

Grand Rounds: The use of GnRH analogs beyond precocious puberty

Erica A Eugster, MD

*Department of Pediatrics, Section of Pediatric Endocrinology, Riley Hospital for Children,
Indiana University School of Medicine, Indianapolis, IN*

Abbreviated Title: GnRH analogs beyond precocious puberty

Key words: use, GnRH analogs, precocious puberty

Abbreviations: GnRHa, CPP

Disclosure statement: The author has nothing to disclose. Dr. Jack Fuqua (acknowledgments section) has nothing to disclose.

Corresponding authors contact information:

Dr. Erica A. Eugster
Riley Hospital for Children #5960
705 Riley Hospital Drive
Indianapolis, IN 46202
317 944-3889
317 944-3882
eeugster@iu.edu

This is the author's manuscript of the article published in final edited form as:
Eugster, E. A. (2015). The Use of Gonadotropin-Releasing Hormone Analogs beyond Precocious Puberty.
The Journal of Pediatrics, 167(2), 481–485. <http://doi.org/10.1016/j.jpeds.2015.05.031>

Case: A 9 year 3 month old girl is referred for concerns about early puberty. Her mother reports progressive breast development for at least a year along with adult body odor requiring deodorant use for the past 6 months. The mother has not noted any body hair, vaginal discharge or bleeding, but states that her daughter has been rapidly outgrowing shoes and clothing. There is no history of exogenous hormone exposure, and the child has otherwise been healthy. Past medical history reveals that the child was born at term with a birth weight of 7# 5oz and a length of 20 inches. Family history reveals that the mother is 5'3" and had menarche at age 12. The father is 5'7" and was an average age at the onset of puberty. The child is an honor-roll student in the 4th grade and lives at home with her parents and 6 year old brother. Review of systems reveals increased "moodiness" and is otherwise non-contributory. On physical exam, height is 140 cm (86th percentile) and weight is 44 kg (97th percentile). BMI is 22.4 kg/m² (96th percentile, z-score 1.75). HEENT exam reveals a normal thyroid to palpation. Breasts are Tanner stage III-IV and no axillary hair is noted. GU exam reveals a normal female with pubic hair Tanner stage II and an estrogenized vaginal mucosa. A bone age x-ray is advanced at 12 years giving the child a predicted adult height (using the average Bayley-Pinneau Table)(1) of ~59", compared with her target height of 62.5". Having heard that early puberty will "stunt growth," and concerned about her daughter's ability to handle having periods, the mother requests that her child be treated to suppress puberty.

Introduction

This case represents a common reason for referral to the pediatric endocrine clinic. Although this child is within the normal range for the onset of puberty in girls, she has clearly had a rapid tempo of progression, and now has what is often characterized as a "poor" prognosis for adult height. Additional concerns include potential negative psychological consequences of being an early bloomer along with apprehensions about menarche, which seems imminent. The referral

by her primary care pediatrician is based on the presumption that stopping puberty will alleviate these concerns. What is the evidence to support or refute this hope?

Development of the long-acting analogs of gonadotropin releasing hormone (GnRHAs) in the 1980's revolutionized the treatment of central precocious puberty (CPP) worldwide (2-6). Since the advent of these drugs as first-line therapy for CPP, a plethora of GnRHAs have been developed that utilize different routes of administration, employ unique delivery systems and have varying durations of action (7, 8). Given the undisputed success of GnRHAs in the setting of CPP, it is not surprising that there has been sustained interest in the potential for their use beyond precocious puberty. Indeed, continued linear growth well into young adulthood has long been recognized as a hallmark of untreated hypogonadotropic hypogonadism (9). Thus, the idea of rendering a child with normally timed puberty pharmacologically hypogonadal for the purposes of increasing adult height seems logical. Unfortunately, despite the anticipated benefit of putting puberty temporarily on hold in settings other than CPP, a meaningful increase in height has not generally been borne out by the studies conducted to date. Even among girls with CPP, a predictable and significant increase in adult stature occurs only in those who are treated at ≤ 6 years, while those treated at between 6-8 years have a variable outcome(10). In contrast, no benefit in terms of height has been seen from the use of GnRHAs in girls with CPP who are ≥ 8 years (11, 12). Outside of precocious puberty, GnRHa treatment has also been investigated for use in children with short stature/poor predicted adult height, growth hormone deficiency, congenital adrenal hyperplasia, and profound primary hypothyroidism, in all cases also with the goal of increasing adult height. This paper will review the experience using GnRHAs in each of these clinical situations with a focus on efficacy, safety and the risk/benefit ratio. An additional important consideration is the high cost of GnRHAs, which approximate ~\$20-\$40k for two years of

treatment. Although beyond the scope of this review, GnRHAs have been prescribed for considerations other than increasing height in children with developmental delay, gender dysphoria and in those undergoing genotoxic chemotherapy.

GnRHAs in Short Stature/Poor Predicted Adult Height

The most frequently explored indication for GnRHa therapy beyond precocious puberty has been in otherwise healthy children with a variety of forms of short stature or poor predicted adult height, as in our Case (13). Patient subgroups have included children with idiopathic/genetic short stature, those born small for gestational age, with early fast puberty and adopted girls. Several studies have been conducted during the last 20 years. Some of these have employed GnRHAs as monotherapy while others have investigated the combination of GnRHAs and growth hormone (GH) used simultaneously. Most sample sizes have ranged from <10-~40, and the duration of treatment has typically been anywhere from 2 to 4 years (14-16). Common limitations of existing trials have been a retrospective design, failure to include a control group, and/or mixed populations of subjects. In notable contrast to many other studies, a placebo-controlled trial of GnRHAs in short adolescents with a variety of diagnoses was conducted, the results of which were published in 2003 (17). In this rigorously designed trial, 47 adolescents with a low predicted adult height received a GnRHa or placebo for 3.5 years and were followed until linear growth was complete. A subset of patients in each group were also treated with GH. Although a 4.2 cm increase above the initial predicted height was seen in the experimental group, a significant decrement in bone mineral density compared with control was also noted. Thus, the authors concluded that using GnRHAs to augment height in adolescents with normally-timed puberty is not a reasonable strategy.

Results from the combination of GnRHAs and GH in the setting of short stature have been mixed. However, few studies have been randomized and have followed children to adult height. While gains in height are often defined as the difference between predicted height at the start of treatment and achieved height, it is widely acknowledged that height prediction methods are flawed (18). Controlled studies have compared combination GnRHa and GH to either no treatment, GnRHa therapy alone or GH therapy alone. The heterogeneity in study design, along with the fact that the majority of treated subjects have been girls, renders it difficult to compare one trial to another and to derive firm conclusions. In studies to adult height, the benefit of combination therapy has ranged from 0-4 cm compared with controls and therefore even the most favorable outcomes have been of minimal magnitude (19-22). One of the arguably strongest studies undertaken to date randomly assigned 32 short adolescents with idiopathic short stature or born small for gestational age and early normal puberty to a GnRHa and GH or no treatment for 3 years. While treated children achieved an adult height that was 4.9 cm above that predicted at baseline, no difference in final height between groups was seen (23). That 50% of the predicted height gain at discontinuation of treatment was lost during follow-up in the experimental group illustrates that height predictions tend to over predict height in children with short stature and early normal puberty, justifying use of the “average” rather than “accelerated” height prediction tables as in our Case. This study also found a trend toward lower bone mineral density at the lumbar spine, albeit one that did not reach statistical significance. On balance, no clear rationale exists for the use of GnRHAs and GH in short children with on-time puberty.

GnRHAs in Growth Hormone Deficiency

Children with growth hormone deficiency (GHD), particularly those diagnosed late, have been another population of interest in which to study the effect of GnRHAs in addition to GH

to optimize adult height (24). A number of studies designed to address this possibility have been completed since the 1990's. Here again we find few randomized trials, small sample sizes and a dearth of data regarding adult height (25, 26). Studies reporting benefit that followed subjects to final height show an increase of ~1-2 standard deviation scores (SDS) in height in the combination treatment group compared with GH alone(27, 28). One such study randomized pubertal children with GHD to receive GH plus a GnRHa (n=7) or to receive GH alone (n=10) until a bone age of 14 was reached in girls and of 16 was reached in boys. After 3 years of combined therapy, the group treated with GH plus a GnRHa had a notable decrease in the rate of skeletal maturation that translated into a near final height SDS that was significantly higher than that in the GH treatment alone group (-1.3 vs -2.7, $p<0.05$)(29). While the experimental group was found to have a significantly lower bone mineral content at 3 years than subjects in whom physiologic puberty had been allowed to progress, the differences between groups had resolved by the time near final height was reached (30).

Regrettably, not all studies have demonstrated such positive results. A review of all patients with idiopathic GHD in the Kabi International Growth Study (KIGS) database who were also treated with GnRHAs and had attained adult height was performed (31). In fact, the 39 adolescents who had received combination therapy fared worse than the 1,893 treated with GH alone, with both boys and girls achieving a final height SDS below that reached by their counterparts who had gone through puberty normally. Given these conflicting results, it seems reasonable to conclude that the use of GnRHAs in this setting should be limited to large-scale, prospective clinical trials.

GnRHAs in Congenital Adrenal Hyperplasia

It has long been recognized that children with classic congenital adrenal hyperplasia (CAH) are at risk for a significant loss of height potential and ultimate short stature (32). Individual patient characteristics that confer a higher likelihood of advanced skeletal maturation and earlier epiphyseal fusion include late diagnosis, poor control of CAH and development of secondary CPP (33). Thus far, a very limited number of studies have explored whether the addition of a GnRHa, typically combined with GH (above and beyond the standard medical treatment of CAH), might ameliorate the height deficit in these patients. In one small study, 14 patients predicted to be >1 SD below their target height were treated with a GnRHa and GH for four years. They achieved an adult height that was 1 SDS greater than a matched untreated historical control group(34). A second non-randomized study by the same investigators offered GnRHa therapy as an adjunct to GH in children with CAH predicted to be short who had the onset of puberty at < age 10 in girls and < age 11 in boys. While an overall increase in achieved over baseline predicted adult height was seen, no difference in the outcome between those receiving a GnRHa and those treated with GH alone was found(35). At this point, there appears to be no rationale for the use of GnRHAs alone for the purpose of increasing adult height in children with CAH and normally-timed puberty(36).

Secondary CPP refers to the early onset of central puberty that develops during treatment of peripheral precocious puberty (PPP), particularly in children with significantly advanced skeletal maturation at the time of diagnosis. . Several small studies have demonstrated a significant improvement in adult height in children with CAH and secondary CPP who were treated with a GnRHa (37-40). However, none have been randomized prospective trials, which likely explains why routine use of GnRHAs to treat secondary CPP in children with CAH is not recommended by consensus guidelines (41). That being said, GnRHAs are commonly used to treat secondary CPP

in other rare forms of PPP such as familial male limited precocious puberty and McCune-Albright syndrome(42). Since the physiology and treatment of abnormally early central puberty on the background of PPP is unlikely to be substantially different from that of CPP alone, the suggestion that GnRHAs be prescribed in that situation only in the context of research is unlikely to be followed by clinicians and might be considered unduly restrictive.

GnRHAs in Profound Primary Hypothyroidism

A frequent consequence of longstanding severe hypothyroidism is a loss of height potential due to rapid bone age advancement that outpaces linear growth acceleration once treatment is initiated, particularly in peripubertal-aged children(43). Although GnRHa treatment has been postulated as one conceivable approach to prolong the opportunity for growth, most of the published reports in this area have been merely anecdotal (44-46). The studies that have been performed have been retrospective, and have failed to find any benefit from the addition of a GnRHa to levothyroxine in children with profound hypothyroidism (47, 48). Thus, there are insufficient data to conclude whether or not GnRHAs have a place in the therapeutic armamentarium of children presenting with severe primary hypothyroidism. Rather, they should be used only in the context of prospective trials which can ultimately be used to inform clinical management.

Safety and Psychological Concerns

GnRHAs have an excellent track record of safety in the setting of CPP and are tolerated without difficulty in the vast majority of children. The most common adverse events associated with monthly and extended release injectable formulations are local site reactions such as sterile abscess formation (49). Difficulty with implant localization or breakage is the most frequent issue

encountered with the subcutaneous histrelin implant, which requires a minor surgical procedure usually performed using local anesthesia. Nonetheless, one cannot infer that the same safety profile exists when these medications are prescribed in on-time puberty versus in CPP. Even short term administration of a GnRHa to healthy young men causes extreme alterations in body composition, protein synthesis and calcium kinetics (50, 51). Of at least equal importance is the psychological impact of artificially manipulating the sex steroid milieu during adolescence. It is striking that published information on this aspect of GnRHa therapy beyond precocious puberty is virtually nonexistent. To the contrary, concerns about negative psychological sequelae of allowing early-normal puberty to proceed unchecked are often voiced by parents and providers, and are likely based on the known association between high-risk behaviors and early maturation in girls (52). Whether treatment of on-time puberty with a GnRHa would alter this trajectory is unknown. Even among girls with CPP, no clear conclusions regarding psychological distress in either treated or untreated patients can be derived from existing studies (53, 54). This is an area in which more data are clearly needed.

Consensus and Current Practice

Cumulative experience to date regarding the effectiveness of GnRHAs in increasing height in children with normally timed puberty is summarized in the Table. A 2009 international consensus conference on GnRHAs concluded that their use in conditions other than CPP cannot be routinely suggested and that further investigation is needed (55). It is interesting to contemplate whether such position statements, which are based primarily on expert opinion, have any bearing on actual clinical practice. A review of GnRHa use at a large tertiary care center since 2009 revealed that nearly one-third of the 260 patients in whom it had been prescribed did not meet criteria for CPP (56). Likely reasons for this include physicians' anecdotal experiences of

perceived success in individual patients, and the pressure to “do something” when faced with a pubertal child whose height prediction falls well below the normal range. Since GnRHAs are being used in the clinical domain for conditions other than precocious puberty and are often covered by insurers, there seems little incentive to hold out for objective evidence from clinical trials. Nevertheless, a collective entreaty to the pediatric endocrine community to embark on such trials, if successful, would simultaneously advance scientific knowledge and improve patient care.

Acknowledgments: Dr. Jack Fuqua for his critical review of this manuscript

Reference List

- (1) Greulich W, Pyle S. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford University Press, Stanford, California; 1959.
- (2) Breyer P, Haider A, Pescovitz OH. Gonadotropin-releasing hormone agonists in the treatment of girls with central precocious puberty. *Clin Obstet Gynecol* 1993 Sep;36:764-72.
- (3) Carel JC, Ecosse E, Nicolino M, Tauber M, Leger J, Cabrol S, et al. Adult height after long term treatment with recombinant growth hormone for idiopathic isolated growth hormone deficiency: observational follow up study of the French population based registry.[comment]. *BMJ* 2002 Jul 13;325:70.
- (4) Heger S, Partsch CJ, Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions,

- body composition, bone mineral density, and reproductive function.[erratum appears in J Clin Endocrinol Metab 2000 Feb;85:657]. Journal of Clinical Endocrinology & Metabolism 1999 Dec;84:4583-90.
- (5) Klein KO, Barnes KM, Jones JV, Feuillan PP, Cutler GB, Jr. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. Journal of Clinical Endocrinology & Metabolism 2001 Oct;86:4711-6.
- (6) Mul D, Bertelloni S, Carel JC, Saggese G, Chaussain JL, Oostdijk W. Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: final height results. Hormone Research 2002;58:1-7.
- (7) Nebesio TD, Eugster EA. Current concepts in normal and abnormal puberty. Curr Probl Pediatr Adolesc Health Care 2007 Feb;37:50-72.
- (8) Fuqua JS. Treatment and outcomes of precocious puberty: an update. J Clin Endocrinol Metab 2013 Jun;98:2198-207.
- (9) Copeland KC, Paunier L, Sizonenko PC. The secretion of adrenal androgens and growth patterns of patients with hypogonadotropic hypogonadism and idiopathic delayed puberty. J Pediatr 1977 Dec;91:985-90.
- (10) Clemons RD, Kappy MS, Stuart TE, Perelman AH, Hoekstra FT. Long-term effectiveness of depot gonadotropin-releasing hormone analogue in the treatment of children with central precocious puberty. Am J Dis Child 1993 Jun;147:653-7.

- (11) Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. *J Clin Endocrinol Metab* 2007 Sep;92:3483-9.
- (12) Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, et al. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab* 2010 Jan;95:109-17.
- (13) Carel JC. Management of short stature with GnRH agonist and co-treatment with growth hormone: a controversial issue. *Mol Cell Endocrinol* 2006 Jul 25;254-255:226-33.
- (14) Bouvattier C, Coste J, Rodrigue D, Teinturier C, Carel JC, Chaussain JL, et al. Lack of effect of GnRH agonists on final height in girls with advanced puberty: a randomized long-term pilot study. *J Clin Endocrinol Metab* 1999 Oct;84:3575-8.
- (15) Carel JC, Hay F, Coutant R, Rodrigue D, Chaussain JL. Gonadotropin-releasing hormone agonist treatment of girls with constitutional short stature and normal pubertal development. *J Clin Endocrinol Metab* 1996 Sep;81:3318-22.
- (16) Lazar L, Kauli R, Pertzalan A, Phillip M. Gonadotropin-suppressive therapy in girls with early and fast puberty affects the pace of puberty but not total pubertal growth or final height. *J Clin Endocrinol Metab* 2002 May;87:2090-4.
- (17) Yanovski JA, Rose SR, Municchi G, Pescovitz OH, Hill SC, Cassorla FG, et al. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med* 2003 Mar 6;348:908-17.

- (18) Topor LS, Feldman HA, Bauchner H, Cohen LE. Variation in methods of predicting adult height for children with idiopathic short stature. *Pediatrics* 2010 Nov;126:938-44.
- (19) Balducci R, Toscano V, Mangiantini A, Municchi G, Vaccaro F, Picone S, et al. Adult height in short normal adolescent girls treated with gonadotropin-releasing hormone analog and growth hormone. *J Clin Endocrinol Metab* 1995 Dec;80:3596-600.
- (20) Mul D, Oostdijk W, Waelkens JJ, Drop SL. Final height after treatment of early puberty in short adopted girls with gonadotrophin releasing hormone agonist with or without growth hormone. *Clin Endocrinol (Oxf)* 2005 Aug;63:185-90.
- (21) Pasquino AM, Pucarelli I, Roggini M, Segni M. Adult height in short normal girls treated with gonadotropin-releasing hormone analogs and growth hormone. *J Clin Endocrinol Metab* 2000 Feb;85:619-22.
- (22) Tuvemo T, Jonsson B, Gustafsson J, Albertsson-Wikland K, Aronson AS, Hager A, et al. Final height after combined growth hormone and GnRH analogue treatment in adopted girls with early puberty. *Acta Paediatr* 2004 Nov;93:1456-62.
- (23) van Gool SA, Kamp GA, Visser-van BH, Mul D, Waelkens JJ, Jansen M, et al. Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. *J Clin Endocrinol Metab* 2007 Apr;92:1402-8.
- (24) Mauras N. Strategies for maximizing growth in puberty in children with short stature. *Pediatr Clin North Am* 2011 Oct;58:1167-79, x.

- (25) Cassorla F, Mericq V, Eggers M, Avila A, Garcia C, Fuentes A, et al. Effects of luteinizing hormone-releasing hormone analog-induced pubertal delay in growth hormone (GH)-deficient children treated with GH: preliminary results. *J Clin Endocrinol Metab* 1997 Dec;82:3989-92.
- (26) Adan L, Souberbielle JC, Zucker JM, Pierre-Kahn A, Kalifa C, Brauner R. Adult height in 24 patients treated for growth hormone deficiency and early puberty. *J Clin Endocrinol Metab* 1997 Jan;82:229-33.
- (27) Tanaka T, Satoh M, Yasunaga T, Horikawa R, Tanae A, Katsumata N, et al. When and how to combine growth hormone with a luteinizing hormone-releasing hormone analogue. *Acta Paediatr Suppl* 1999 Feb;88:85-8.
- (28) Saggese G, Federico G, Barsanti S, Fiore L. The effect of administering gonadotropin-releasing hormone agonist with recombinant-human growth hormone (GH) on the final height of girls with isolated GH deficiency: results from a controlled study. *J Clin Endocrinol Metab* 2001 May;86:1900-4.
- (29) Mericq MV, Eggers M, Avila A, Cutler GB, Jr., Cassorla F. Near final height in pubertal growth hormone (GH)-deficient patients treated with GH alone or in combination with luteinizing hormone-releasing hormone analog: results of a prospective, randomized trial. *J Clin Endocrinol Metab* 2000 Feb;85:569-73.
- (30) Mericq V, Gajardo H, Eggers M, Avila A, Cassorla F. Effects of treatment with GH alone or in combination with LHRH analog on bone mineral density in pubertal GH-deficient patients. *J Clin Endocrinol Metab* 2002 Jan;87:84-9.

- (31) Reiter EO, Lindberg A, Ranke MB, Price DA, Albertsson-Wikland K, Cowell CT, et al. The KIGS experience with the addition of gonadotropin-releasing hormone agonists to growth hormone (GH) treatment of children with idiopathic GH deficiency. *Horm Res* 2003;60(Suppl 1):68-73.
- (32) Muthusamy K, Elamin MB, Smushkin G, Murad MH, Lampropulos JF, Elamin KB, et al. Clinical review: Adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis. *J Clin Endocrinol Metab* 2010 Sep;95:4161-72.
- (33) Eugster EA, Dimeglio LA, Wright JC, Freidenberg GR, Seshadri R, Pescovitz OH. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. *J Pediatr* 2001 Jan;138:26-32.
- (34) Lin-Su K, Vogiatzi MG, Marshall I, Harbison MD, Macapagal MC, Betensky B, et al. Treatment with growth hormone and luteinizing hormone releasing hormone analog improves final adult height in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2005 Jun;90:3318-25.
- (35) Lin-Su K, Harbison MD, Lekarev O, Vogiatzi MG, New MI. Final adult height in children with congenital adrenal hyperplasia treated with growth hormone. *J Clin Endocrinol Metab* 2011 Jun;96:1710-7.
- (36) Javed A, Lteif A, Kumar S. Update on treatment strategies for optimization of final adult height in children with congenital adrenal hyperplasia. *Pediatr Endocrinol Rev* 2012 Nov;10:164-73.

- (37) Dacou-Voutetakis C, Karidis N. Congenital adrenal hyperplasia complicated by central precocious puberty: treatment with LHRH-agonist analogue. *Ann N Y Acad Sci* 1993 May 28;687:250-4.
- (38) Longui CA, Kochi C, Calliari LE, Modkovski MB, Soares M, Alves EF, et al. Near-final height in patients with congenital adrenal hyperplasia treated with combined therapy using GH and GnRHa. *Arq Bras Endocrinol Metabol* 2011 Nov;55:661-4.
- (39) Soliman AT, Allamki M, alSalmi I, Asfour M. Congenital adrenal hyperplasia complicated by central precocious puberty: linear growth during infancy and treatment with gonadotropin-releasing hormone analog. *Metabolism* 1997 May;46:513-7.
- (40) Pescovitz OH, Comite F, Cassorla F, Dwyer AJ, Poth MA, Sperling MA, et al. True precocious puberty complicating congenital adrenal hyperplasia: treatment with a luteinizing hormone-releasing hormone analog. *J Clin Endocrinol Metab* 1984 May;58:857-61.
- (41) Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010 Sep;95:4133-60.
- (42) Eugster EA. Peripheral precocious puberty: causes and current management. *Horm Res* 2009 Jan;71 Suppl 1:64-7.
- (43) Rivkees SA, Bode HH, Crawford JD. Long-term growth in juvenile acquired hypothyroidism: the failure to achieve normal adult stature. *N Engl J Med* 1988 Mar 10;318:599-602.

- (44) Quintos JB, Salas M. Use of growth hormone and gonadotropin releasing hormone agonist in addition to L-thyroxine to attain normal adult height in two patients with severe Hashimoto's thyroiditis. *J Pediatr Endocrinol Metab* 2005 May;18:515-21.
- (45) Watanabe T, Minamitani K, Minagawa M, Wataki K, Ohnishi H, Yasuda T, et al. Severe juvenile hypothyroidism: treatment with GH and GnRH agonist in addition to thyroxine. *Endocr J* 1998 Apr;45 Suppl:S159-S162.
- (46) Miyazaki R, Yanagawa N, Higashino H, Kobayashi Y. LHRH analogue and growth hormone did not improve the final height of a patient with juvenile hypothyroidism accompanied by precocious puberty. *Arch Dis Child* 2000 Jul;83:87.
- (47) Teng L, Bui H, Bachrach L, Lee P, Gagne N, Deal C, et al. Catch-up growth in severe juvenile hypothyroidism: treatment with a GnRH analog. *J Pediatr Endocrinol Metab* 2004 Mar;17:345-54.
- (48) Nebesio TD, Wise MD, Perkins SM, Eugster EA. Does clinical management impact height potential in children with severe acquired hypothyroidism? *J Pediatr Endocrinol Metab* 2011;24:893-6.
- (49) Manasco PK, Pescovitz OH, Blizzard RM. Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993 Aug;123:334-5.
- (50) Murras N, Hayes V, Welch S, Rini A, Helgeson K, Dokler M, et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J Clin Endocrinol Metab* 1998 Jun;83:1886-92.

- (51) Mauras N, Hayes VY, Vieira NE, Yergey AL, O'Brien KO. Profound hypogonadism has significant negative effects on calcium balance in males: a calcium kinetic study. *J Bone Miner Res* 1999 Apr;14:577-82.
- (52) Mrug S, Elliott MN, Davies S, Tortolero SR, Cuccaro P, Schuster MA. Early puberty, negative peer influence, and problem behaviors in adolescent girls. *Pediatrics* 2014 Jan;133:7-14.
- (53) Walvoord E, Mazur T. Behavioral problems in idiopathic central precocious puberty: fact or fiction? *Pediatric Endocrine Reviews* 2007;4(Suppl 3):7.
- (54) Schoelwer MJ, Donahue KL, Bryk K, Didrick P, Berenbaum SA, Eugster EA. Psychological assessment of mothers and their daughters at the time of diagnosis of precocious puberty. *Int J Pediatr Endocrinol* 2015;2015:5.
- (55) Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009 Apr;123:e752-e762.
- (56) Watson SE, Greene A, Lewis K, Eugster EA. Bird's-Eye View of GnRH Analog Use in a Pediatric Endocrinology Referral Center. *Endocr Pract* 2015 Feb 9;1-15.

Table: Effectiveness of GnRHAs in conditions other than precocious puberty

Indication	Efficacy in Increasing Height	Safety concerns	Other	Ref #
Short stature/Poor predicted adult height	<ul style="list-style-type: none"> • Minimal to no efficacy when used alone in short stature • Minimal efficacy when used in combination with growth hormone 	<ul style="list-style-type: none"> • Decreased bone mineral density • Psychological impact? 	<ul style="list-style-type: none"> • Small sample sizes • Limited data on adult height • Mixed subjects 	<ul style="list-style-type: none"> • 13-23
Growth Hormone Deficiency	<ul style="list-style-type: none"> • Possible efficacy when used in combination with growth hormone 	<ul style="list-style-type: none"> • Decreased bone mineral density • Psychological impact? 	<ul style="list-style-type: none"> • Limited data on adult height • Conflicting results; more research needed 	<ul style="list-style-type: none"> • 24-31
Congenital Adrenal Hyperplasia	<ul style="list-style-type: none"> • No evidence of efficacy when used alone • Possible efficacy when combined with growth hormone • Likely effective in secondary CPP 	<ul style="list-style-type: none"> • Psychological impact? 	<ul style="list-style-type: none"> • No randomized studies have been conducted • Not recommended by CAH practice guidelines 	<ul style="list-style-type: none"> • 32-42
Profound Primary Hypothyroidism	<ul style="list-style-type: none"> • No evidence of efficacy 	<ul style="list-style-type: none"> • Psychological impact? 	<ul style="list-style-type: none"> • No randomized studies have been conducted 	<ul style="list-style-type: none"> • 43-48