Mini Review

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2018;90:1–7
DOI: 10.1159/000491103

Received: March 24, 2018
Accepted: June 20, 2018
Published online: July 26, 2018

Toward More Targeted and Cost-Effective Gonadotropin-Releasing Hormone Analog Treatment in Girls with Central Precocious Puberty

Paul B. Kaplowitz[a] Philippe F. Backeljauw[b] David B. Allen[c]

[a]Division of Endocrinology, Children's National Health System, Washington, DC, USA; [b]Division of Endocrinology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [c]Division of Pediatric Diabetes and Endocrinology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Keywords
Precocious puberty · Central precocious puberty · Gonadotropin-releasing hormone analogs · Hormone therapy · Cost-effectiveness

Abstract
The use of gonadotropin-releasing hormone analogs (GnRHa) for the treatment of central precocious puberty (CPP), especially in girls, has increased rapidly in recent years. In the context of a secular trend towards earlier puberty onset, many girls now treated for CPP are healthy children experiencing puberty onset within the early end of the normal range. Justifications for GnRHa treatment include the preservation of adult height (AH) potential and the alleviation of presumed distress of early maturation and menarche. With a case of a family requesting treatment for an 8-year-old girl in early puberty as a background, studies of the effect of untreated CPP and of GnRHa treatment of CPP on AH are reviewed. In addition, the limited evidence relating CPP to significant psychological distress – in part due to early menses, and for the amelioration of such distress by GnRHa treatment – is discussed. Taken together, current information suggests that for girls with mildly early onset of puberty (ages 7–9 years), an informed assent discussion with the family should include the consideration of reassurance and observation for many girls who might otherwise receive 2–4 years of GnRHa treatment for a poorly defined benefit and at a cost of at least $20–30,000 per year.

Introduction

Gonadotropin-releasing hormone analogs (GnRHa) are modified preparations of native GnRH designed to increase its potency and half-life and were initially approved for the treatment of prostate cancer. Daily injections of GnRHa were also found to suppress the hypothalamic-pituitary-gonadal axis in children with central precocious puberty (CPP) [1]. In 1986, the first long-term study of daily GnRHa treatment in 27 children (21 female and 6 male) treated for 2–4 years showed that GnRHa treatment clearly slowed growth velocity and skeletal maturation, while increasing predicted adult height (PAH) [2, 3]. In that study, the mean age at treatment ini-

KARGER

E-Mail karger@karger.com
www.karger.com/hrp

Paul B. Kaplowitz, MD
Division of Endocrinology, Children's National Health System
111 Michigan Ave. NW
Washington, DC 20010 (USA)
E-Mail pkaplowi@childrensnational.org

tiation (5.2 years), growth rate (10.9 cm/year), bone age advancement (>3 years), estradiol in girls (42 pg/ml), testosterone in boys (471 ng/dL), breast Tanner stage (mean 3.3), and testicular volume (16 mL) indicate that this cohort was younger and progressing more rapidly than the great majority of children with CPP treated today. In 1993 the USFDA approved the monthly version of a GnRHa (Lupron Depot®) to treat CPP. Over the past 25 years, the use of GnRHa to treat CPP has steadily increased, and several additional formulations have been introduced, including a 3-month injectable form of Lupron® and an implant called Supprelin®, which releases the GnRHa histrelin for at least 1 year. Most recently, a 6-month GnRHa, Triptodur®, has received USFDA approval (2017).

While the use of GnRHa to treat CPP has been rising, the mean age of onset of puberty, at least in girls, appears to be declining. Whereas during the 1960s to 1970s, the mean age of thelarche was 10.5–11 years, data from the late 1980s and 1990s suggest a significant decline in the mean age of thelarche, with less decline in the mean age of menarche. In a landmark study of more than 17,000 girls (ages 3–12 years) screened in physicians' offices around the country [4], the mean age at the onset of breast development was 8.87 years for African-American and 9.96 years for Caucasian girls. Furthermore, 5% of the Caucasian 7-to-8-year-old girls and 15.4% of the African-American 7-to-8-year-old girls already had breast development. More recently, in nearly 1,000 7-to-8-year-old girls, 10% of the Caucasian, 23% of the African-American, and 15% of the Hispanic girls had reached at least Tanner 2 breast development [5]. Studies in both the US and worldwide have implicated the rising incidence of obesity as a major factor in the decline in the age of puberty onset in girls [6, 7]. Consequently, continued adherence to prior definitions for precocious puberty (breast development before 8 years of age) has resulted in an increasing proportion of girls being categorized as "precocious." In response to this secular trend of earlier puberty, guidelines were proposed recommending that precocious puberty be redefined as the onset of breast development before 7 years for Caucasian girls and before 6 years for African-American girls [8]. However, such recommendations were criticized for increasing the risk of missing pathologic early puberty occurring in girls between 6 and 8 years of age [9]. As a result, the traditional definition of female precocious puberty (i.e., starting before the age of 8 years) is still what most primary care providers adhere to in deciding which patients to refer for further evaluation.

Ambiguity in the diagnostic criteria for sexual precocity provides a fertile environment for an increase in the treatment of borderline CPP cases, i.e., with pubertal onset between 7 and 9 years of age. In this regard, GnRHa therapy has been another example of "expansive biotechnology", where a medical intervention for a specific disease or disabling condition expands into a therapy to reduce disability, lessen disadvantage, or even lessen anxiety. The combination of parental expectations, well-intending prescribers, and pressures of the market place can lead to increased utilization of certain drugs, devices, and procedures, and may prevail over considerations of efficient and equitable distribution of resources. Availability of treatment itself can encourage the "medicalization" of physiologic variations of normal as disorders. Justification of treatment often relies on assumptions about morbidity (e.g., psychological distress) or undesired outcomes (e.g., reduced AH) that seem reasonable but, in fact, are not well documented. In these situations, it is challenging to discern if GnRHa therapy for early puberty is a medically necessary intervention for which the benefit justifies its burden on the patient and family as well as the high cost. While prices vary widely depending on the source of information, the cost of Supprelin without factoring in the cost of insertion is at least $20,000–30,000 annually, and for cash-paying customers using the Drugs.com discount card it is listed at $32,000. Anecdotal reports indicate that this can be higher in specific situations. The cost of Lupron therapy depends on the formulation prescribed but can run as high as $50,000 per year for the 30 mg 3-month injection.

After the approval of monthly Lupron Depot, an expert proposed that treatment be limited to patients with complete and progressive CPP with pubertal hormone concentrations plus abnormal height potential (PAH < 5th %ile) or psychosocial morbidity/distress (e.g., menses in mentally or emotionally immature individuals) [10]. An indicator of the rapid expansion of GnRHa use in recent years is data provided by a marketer of GnRHa, showing that between 2012 and 2017, the median age of GnRHa therapy initiation in girls (which is likely several months after the onset of pubertal changes) was 9.0 years for both Supprelin and Depot Lupron Ped® [11]. Furthermore, only 11.6% of the patients who had received Lupron Depot and 15.1% of the patients who had received Supprelin were started on treatment before the age of 8 years. These data indicate that the majority of girls now being treated for CPP are starting puberty at the early end of the normal range. The treatment of boys is much less common, accounting for only 14% of the Supprelin and 18% of the Lupron prescriptions [11]. Because there

is less controversy about the treatment of boys with CPP, we will focus on CPP in girls only.

The following case scenario illustrates different factors that influence the decision to initiate pubertal suppression. These factors are then critically evaluated for available evidence supporting prescribing – or withholding – GnRHa therapy.

An 8-year-old Caucasian female was noted to have breast development at the age of 7 years 9 months by her parents. Family history is negative for early puberty. The parents are of average height (the girl's target height is 5'4" or 162.5 cm). Growth earlier in childhood had been at the 75th percentile in height and the 90th percentile in weight, but is now at the 90–95th percentile (137 cm) in height and weight. Examination revealed Tanner stage 2 breast development (3 cm of glandular breast tissue bilaterally) and a few pubic hairs on the labia majora. Bone age is 10 years, yielding a PAH of 164 cm (5'4.5"). The child is in 3rd grade and has no apparent emotional issues. Her parents request treatment to suppress puberty because (1) they were told by the pediatrician that without treatment she would stop growing early and end up short, and (2) they are not ready for her to start her menstrual cycles.

Do GnRH Analogs Increase AH in Children with CPP?

The primary rationale for CPP suppression is concern that growth plates will fuse prematurely resulting in height attainment significantly below the genetic target height. Indeed, the treatment of children with very early-onset CPP often results in an AH which significantly exceeds PAH at the initiation of therapy. In a study of girls who started treatment before the age of 5 years, the AH (164.6 cm) far exceeded the mean AH of a separate group of untreated females (152.5 cm). However, for patients started on treatment after the age of 5 years, the results were much less impressive (mean AH of 157.6 cm) [12]. This dependence of an increased height on a younger age of GnRHa treatment initiation has been found in other studies [13, 14]. In 46 Italian girls with onset of puberty between 7.5 and 8.5 years either treated with monthly GnRHa or not treated, the mean AHs were similar (158.1 ± 6.2 cm in the treated group and 158.6 ± 6.0 cm in the untreated group) and were not significantly different from the mid-parental height (MPH) [13]. In a study from Israel of 22 girls diagnosed before the age of 6 years, 38 girls diagnosed between ages 6 and 8 years, and 55 girls between ages 8 and 9 years, all groups had a similar mean PAH (152.8–154.6 cm) prior to the onset of therapy. Those starting treatment before 6 years had a mean AH of 162.8 cm, which actually exceeded their MPH of 159.3 cm. The patients with treatment onset at 6–8 years had a mean AH of 157.9 cm, equal to their MPH. For those with onset between ages 8 and 9 years, a mean height of 153.9 cm was achieved, 3 cm below their MPH [14]. In contrast, an Italian study of 87 girls with CPP treated with GnRHa at a mean age of 8.4 years for an average of 4.2 years (until a mean age of 12.6 years) found that treatment resulted in AHs which were about 5 cm greater than both pretreatment PAH and a matched untreated group, and slightly better than MPH. Furthermore, the results were similar for girls ≤7 years and >7 years at the time of their first visit [15].

A recent review of this topic [16] highlighted several problems with assessing the effect of GnRHa treatment on AH. These include (1) a lack of well-designed, randomized, controlled studies, and (2) problems in estimating PAH based on bone age. Such PAH estimations are affected by the imprecision of bone age interpretation and the use of any of several methods, including the widely used Bayley-Pinneau tables (based on radiographs of Caucasian children between 1931 and 1942), which vary in how accurately they predict AH. (3) In addition, many studies likely contain a mix of girls with both rapidly progressive and slowly advancing to nonprogressive CPP, with the latter group typically reaching a normal AH without any intervention [17, 18]. A table in this review summarizing 29 studies from 1994 to 2015 found that mean (AH – PAH) varied from 2 to 10 cm.

Reflecting the lack of firm data on this point, a consensus statement by the North American and European Pediatric Endocrine Societies made the following recommendations:

- "The greatest height gain has been observed in girls with onset of puberty at <6 years (average height gain 9–10 cm). Girls with onset between 6 and 8 comprise a heterogeneous group that may have a moderate benefit ranging from 4.5 to 7.2 cm.… *The decision to initiate therapy in girls with onset after age 6 should be individualized*" [19].
- "Progressive pubertal development and growth acceleration should be documented over a 3-to-6-month period before GnRH therapy" was included because, as noted, some girls display slowly progressive CPP and achieve AHs within their target range without intervention [17, 18].

Perhaps a more relevant question to address in justifying GnRHa treatment is how often girls with untreated CPP fail to reach a normal AH. In a report of girls (n =

20) initially evaluated at a mean age of 7 ± 2.4 years after a mean onset of breast tissue at 5.6 ± 1.6 years, mean AH was 161.4 cm. There was a good correlation between Bayley-Pinneau predicted heights at the initial visit and final height ($r = 0.85$), and 90% achieved a normal AH of >153 cm, which is notable considering the young age at which most girls in the study started puberty [20]. A more recent and larger study from Thailand followed 104 girls with breast development starting between the ages of 7.0 and 9.0 years until near-final height. Although the average age at menarche was also early at 10.2 years, the near AH was 154.0 cm, which was similar to the MPH of 153.1 cm [21]. Unfortunately, there are few other studies examining this question, likely due to the evolution of "standard practice" in recent years to treat rather than monitor girls with CPP. In one study, girls with CPP who had a PAH of <155 cm were treated, while another 52 girls who had a PAH of >155 cm (puberty onset at a mean age of 7.1 years) were monitored only. They reported a mean AH for the untreated girls of 163 cm, close to their mean PAH of 164.5 cm [22]. It appears reasonable to conclude that the majority of girls evaluated for CPP after the age of 6 years will have a PAH at the initial evaluation within the normal adult range (i.e., 5'1" or 155 cm or greater). Thus, treating girls with mildly early CPP is seldom required to avoid an abnormally short AH but is often done to address parental concerns about differences in family expectations for height (i.e., the PAH normal but below MPH) or anticipated psychological harm.

Do Girls with CPP Have More Psychological Problems than Prepubertal Girls Their Age?

There is a pervasive belief that girls with CPP have a higher incidence of behavioral problems than prepubertal girls of similar age. In an early study investigating this question, 9 of 33 girls (27%) with CPP who took the Child Behavior Checklist scored ≥2 SD above the mean on the total behavior problem scale and 48% scored >2 SD above the mean on the social withdrawal scale. The authors concluded that while "elevated sex steroid levels might contribute to increased aggressive and hyperactive behaviors, they may be modified by social and environmental factors" [23]. In one of the few studies that looked at behavioral changes during CPP treatment, all 20 girls with CPP expressed concerns about physical differences from their peers at baseline. Fifteen girls who were followed during treatment felt less embarrassed about pubertal development as breast tissue regressed. However, elevated scores of withdrawal, anxiety/depression, and somatic complaints persisted [24].

Another study of 36 girls with signs of early puberty included 15 patients with CPP, 8 with premature adrenarche, and 13 had early normal puberty. All girls with CPP were treated with GnRHa. Baseline psychological assessments of cognitive competence, peer acceptance, physical competence, and maternal acceptance were, on average, normal in all groups. After 1 year of follow-up, findings were "largely reassuring regarding concerns of adverse psychological consequences of early puberty in girls" [25]. A study of 15 girls with CPP and 15 age-matched controls reported the only detectable difference in a large battery of tests was that treated girls showed higher emotional reactivity on 1 of 2 tests. Overall, these authors concluded that treated CPP girls did not differ in their cognitive or psychological functioning from control girls [26]. In summary, with few studies, utilizing different patient selection criteria and reporting disparate prevalence of behavioral problems in CPP girls, it remains unclear if psychosocial stress should be considered a predictable consequence of early puberty supporting a decision to start GnRHa therapy, and if so, whether treatment relieves such stress.

Is the Prevention of Potential Early Menarche in Girls with CPP Necessary?

Parents who request treatment for girls with CPP often fear their daughter will not be able to handle the stress of experiencing and caring for early menses. For girls whose puberty starts before the age of 7 years and who may reach menarche by the age of 9 years, this concern is appropriate and should be addressed. However, when puberty starts at close to the age of 8 years and is not suppressed, menarche usually does not occur until the age of 10 years or later, as US studies indicate that it takes 2.4–3 years to progress from thelarche to menarche [27, 28]. How strong is the evidence that girls having menarche close to 10 years of age experience significant distress and, if so, benefit from GnRHa treatment designed to delay menarche until the age of 11 years or later? There are no studies that directly address this question in a controlled setting. It is understandable that anxiety associated with early menses is often experienced by parents. It also seems reasonable that a girl prepared for early menses by a calm and reassuring parent or guardian may handle it better. However, in the absence of data and in the presence of so much individual family variation on this

issue, counseling parents who desire treatment to delay menses remains challenging. One suggestion could be to point out that (1) many early-maturing girls progress slowly and do not have menarche before the age of 10 years; (2) most girls having menarche between the ages of 9 and 10 years adjust to having menstrual periods well after the first couple of cycles; and (3) if menses do start early and are deemed too stressful, initiation of GnRHa could still promptly suppress subsequent menses or, alternatively, the child could be started on Depo-Provera® to reduce the amount and frequency of bleeding at a minimal cost. The latter option is especially relevant for the care of children with developmental disabilities, in whom treatment solely to suppress menses may alleviate significant distress for patient and care providers. However, its use needs to be balanced against the available evidence of a dose-response relationship between medroxyprogesterone acetate exposure and the increased risk for decreased bone mineralization [29].

Should Healthy Girls with Mildly Early Puberty Onset Be Treated with GnRHa?

When pituitary growth hormone (GH) was the only treatment for GH deficiency, only those children with growth failure due to severe GH deficiency received it. The advent of an unlimited supply of recombinant human GH was followed by an expansion in the treatment of greater numbers of children for a wide variety of underlying growth-limiting diagnoses. The rationale for GH treatment in most non-GH-deficient children is to prevent presumed adverse psychosocial consequences of a short stature. Often in response to parental concerns, children who are short but healthy, growing parallel to but below the normal height curve, and in some cases at a percentile consistent with parental heights, are receiving GH treatment. Current practice suggests that a similar expansion in therapeutic scope has occurred with the use of GnRHa for treatment of early-maturing girls. Initial trials of GnRHa therapy focused on children with very early-onset and rapidly progressing puberty, whereas the treatment of 7-to-9-year-old girls for several years to possibly and modestly increase AH (perhaps 5 cm) seems analogous to using GH to slightly increase the AH of a healthy boy with a PAH in the low normal range. Similar to the GH experience, industry support for clinical research trials, which included girls who were borderline early maturers, coupled with the physicians' desire to address parental concerns, fostered investigation – and acceptance – of the treatment of children with puberty onset at ages that overlap with normal variation.

One factor that may impact decision making in borderline cases is a history of being born small for gestational age, for which an association with more rapid pubertal progression, bone age advancement, and shorter AH has been shown [30].

How Long Should the Treatment of CPP with GnRHa Continue?

To return to on our previous case:

The parents express a strong desire to treat their daughter to delay the onset of menses. She is started on Lupron Depot Ped® 11.25 mg given intramuscularly every 3 months. At her next visit 4 months later, she is growing at a normal rate, and the breast tissue has regressed. Treatment is planned to continue until the age of 10 years. However, 1 year later, when she is 9 ¾ and receiving her last scheduled dose of GnRHa, the parents ask to continue the treatment for another year because they are concerned that their child is too emotionally fragile to handle menses. Based on the latest bone age, her PAH is 5'5".

There are no widely accepted guidelines for how long to continue treatment with a GnRHa for CPP, and individual practice varies widely. The consensus statement on the use of GnRHa lists "maximizing height, synchronizing puberty with peers, ameliorating psychological distress, and facilitating care of the developmentally delayed child" as factors to consider [19]. In the studies reviewed, the mean age of treatment discontinuation varied from 10.6 to 12 years, with a mean bone age at discontinuation ranging from 12.1 to 13.9 years and a mean age of menarche at 12.3 years [19]. In the minority of patients for whom the PAH at both the start of treatment and after 1–2 years of therapy is <5'0" or 152.5 cm, continuing treatment for longer could be justified by a study suggesting that discontinuation of treatment at a bone age of 12 years has been associated with the best AH (notably, in this study the benefit of GnRHa therapy was quite variable with a mean gain in AH after therapy of only 2.9 ± 6.0 cm, and less for girls started on treatment after age 6 years) [31]. An important question for those girls whose treatment is based on the desire to delay menarche is whether the targeted age at menarche should be closer to 10, 11, or 12 years, and to what extent parents should have the final say on when their child should be allowed to reach menarche. After discontinuation of GnRHa therapy, menarche occurs on the average 1.4 years later (range 0.7–2.4) [14]. Stopping

treatment by the age of 10 years should, for most girls, ensure that menarche will not occur until the age of 10.5–12.0 years, and most likely not before the age of 11 years. It is difficult to defend an expectation for insurance companies or public funds to continue to pay $30,000 or more per year for GnRHa in order to delay menarche until the age of 12 years or later, which is close to the population average. Consequently, it seems reasonable in most cases to discontinue GnRHa no later than 10 years, with exceptions made in rare cases of severe psychosocial stress and, perhaps, a very low PAH. More study is needed to confirm that prolonged treatment beyond the age of 10 years is beneficial and does not inadvertently affect height outcomes negatively by further suppressing an adequate growth spurt. If treatment is stopped by age 10, the resumption of thelarche would be close to the current population average, and the suppression of menses by other, much less costly measures such as Depo-Provera are available and effective if needed.

Summary

Treatment decisions with GnRHa therapies, as all medical interventions, should attempt to balance benefits, risks, and costs for the individual child. Toward this goal, the following should be included in an informed discussion when GnRHa treatment is being considered for an early-maturing girl (e.g., onset between 7–9 years of age):

1 Your child's AH, especially if she is taller than the average now, will probably be normal and may not significantly increase with treatment;
2 It is uncertain whether your child will experience adverse psychosocial stress from early puberty or, if she does, whether GnRHa treatment would prevent or alleviate such stress;
3 Your child may have slow progression of puberty so that menses may not occur as early as feared. In many situations, a follow-up visit in 4–6 months to evaluate growth velocity and any change in the amount of breast development will make it easier to decide if your child is progressing rapidly enough to justify treatment;
4 It is not necessary to prevent a first menstrual period to intervene and stop subsequent menses;
5 Cost of treatment is high and need to be added to the cost and stress associated with the follow-up clinic visits and periodic injections or having an implant placed.

Such a discussion encourages thoughtful consideration of therapeutic restraint, reassurance, and observation of many girls who might otherwise receive 2–4 years of treatment for a poorly defined benefit achieved at a very high cost.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

1 Comite F, Cutler GB Jr, Rivier J, Vale WW, Loriaux DL, Crowley WF Jr. Short-term treatment of idiopathic precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone. A preliminary report. N Engl J Med. 1981 Dec;305(26):1546–50.
2 Pescovitz OH, Comite F, Hench K, Barnes K, McNemar A, Foster C, et al. The NIH experience with precocious puberty: diagnostic subgroups and response to short-term luteinizing hormone releasing hormone analogue therapy. J Pediatr. 1986 Jan;108(1):47–54.
3 Comite F, Cassorla F, Barnes KM, Hench KD, Dwyer A, Skerda MC, et al. Luteinizing hormone releasing hormone analogue therapy for central precocious puberty. Long-term effect on somatic growth, bone maturation, and predicted height. JAMA. 1986 May;255(19):2613–6.
4 Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997 Apr;99(4):505–12.
5 Biro FM, Galvez MP, Greenspan LC, Succop PA, Vangeepuram N, Pinney SM, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics. 2010 Sep;126(3):e583–90.
6 Kaplowitz PB. Link between body fat and the timing of puberty. Pediatrics. 2008 Feb;121 Suppl 3:S208–17.
7 Shalitin S, Kiess W. Putative effects of obesity on linear growth and puberty. Horm Res Paediatr. 2017;88(1):101–10.
8 Kaplowitz PB, Oberfield SE; Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Pediatrics. 1999 Oct;104(4 Pt 1):936–41.
9 Midyett LK, Moore WV, Jacobson JD. Are pubertal changes in girls before age 8 benign? Pediatrics. 2003 Jan;111(1):47–51.
10 Rosenfield RL. Selection of children with precocious puberty for treatment with gonadotropin releasing hormone analogs. J Pediatr. 1994 Jun;124(6):989–91.
11 Grubb E, Dragnic S. AbbVie Data in File, March 23, 2018.

12 Paul D, Conte FA, Grumbach MM, Kaplan SL. Long-term effect of gonadotropin-releasing hormone agonist therapy on final and near-final height in 26 children with true precocious puberty treated at a median age of less than 5 years. J Clin Endocrinol Metab. 1995 Feb;80(2):546–51.
13 Cassio A, Cacciari E, Balsamo A, Bal M, Tassinari D. Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5-8.5 years. Arch Dis Child. 1999 Oct;81(4):329–32.
14 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(9):3483–9.
15 Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. J Clin Endocrinol Metab. 2008 Jan;93(1):190–5.
16 Bereket A. A critical appraisal of the effect of gonadotropin-releasing hormone analog treatment on adult height of girls with central precocious puberty. J Clin Res Pediatr Endocrinol. 2017 Dec;9 Suppl 2:33–48.
17 Palmert MR, Malin HV, Boepple PA. Unsustained or slowly progressive puberty in young girls: initial presentation and long-term follow-up of 20 untreated patients. J Clin Endocrinol Metab. 1999 Feb;84(2):415–23.
18 Massart F, Federico G, Harrell JC, Saggese G. Growth outcome during GnRH agonist treatments for slowly progressive central precocious puberty. Neuroendocrinology. 2009;90(3):307–14.
19 Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, et al.; ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009 Apr;123(4):e752–62.
20 Bar A, Linder B, Sobel EH, Saenger P, DiMartino-Nardi J. Bayley-Pinneau method of height prediction in girls with central precocious puberty: correlation with adult height. J Pediatr. 1995 Jun;126(6):955–8.
21 Jaruratanasirikul S, Thongkum K, Krisaneepaiboon S, Sriplung H. Girls with early puberty attain a near-final height similar to their target height. J Pediatr Endocrinol Metab. 2011;24(5-6):339–45.
22 Allali S, Lemaire P, Couto-Silva AC, Prété G, Trivin C, Brauner R. Predicting the adult height of girls with central precocious puberty. Med Sci Monit. 2011 Jun;17(6):PH41–8.
23 Sonis WA, Comite F, Blue J, Pescovitz OH, Rahn CW, Hench KD, et al. Behavior problems and social competence in girls with true precocious puberty. J Pediatr. 1985 Jan;106(1):156–60.
24 Xhrouet-Heinrichs D, Lagrou K, Heinrichs C, Craen M, Dooms L, Malvaux P, et al. Longitudinal study of behavioral and affective patterns in girls with central precocious puberty during long-acting triptorelin therapy. Acta Paediatr. 1997 Aug;86(8):808–15.
25 Schoelwer MJ, Donahue KL, Didrick P, Eugster EA. One-year follow-up of girls with precocious puberty and their mothers: do psychological assessments change over time or with treatment? Horm Res Paediatr. 2017;88(5):347–53.
26 Wojniusz S, Callens N, Sütterlin S, Andersson S, De Schepper J, Gies I, et al. Cognitive, emotional, and psychosocial functioning of girls treated with pharmacological puberty blockage for idiopathic central precocious puberty. Front Psychol. 2016 Jul;7:1053.
27 Biro FM, Huang B, Crawford PB, Lucky AW, Striegel-Moore R, Barton BA, et al. Pubertal correlates in black and white girls. J Pediatr. 2006 Feb;148(2):234–40.
28 Cabrera SM, Bright GM, Frane JW, Blethen SL, Lee PA. Age of thelarche and menarche in contemporary US females: a cross-sectional analysis. J Pediatr Endocrinol Metab. 2014 Jan;27(1-2):47–51.
29 Lange HL, Manos BE, Gothard MD, Rogers LK, Bonny AE. Bone Mineral Density and Weight Changes in Adolescents Randomized to 3 Doses of Depot Medroxyprogesterone Acetate. J Pediatr Adolesc Gynecol. 2017 Apr;30(2):169–75.
30 Verkauskiene R, Petraitiene I, Albertsson Wikland K. Puberty in children born small for gestational age. Horm Res Paediatr. 2013;80(2):69–77.
31 Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Antoniazzi F, et al. Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. Eur J Endocrinol. 1999 Aug;141(2):140–4.