 Cochrane review found a significant proportion of pre-pubertal boys undergoing this treatment suffered mild morphological abnormalities of their vertebrae. More evidence is needed to demonstrate safety and efficacy of aromatase inhibitors before they can be routinely prescribed to promote growth in children with short stature.

Supporting evidence

- Diaz-Thomas A, Shulman D. Use of aromatase inhibitors in children and adolescents: what's new? Curr Opin Pediatr. 2010; 22(4):501–7.
- Mauras N, Ross JL, Gagliardi P, et al. Randomized trial of aromatase inhibitors, growth hormone or combination in pubertal boys with idiopathic short stature. J Clin Endocrinol Metab. 2016; 6:jc20162891.
- McGrath N, O'Grady MJ. Aromatase inhibitors for short stature in male children and adolescents. Cochrane Database of Systematic Reviews 2015; 10: CD010888..
- Wit JM, Hero M, Nunezs SB. Aromatase inhibitors in paediatrics, Nature Reviews Endocrinology. 2012;8:135–147.

How was this list created?

A working group of lead clinicians from APEG brainstormed an initial list of 11 low-value practices in paediatric endocrinology and a preliminary review of the evidence for each was undertaken. An online survey was developed based on these 11 recommendations along with a summary of the evidence for each, and circulated to APEG members for their feedback. For each recommendation, respondents were asked to assign a score from 1 to 5 (where 1 = strongly disagree and 5 = strongly agree) on two criteria: 'The recommendation is evidence based' and 'The recommendation is relevant to paediatric endocrinology in Australasia'. Based on the recommendations which received the highest average total scores, and after a final in-depth review of the related evidence, the final top five were chosen and approved by APEG.