

PEDIATRICS

Consensus Statement on the Use of GnRH Analogs in Children

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Short Title: Consensus Statement on GnRH Analogs in Children

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Abstract

OBJECTIVE: Gonadotropin releasing hormone analogs (GnRHa) revolutionized the treatment of central precocious puberty (CPP). However, questions remain regarding their optimal use in CPP and other conditions. The Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology convened a consensus conference to review the clinical use of GnRHa in children and adolescents.

PARTICIPANTS: When selecting the 30 participants, consideration was given to equal representation from North America (United States and Canada) and Europe, male:female ratio, and balanced spectrum of professional seniority and expertise.

EVIDENCE: Preference was given to articles written in English with long-term outcome data. The United States Public Health Grading System was used to grade evidence and rate strength of conclusions. When evidence was insufficient, conclusions were based on expert opinion.

CONSENSUS PROCESS: Participants were divided into working groups with assigned topics and specific questions. Written materials were prepared and distributed before the conference, revised based on input during the meeting, and presented to the full assembly for final review. If consensus could not be reached, conclusions were based on majority vote. All participants approved the final statement.

CONCLUSIONS: The efficacy of GnRHa to increase adult height is undisputed only in early onset (girls younger than 6 yr) CPP. Other key areas, such as the psychosocial effects of CPP and their alteration by GnRHa, need further study. Few controlled prospective studies have been performed with GnRHa in children, and many conclusions rely in part on collective expert opinion. The conference did not endorse commonly voiced concerns regarding the use of GnRHa, such as promotion of weight gain or long-term diminution of bone mineral density. Use of GnRHa in conditions other than CPP requires further investigation and cannot be suggested routinely.

Introduction

Gonadotropin releasing hormone analogs (GnRHa) are standard of care for treatment of central precocious puberty (CPP). However, despite a favorable record of safety and efficacy, significant questions remain regarding their use. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to examine GnRHa therapy in pediatric patients. This conference did not address whether historically defined normal ages for the onset of puberty should be modified but used the operational definition of *precocious puberty* as puberty beginning prior to age 8 yr in girls and 9 yr in boys.

Methods

Participant Selection. Consideration was given to equal representation from North America (United States and Canada) and Europe; male:female ratio; and balanced spectrum of professional seniority and expertise.

Process. Thirty participants were divided into 6 groups with assigned topics and designated chairpersons. Each participant prepared a summary of the literature regarding a question that was distributed prior to the conference (held over 3 days in November, 2007). Each group revised the summaries and presented them to the full conference. If consensus could not be reached, conclusions were made based on a vote of all participants. This report is organized around the questions that were addressed, has been approved by the participants, and endorsed by LWPES and ESPE.

Evaluation of Evidence. Preference was given to articles written in English with long-term outcome data published between 1990 and 2007. The United States Public Health Grading System(1) was used to grade the evidence and strength of recommendations (Quality of evidence: I, data from ≥ 1 properly randomized controlled trial; II, from other clinical studies; III, from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. Strength of recommendation: A, good evidence to support use; B, moderate evidence to support use; C, poor evidence to support recommendation; D, moderate evidence against use; E, strong evidence against use). Grading was reviewed by the full conference under the guidance of a methodologist/biostatistician. This report is a not a practice guideline; nonetheless, we aimed to adhere to modified AGREE criteria(2).

Section I: Initiation of GnRHa therapy for CPP

Clinical criteria

The most important clinical criteria for GnRHa treatment is documented progression of pubertal development. This is based on the recognition that many patients with CPP have a slowly or non-progressive form and achieve adult height (AH) within their target range without GnRHa(3-7). Accelerated growth velocity and skeletal maturation are other features of sustained and/or rapidly progressing CPP(8). However some patients with slowly progressive CPP and advanced bone age (BA) reach normal AH without intervention(3).

Conclusions. Progressive pubertal development and growth acceleration should be documented over a 3-6 month period prior to GnRHa therapy. This observational period may not be necessary if the child is \geq Tanner stage III (breast), particularly with advanced skeletal maturation (*CIII*).

Chronological age (CA) and psychosocial criteria

Common reasons for GnRHa therapy are potential for compromise in adult stature, inability to adapt oneself to menarche, and psychosocial difficulties. Most of the evidence concerns height outcomes (predicted versus actual AH) and age at initiation of therapy, but no randomized controlled trials quantifying the effect of therapy on AH are available. The Bayley-Pinneau method is commonly used to predict AH and is likely better than other prediction methods(9); however, in some instances, it may over predict height by several centimeters(10,11).

The greatest height gain is observed in girls with onset of puberty under 6 years [average gain 9-10 cm, but with variation among studies(6,12-16)]. Girls with onset between 6 and 8 years comprise a heterogeneous group that may have a moderate benefit ranging from 4.5 ± 5.8 (13) to 7.2 ± 5.3 cm(6). Insufficient data exist to relate chronologic age to height outcomes among boys(17).

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Data regarding the psychosocial impact of untreated or treated CPP are inconclusive and whether delaying puberty with GnRHa may improve social functioning is still an open question. Early menarche in the general population is associated with risk-taking behavior(18), but it is unclear whether such data can be generalized to CPP. In patients with severe developmental delay, CPP may be associated with inappropriate behavior. If suppression of menses is the primary goal, GnRHa is only one of several therapeutic options, including progestogens that could be considered(19).

Conclusions. Girls with onset of progressive CPP before age 6 years benefit most in terms of height from GnRHa. The decision to initiate therapy in girls with onset *after* age 6 should be individualized (**BII**). Treatment should be considered in all boys with onset of progressive CPP before 9 years who have compromised height potential (**CIII**). The use of GnRHa solely to influence the psychosocial consequences of CPP or to delay menarche should be considered carefully given the absence of convincing data (**CIII**). Further studies evaluating the effects of GnRHa therapy on quality of life and psychosocial functioning are needed.

Adopted children

Boys and girls adopted internationally are at risk of CPP, although data are limited in boys(20,21). Response to GnRHa in adopted girls with precocious or early normal puberty appears comparable to that seen in non-adopted girls(22). Adopted children may be at increased risk of emotional and behavioral problems(23), but no data are available to demonstrate that GnRHa therapy improves psychological wellbeing(24).

Conclusions. Although international adoption constitutes a risk factor for CPP, adopted children should be treated no differently than non-adopted children with CPP (**CIII**).

Hormonal criteria

LH measurements are the most valuable biochemical parameter for the diagnosis of CPP. As

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prepubertal LH levels are <0.1 IU/L , LH assays used should have a detection limit near 0.1 IU/L(25-27). In one study of normal children, basal LH levels distinguished prepubertal (LH <0.2 IU/L) and pubertal males with 100% sensitivity and specificity but 50% of girls with Tanner stage 2 breasts had levels in the prepubertal range(27).

LH can be measured after stimulation with GnRH (single serum sample at 30-40 min (27-29)) or with a GnRHa, such as aqueous leuprolide (single sample at 60 min(30,31)). Peak LH values show an overlap between prepubertal and early pubertal children. As with basal LH, variability among assays and paucity of normative data hamper the development of diagnostic cut-offs for CPP although an (assay-specific) prepubertal limit of peak LH of 3.3 to 5.0 IU/L has been suggested(25,27,28).

LH levels provide more information than FSH. However, the stimulated LH/FSH ratio may help differentiate progressive CPP, which tends to have higher LH/FSH ratios, from non progressive variants that do not require GnRHa therapy(32-34).

For estradiol, the most sensitive measurements (tandem mass spectrometry, MS) have shown that prepubertal levels may be <1 pg/ml (3.7 pmol/L) and undetectable with commonly available assays(35). Thus, in non MS assays, measurable estradiol only confirms relatively advanced puberty. Similarly, testosterone assays with detection limits >10 ng/dL may not discriminate prepubertal from early pubertal levels(36) . For estradiol and testosterone, the laboratory used must have a defined prepubertal range.

Conclusions. Sensitive assays with pediatric norms should be used and stimulation results interpreted depending on agent used (**BII**). The same caveats are important if hormonal testing is used to monitor therapy (see below). Basal LH levels are useful screening tests and may be diagnostic (**BII**). Stimulated LH levels are important but interpretation suffers from assay variability and absence of clear diagnostic cutoffs (**BII**). Gonadal sex steroid levels can add information in support of the diagnosis but are not sufficient (**BII**).

Pelvic ultrasound

Patients with CPP have increased ovarian and uterine dimensions compared to prepubertal controls and girls with premature thelarche(37). For CPP, cutoff values for uterine length range from 3.4 to 4.0 cm. The presence of an endometrial echo is highly specific (~100%) but less sensitive (42 to 87%)(34). The cutoffs for a pubertal ovarian volume range between 1-3 ml (volume = length x width x height x 0.5233)(38).

Conclusions. Pelvic ultrasound is helpful in differentiating CPP from premature thelarche as and adjunct to GnRH stimulation (**BII**).

CNS imaging

CPP may be a sign of CNS pathology. Unsuspected intracranial pathology has been reported in 8% of girls(39,40) and 40% of boys(41) without neurological findings or neurofibromatosis. The percentage of children with unsuspected intracranial pathology decreases with age(39-41). Only 2-7% of girls who have onset of CPP between 6 and 8 years of age have unsuspected pathology, and only about 1% have a tumor such as a glioma or astrocytoma(39,40). Factors that may decrease the likelihood of finding a tumor include racial/ethnic background, family history of CPP, and adoption.

Conclusions. All boys with CPP and girls with CPP at less than 6 years of age should have a head MRI. It is controversial whether all girls who develop CPP between 6-8 years of age require head MRIs. Girls with neurological findings and rapid pubertal progression are more likely to have intracranial pathology and require an MRI examination (**BII**).

Section II: Available GnRH α and therapeutic regimens for CPP

Currently available therapeutic regimens

All available GnRH α are effective despite different routes of administration, dosing, and duration of action (Tables 1, 2 and 3)(42,43). The depot preparations are preferred because of

1 improved compliance (44-46). In most children, monthly injections adequately suppress the
2 gonadotropic axis, but some children require more frequent injections or higher than standard doses.
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4 The 3 month formulations are comparable to monthly dosing, but no randomized comparative trial is
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6 available(42,47-49). In one prospective trial, 7.5 mg leuprolide monthly suppressed LH more
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8 effectively than 11.25 mg three-monthly, although sex steroid concentrations were equally
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10 inhibited(50). The 50 mg histrelin acetate implant provides sustained suppression for 12
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12 months(51,52).
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19 **Conclusions.** A variety of GnRHa formulations are available and efficacious. The choice of a
20 particular agent depends on patient and physician preference (*CIII*).
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22 *Treatment monitoring*

23 Progression of breast or testicular development is suggestive of treatment failure(52-56), but
24 progression of pubic hair may indicate normal adrenarche. Growth velocity, height SDS and BA
25 advancement should decline during treatment. Vaginal bleeding may occur after the first administration
26 of GnRHa, but subsequent bleeding suggests lack of efficacy or incorrect diagnosis. Markedly
27 decreased growth velocity (≤ -2 SDS) or rapid BA advancement should also prompt re-assessment. BA
28 can be used to update AH prediction understanding that the Bayley-Pinneau method may overestimate
29 AH(57). If elevated, random LH levels using an ultrasensitive assay, indicate lack of suppression.
30 Stimulated LH values (using GnRH, aqueous GnRHa, or the free GnRHa contained in depot
31 preparations) can also be used to assess effectiveness. FSH levels are not usually used to monitor
32 suppression. If measured, testosterone and estradiol levels should be in a prepubertal range for the
33 assay used(44,51,53-56,58). No long-term data provide compelling support for any specific short-term
34 monitoring scheme.
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56 **Conclusions.** GnRHa injection dates should be recorded and adherence with dosing interval
57 monitored (*BII*). Tanner stage and growth should be assessed every 3-6 months, and BA monitored
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2 periodically (*BII*). There was no consensus about the routine use of random or stimulated
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4 measurements of gonadotropins or sex steroids for monitoring therapy. In patients with suboptimal
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6 clinical response, there was consensus about need for comprehensive reassessment (*CIII*). Additional
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8 information on the relationship between on-treatment measures of gonadotropic axis suppression and
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10 outcomes are needed.
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13 14 *Adverse events*

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16 GnRHa are generally well tolerated in children and adolescents. Systemic complaints, such as
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18 headaches or hot flashes occur occasionally but are usually short-term and do not interfere with
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20 therapy. Local adverse events occur in about 10-15% of patients and necessitate a change in agent
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22 when persistent because they can result in sterile abscesses in a fraction of the patients(54,55,59).
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24 Although exceedingly rare, anaphylaxis has been described.
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28 29 *Potential new therapeutic agents for the treatment of CPP*

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31 GnRH *antagonists* cause immediate and direct inhibition at the level of pituitary GnRH
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33 receptors(60). Theoretical advantages over GnRHa include eliminating the initial “flare” in
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35 gonadotropic axis activation as well as rapid recovery of suppression once therapy is withdrawn.
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37 Depot and non-peptide orally active GnRH antagonists are under development(61), and could be
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39 evaluated in children with CPP in the future.
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47 48 *Therapeutic agents that can be combined with GnRHa for the treatment of CPP*

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50 Adjunctive therapies that may improve outcomes (AH, for example) of GnRHa therapy include
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52 pure or selective E2 receptor blockers, aromatase inhibitors (62), pure anti-androgens, sex steroids(63)
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54 or non-aromatizable anabolic steroids(64). The addition of oxandrolone increased AH compared to
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56 GnRHa alone in a small non randomized study (n=10)(64). The addition of growth hormone (GH)
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58 increased AH compared to GnRHa alone in girls with CPP and slow growth velocity in small (n=10)
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and =17), non randomized series (65,66). The addition of GH increased height outcome in a randomized controlled study (n=46) in adopted girls with precocious or early puberty (22). However, no large scale randomized controlled trials evaluating the addition of GH to GnRHa in CPP have been performed.

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Conclusions. The addition of GH or oxandrolone to GnRHa cannot be routinely recommended. These adjunctive therapies require validation by larger studies with consideration of potential side effects (*CIII*).

20 21 ***Section III. Discontinuation of GnRHa therapy in CPP***

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Factors that could influence the decision to stop GnRHa treatment depend on the primary goal(s) of therapy including maximizing height, synchronizing puberty with peers, ameliorating psychological distress, and facilitating care of the developmentally delayed child. Available data only permit analysis of factors that impact AH among girls.

Treatment duration. Several studies have reported a direct relationship between treatment duration and AH(14,15,67-69) and an inverse relationship between age at pubertal onset or at initiation of therapy and AH(6,14,67-69). However, deciphering the respective influences of age at onset of puberty, age at initiation of therapy and treatment duration is problematic since these variables are interrelated. Undue delay in initiation of therapy (more than 1-2 years) may compromise AH.

Parent/patient preference, anticipated time of menarche, CA and BA. In studies examined, the wishes of the patient and family and the physician's decision were stated as deciding factors for cessation of treatment (13,15,68,70-73). The mean age at treatment discontinuation ranged from 10.6 to 11.6 yr with mean BA ranging from 12.1 to 13.9 yr, and mean age at menarche of \approx 12.3 yr. Discontinuation at $CA \approx 11.0$ yr(13) and $BA \approx 12.0$ yr(14,67) has been associated with maximum AH. However BA is not an appropriate single variable because a $BA \approx 12.0$ yr can be observed at different

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CAs and because BA is unreliable to predict height gain after treatment(12-15,72). One study has suggested that height gain after treatment may be higher in those with early (<6 yr) vs late treatment (6).

Height and growth velocity. Although growth velocity during therapy(6,13-15,67-69,71,72) and height at interruption of therapy are positively associated with AH(6,13,14), they cannot be used as independent factors for deciding when to stop treatment. In a child with unexplained marked deceleration of growth, consideration might be given to stopping treatment or to introducing adjunct therapies.

Conclusions. There is insufficient evidence to rely on any *one* clinical variable (CA, duration of therapy, BA, height, target height, growth velocity) to make the decision to discontinue treatment (*CIII*). It is, therefore, reasonable to consider these parameters and informed parent and patient preferences, with the goal of menarche occurring near the population norms (*CIII*).

Section IV. Outcomes of GnRHa therapy for CPP

Reproductive function

In girls, follow-up studies have been performed in late teens(68,69,74-76) and up to 31 yr in one study(77) and have reported that ovarian function was not impaired(68,69,74,75,78,79). Menses began 2 to 61 months (mean \approx 16 month) after end of treatment(69,74-77). Regular ovarian cycles occurred in 60% to 96% of the patients, without differences from reference populations(69,74-77). Infertility has not been reported. Of 28 reported pregnancies(69,74,75,77), 7 were terminated and 21 resulted in healthy children(69,75,77). In boys, three small studies showed no differences from controls in gonadal function at the age of 15 to 18 years (68,78,79). Paternity rates have not been reported.

Conclusions. The available data suggest that gonadal function is not impaired in girls treated

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2 with GnRHa (*BII*). Nevertheless, available data are limited. Long-term data on fecundity and ovarian
3 reserve of treated patients with CPP are needed.
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7 *BMI and correlates of metabolic syndrome*

10 Childhood obesity is associated with earlier pubertal development in girls and early sexual
11 maturation is associated with increased prevalence of overweight and obesity. There has been concern
12 that GnRHa therapy may affect BMI. Eleven studies address BMI outcome in girls with
13 CPP(6,12,49,69,75,80-85), 2 include boys(78,80) and 1 includes girls with early puberty (onset at age 8
14 and 9 yr)(86). Before GnRHa treatment, mean BMI SDS was above average in girls with CPP in all
15 studies, while results were split in males(78,80). The combined analysis indicates that BMI SDS did
16 not increase on treatment irrespective of age at presentation. At AH, mean BMI SDS ranged from 0.1
17 to 1.7, with an overall slight decrease from pretreatment BMI. No reports regarding metabolic
18 syndrome and GnRHa treatment were identified.
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21 **Conclusions.** Above average BMI is frequent at diagnosis of CPP. Long-term GnRHa
22 treatment does not appear to cause or aggravate obesity, as judged from BMI (*BII*). Studies of body
23 composition and fat distribution are needed.
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27 *Bone mineral density (BMD)*

30 BMD may decrease during GnRHa therapy. However, subsequent bone mass accrual is
31 preserved and peak bone mass does not seem to be negatively affected by treatment(12,82,87). There
32 is some suggestion that discontinuation of treatment in girls with a BA \leq 11.5 yr may lead to greater
33 BMD(87) and that, as in all adolescents, optimum calcium and vitamin D intake may positively
34 influence bone mass(82).
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36 **Conclusion.** Young adults treated with GnRHa for CPP in childhood ultimately accrue BMD
37 within the normal range for age (*BII*).
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Risk of polycystic ovarian syndrome (PCOS)

The possibility that CPP is a first manifestation of PCOS has been raised(88). PCOS occurred in 0-12% of girls with CPP followed prospectively (12,89-91), as compared to 5-10% in the general population(92). Single studies have reported i) an increased average ovarian size following CPP due to hypothalamic hamartoma(75) ii) a higher prevalence of exaggerated adrenarche in CPP than in controls(93) and iii) the occurrence of signs of PCOS 0.5-4.0 years post-menarche(94).

Conclusions. Follow-up of treated or untreated girls with CPP into the mid-teens suggests that the development of PCOS (**BII**) or polycystic ovary morphology (**CIII**) is not clearly different from that in the general population. Premature adrenarche and early childhood insulin resistance are potential risk factors for PCOS but it is not clear if the presence of these conditions along with CPP increases the eventual risk of PCOS (**CIII**). Longitudinal data through adolescence are needed.

Section V. Psychosocial development

Potential psychological consequences of CPP, including risk for emotional distress and problem behavior, are often used to justify treatment with GnRHa(95,96). Hormonally-induced behavioral changes (e.g., in aggression, sexuality) that occur during normal puberty(97) may occur earlier in children with CPP, perhaps consistent with the hormonal effects on brain development observed in rodents(98).

Limited data are available regarding psychological consequences of CPP, and the few existing studies have limitations that have yielded inconsistent conclusions(99). In 2 studies examining psychological functioning in girls with CPP before and after treatment(24,100), no consistent patterns of change were observed. GnRHa have been suggested to adversely affect mood and cognition in adults (101) but similar effects have not been evaluated in children.

Conclusions. There is little evidence to show whether CPP leads to psychological or

behavioral problems or whether treatment with GnRHa is associated with improved psychological outcome (*CIII*). Thus, no recommendations are possible related to psychosocial outcomes. Controlled studies with standardized instruments are needed.

Section VI. Use of GnRHa in conditions other than CPP

Gonadal protection in children undergoing chemotherapy

Infertility represents one of the main long-term consequences of chemotherapy. Studies evaluating the effects of ovarian suppression by GnRHa during chemotherapy in adult and adolescent patients have yielded inconsistent results(102-104). A prospective, randomized trial in adult women is ongoing.

Conclusions. Routine use of GnRHa for gonadal protection in children undergoing chemotherapy cannot be suggested (*CIII*).

Increasing AH of children with idiopathic short stature (ISS)

The effect of GnRHa therapy on AH has been evaluated in girls with ISS and normal puberty (8-10 yrs of age) with a mean gain compared to predicted height of 0 to 4.2 cm(6,14,15,57,69,71,73,105-110). In boys with rapidly progressing puberty, GnRHa therapy increased AH compared to predicted height(5). The effects of combined GH and GnRHa therapy in children with ISS are controversial(111) with mean gains of 4.4 to 10 cm with combination therapy vs -0.5 to 6.1 cm in untreated controls(112,113). In these studies, one cannot definitively separate the effects of GH from GnRHa. In two randomized studies in adopted girls with normal puberty, GnRHa plus GH was compared with GnRHa alone with a 3 cm height gain with combination therapy(22,114). Disadvantages of the use of GnRHa in children with ISS include: absence of pubertal growth acceleration, delayed puberty with potential psychosocial disadvantage, and decreased bone mineral density. Long-term follow-up studies are lacking.

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Conclusions. GnRHa therapy alone in children with ISS and normally timed puberty is minimally effective in increasing AH, may compromise bone mineral density and cannot be suggested for routine use (*DII*). Combined GnRHa and GH therapy leads to a significant height gain, but may have adverse effects. Routine use of GnRHa in children with ISS being treated with GH cannot be suggested (*CIII*).

Increasing AH of children born small for gestational age (SGA)

Short children born SGA usually have a normal pubertal timing although some of them have rapidly progressing puberty, and may be treated with GH(92,115). Data on the additional effect of GnRHa are limited(113).

Conclusion. Routine use of the combination of GnRHa and GH in children born SGA cannot be suggested (*CIII*).

Increasing AH of children with severe hypothyroidism

Some children with severe hypothyroidism are at risk for rapid progression through puberty and diminished AH. In the only study available, combined GnRHa and LT4 and LT4 alone produced similar gains in height SDS (116).

Conclusions. Routine use of combined therapy with GnRH and LT4 cannot be suggested (*CIII*).

Increasing AH of children with growth hormone deficiency (GHD)

Some children with GH deficiency are short at the start of puberty and at risk for short adult stature. Retrospective studies evaluating the addition of GnRHa to GH involve limited number of subjects and provide controversial results(117-119). Three prospective studies reporting near-adult or AH have shown approximately a 1 SD height gain(120-122), possibly without detrimental effect on BMD(123) .

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Conclusions. Routine use of combined therapy with GnRH and GH in GH deficient children with low predicted AH at onset of puberty cannot be suggested (*CIII*).

Increasing AH of children with congenital adrenal hyperplasia (CAH)

One nonrandomized study examined the effect of combined GH and GnRHa treatment on AH in 14 children with CAH and normal or precocious puberty and found a 1 SD increase in AH in comparison with standard treatment for CAH(124).

Conclusions. Further studies are needed to determine whether GnRHa therapy alone or in combination with GH should be used in children with CAH and low predicted AH. Routine use of GnRHa in CAH cannot be suggested (*CIII*).

Children with autism

Despite one controversial manuscript reporting that GnRHa may benefit behavioral symptoms in children with autism(125), the consensus is that there is no current evidence for GnRHa therapy for this indication (*CIII*).

Summary

Several important observations emerged from this conference. Despite a considerable body of literature on the use of GnRHa, few rigorously conducted and controlled prospective studies are available from which to derive evidence-based recommendations. Most of our conclusions are categorized as *CIII*, a level of evidence that underscores the need for further research in key areas, such as the psychosocial effects of GnRHa treatment for CPP. The efficacy to increase AH is undisputed only in early onset progressive CPP. This highlights the need to increase our knowledge of the pathophysiology and normal limits of puberty and of the physical and psychosocial consequences of treated and untreated CPP. The conference's systematic review also highlighted the lack of objective support for commonly voiced concerns such as the propensity for GnRHa to promote weight gain or to

1
2 lead to long term diminution of bone mineral density. Use of GnRHa in conditions other than CPP
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4 requires further investigation and cannot be routinely suggested.
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Table 1. Characteristics of GnRHa

	Rapid-acting	Monthly depot	3-month depot	12 month implant
Dosing	3-4 times daily (intranasal) or every day (subcutaneous)	every 28 days	every 90 days	every year
Peak serum concentrations	10-45 min	4 hrs	4-8 hrs	1 month
Onset of therapeutic suppression	2-4 weeks	1 month	1 month	1 month
Advantage	Quick on/off	Dosing and efficacy well studied	Fewer injections and fewer compliance concerns	No injections needed
Disadvantage	Multiple daily doses needed / compliance very difficult	Painful injections / suboptimal compliance	Painful injection	Requires surgical procedure for insertion and removal

Table 2. Rapid-acting formulations of GnRH α

GnRH analog	Administration	Starting Dose
Nafarelin	Nasal spray	800 μ g BID
Buserelin	Nasal spray	20-40 μ g/kg/day
Buserelin	Subcutaneous	1200-1800 μ g/day
Leuprolide	Subcutaneous	50 μ g/kg/day
Deslorelin	Subcutaneous	4-8 μ g/kg/day
Histrelin	Subcutaneous	8-10 μ g/kg/day
Triptorelin	Subcutaneous	20-40 μ g/kg/day

Table 3: Depot GnRHa formations(42,47,48)

Depot preps	Brand name	Starting Dose
Goserelin	Zoladex LA	3.6 mg every mo OR 10.8 mg every 3 mo
Buserelin	Suprefact depot	6.3 mg every 2 mo
Leuprolide	Enantone or Lupron-depot	3.75 mg every mo/ OR 11.25 mg every 3 mo
	Prostap SR	4-8 µg/kg/day
	Lupron-depot-PED	7.5, 11.25, or 15 mg every mo (0.2 to 0.3 mg/kg/mo) OR 11.25 mg every 3 mo*
Triptorelin	Decapeptyl, Gonapeptyl	3 or 3.75 mg every mo OR 11.25 mg every 3 mo
Histrelin	Supprelin LA	50 mg implant every year

no data is available on the use of the 22.5 mg 3 mo depot in children

References

1. Kish MA. Guide to development of practice guidelines. *Clin Infect Dis*. 2001;32:851-4.
2. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care*. 2003;12:18-23.
3. 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;84:415-423.
4. Klein KO. Precocious puberty: who has it? Who should be treated? *J Clin Endocrinol Metab*. 1999;84:411-4.
5. Lazar L, Pertzalan A, Weintrob N, et al. Sexual precocity in boys: accelerated versus slowly progressive puberty gonadotropin-suppressive therapy and final height. *J Clin Endocrinol Metab*. 2001;86:4127-32.
6. 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;92:3483-9.
7. Fontoura M, Brauner R, Prevot C, et al. Precocious puberty in girls: early diagnosis of a slowly progressing variant. *Arch Dis Child*. 1989;64:1170-1176.
8. Papadimitriou A, Beri D, Tsialla A, et al. Early growth acceleration in girls with idiopathic precocious puberty. *J Pediatr*. 2006;149:43-6.
9. Zachmann M, Sobradillo B, Frank M, et al. Bayley-Pinneau, Roche-Wainer-Thissen, and Tanner height predictions in normal children and in patients with various pathologic conditions. *J Pediatr*. 1978;93:749-755.
10. Bar A, Linder B, Sobel EH, et al. Bayley-Pinneau method of height prediction in girls with central precocious puberty: correlation with adult height. *J Pediatr*. 1995;126:955-958.
11. Kauli R, Galatzer A, Kornreich L, et al. Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. A comparative study with re-evaluation of predictions by the Bayley-Pinneau method. *Horm Res*. 1997;47:54-61.
12. 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. *J Clin Endocrinol Metab*. 1999;84:4583-90.
13. Carel JC, Roger M, Ispas S, et al. Final height after long-term treatment with triptorelin slow-release for central precocious puberty: importance of statural growth after interruption of treatment. *J Clin Endocrinol Metab*. 1999;84:1973-1978.
14. Arrigo T, Cisternino M, Galluzzi 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;141:140-4.

- 1 15. Klein KO, Barnes KM, Jones JV, et al. Increased final height in precocious puberty after long-
2 term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol*
3 *Metab.* 2001;86:4711-6.
- 4 16. Paul DL, Conte FA, Grumbach MM, et al. Long term effect of gonadotropin-releasing hormone
5 agonist therapy in children with true precocious puberty treated at a median age of less than 5 years. *J*
6 *Clin Endocrinol Metab.* 1995;80:546-551.
- 7 17. Mul D, Bertelloni S, Carel JC, et al. Effect of gonadotropin-releasing hormone agonist
8 treatment in boys with central precocious puberty: final height results. *Horm Res.* 2002;58:1-7.
- 9 18. Kaltiala-Heino R, Marttunen M, Rantanen P, et al. Early puberty is associated with mental
10 health problems in middle adolescence. *Soc Sci Med.* 2003;57:1055-64.
- 11 19. Albanese A, Hopper NW. Suppression of menstruation in adolescents with severe learning
12 disabilities. *Arch Dis Child.* 2007;92:629-32.
- 13 20. Teilmann G, Boas M, Petersen JH, et al. Early pituitary-gonadal activation before clinical signs
14 of puberty in 5- to 8-year-old adopted girls: a study of 99 foreign adopted girls and 93 controls. *J Clin*
15 *Endocrinol Metab.* 2007;92:2538-44.
- 16 21. Teilmann G, Pedersen CB, Skakkebaek NE, et al. Increased risk of precocious puberty in
17 internationally adopted children in Denmark. *Pediatrics.* 2006;118:e391-9.
- 18 22. Tuvemo T, Jonsson B, Gustafsson J, et al. Final height after combined growth hormone and
19 GnRH analogue treatment in adopted girls with early puberty. *Acta Paediatr.* 2004;93:1456-62.
- 20 23. Berg-Kelly K, Eriksson J. Adaptation of adopted foreign children at mid-adolescence as
21 indicated by aspects of health and risk taking--a population study. *Eur Child Adolesc Psychiatry.*
22 1997;6:199-206.
- 23 24. Mul D, Versluis-den Bieman HJ, Slijper FM, et al. Psychological assessments before and after
24 treatment of early puberty in adopted children. *Acta Paediatr.* 2001;90:965-71.
- 25 25. Neely EK, Hintz RL, Wilson DM, et al. Normal ranges for immunochemiluminometric
26 gonadotropin assays. *J Pediatr.* 1995;127:40-6.
- 27 26. Neely EK, Wilson DM, Lee PA, et al. Spontaneous serum gonadotropin concentrations in the
28 evaluation of precocious puberty. *J Pediatr.* 1995;127:47-52.
- 29 27. Resende EA, Lara BH, Reis JD, et al. Assessment of basal and gonadotropin-releasing
30 hormone-stimulated gonadotropins by immunochemiluminometric and immunofluorometric assays in
31 normal children. *J Clin Endocrinol Metab.* 2007;92:1424-9.
- 32 28. Roger M, Lahlou N, Chaussain JL. Gonadotropin-releasing hormone testing in pediatrics. In:
33 Ranke MB, editor. *Diagnostics of endocrine function in children and adolescents.* Heidelberg: Johann
34 Ambrosius Barth Verlag; 1996. p. 346-369.
- 35 29. Eckert KL, Wilson DM, Bachrach LK, et al. A single-sample, subcutaneous gonadotropin-
36 releasing hormone test for central precocious puberty. *Pediatrics.* 1996;97:517-9.

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60
30. Garibaldi LR, Aceto T, Jr., Weber C, et al. The relationship between luteinizing hormone and estradiol secretion in female precocious puberty: evaluation by sensitive gonadotropin assays and the leuprolide stimulation test. *J Clin Endocrinol Metab.* 1993;76:851-6.
31. Ibanez L, Potau N, Zampolli M, et al. Use of leuprolide acetate response patterns in the early diagnosis of pubertal disorders: comparison with the gonadotropin-releasing hormone test. *J Clin Endocrinol Metab.* 1994;78:30-35.
32. Pescovitz OH, Hench KD, Barnes KM, et al. Premature thelarche and central precocious puberty: the relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. *J Clin Endocrinol Metab.* 1988;67:474-9.
33. Oerter KE, Uriarte MM, Rose SR, et al. Gonadotropin secretory dynamics during puberty in normal girls and boys. *J Clin Endocrinol Metab.* 1990;71:1251-8.
34. de Vries L, Horev G, Schwartz M, et al. Ultrasonographic and clinical parameters for early differentiation between precocious puberty and premature thelarche. *Eur J Endocrinol.* 2006;154:891-8.
35. Bay K, Andersson AM, Skakkebaek NE. Estradiol levels in prepubertal boys and girls--analytical challenges. *Int J Androl.* 2004;27:266-73.
36. Wang C, Catlin DH, Demers LM, et al. Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. *J Clin Endocrinol Metab.* 2004;89:534-43.
37. Battaglia C, Mancini F, Regnani G, et al. Pelvic ultrasound and color Doppler findings in different isosexual precocities. *Ultrasound Obstet Gynecol.* 2003;22:277-83.
38. Haber HP, Wollmann HA, Ranke MB. Pelvic ultrasonography: early differentiation between isolated premature thelarche and central precocious puberty. *Eur J Pediatr.* 1995;154:182-6.
39. Chalumeau M, Hadjiathanasiou CG, Ng SM, et al. Selecting girls with precocious puberty for brain imaging: validation of European evidence-based diagnosis rule. *J Pediatr.* 2003;143:445-50.
40. Cisternino M, Arrigo T, Pasquino AM, et al. Etiology and age incidence of precocious puberty in girls: a multicentric study. *J Pediatr Endocrinol Metab.* 2000;13 Suppl 1:695-701.
41. De Sanctis V, Corrias A, Rizzo V, et al. Etiology of central precocious puberty in males: the results of the Italian Study Group for Physiopathology of Puberty. *J Pediatr Endocrinol Metab.* 2000;13 Suppl 1:687-93.
42. Antoniazzi F, Zamboni G. Central precocious puberty: current treatment options. *Paediatric Drugs.* 2004;6:211-31.
43. Crowley WF, Jr., Comite F, Vale W, et al. Therapeutic use of pituitary desensitization with a long-acting lhrh agonist: a potential new treatment for idiopathic precocious puberty. *J Clin Endocrinol Metab.* 1981;52:370-2.
44. Carel JC, Lahlou N, Guazzarotti L, et al. Treatment of central precocious puberty with depot leuprolide acetate. *Eur.J.Endoc.* 1995;132:699-704.

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45. Heinrichs C, Craen M, Vanderschueren-Lodeweyckx M, et al. Variations in pituitary-gonadal suppression during intranasal buserelin and intramuscular depot-triptorelin therapy for central precocious puberty. Belgian Study Group for Pediatric Endocrinology. *Acta Paediatrica*. 1994;83:627-33.
46. Tuvemo T, Gustafsson J, Proos LA, et al. Suppression of puberty in girls with short-acting intranasal versus subcutaneous depot GnRH agonist. *Hormone Research*. 2002;57:27-31.
47. Lahlou N, Carel JC, Chaussain JL, et al. Pharmacokinetics and pharmacodynamics of GnRH agonists: clinical implications in pediatrics. *J Pediatr Endocrinol Metab*. 2000;13 Suppl 1:723-37.
48. Partsch CJ, Sippell WG. Treatment of central precocious puberty. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2002;16:165-89.
49. Paterson WF, McNeill E, Young D, et al. Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. *Clin Endocrinol (Oxf)*. 2004;61:626-34.
50. Badaru A, Wilson DM, Bachrach LK, et al. Sequential comparisons of one-month and three-month depot leuprolide regimens in central precocious puberty. *J Clin Endocrinol Metab*. 2006;91:1862-7.
51. Eugster EA, Clarke W, Kletter GB, et al. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. *J Clin Endocrinol Metab*. 2007;92:1697-704.
52. Hirsch HJ, Gillis D, Strich D, et al. The histrelin implant: a novel treatment for central precocious puberty. *Pediatrics*. 2005;116:e798-802.
53. Tanaka T, Hibi I, Kato K, et al. A dose finding study of a super long-acting luteinizing hormone-releasing hormone analog (Leuprolide acetate depot, TAP-144-SR) in the treatment of central precocious puberty. *Endocrinol Japn*. 1991;38:369-376.
54. Neely EK, Hintz RL, Parker B, et al. Two-year results of treatment with depot leuprolide acetate for central precocious puberty. *J Pediatr*. 1992;121:634-640.
55. Carel JC, Lahlou N, Jaramillo O, et al. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). *J Clin Endocrinol Metab*. 2002;87:4111-6.
56. Carel JC, Blumberg J, Seymour C, et al. Three-month sustained-release triptorelin (11.25 mg) in the treatment of central precocious puberty. *Eur J Endocrinol*. 2006;154:119-24.
57. Carel JC, Lahlou N, Roger M, et al. Precocious puberty and statural growth. *Hum Reprod Update*. 2004;10:135-47.
58. Lee PA, Page JG, Group LS. Effects of leuprolide in the treatment of central precocious puberty. *J Pediatr*. 1989;114:321-324.
59. Manasco PK, Pescovitz OH, Blizzard RM. Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr*. 1993;123:334-335.

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56
57
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59
60
60. Roth C. Therapeutic potential of GnRH antagonists in the treatment of precocious puberty. *Expert Opin Investig Drugs*. 2002;11:1253-9.
61. Schultze-Mosgau A, Griesinger G, Altgassen C, et al. New developments in the use of peptide gonadotropin-releasing hormone antagonists versus agonists. *Expert Opin Investig Drugs*. 2005;14:1085-97.
62. Eugster EA. Aromatase inhibitors in precocious puberty: rationale and experience to date. *Treat Endocrinol*. 2004;3:141-51.
63. Lampit M, Golander A, Guttmann H, et al. Estrogen mini-dose replacement during GnRH agonist therapy in central precocious puberty: a pilot study. *J Clin Endocrinol Metab*. 2002;87:687-90.
64. Vottero A, Pedori S, Verna M, et al. Final height in girls with central idiopathic precocious puberty treated with gonadotropin-releasing hormone analog and oxandrolone. *J Clin Endocrinol Metab*. 2006;91:1284-7.
65. Pasquino AM, Pucarelli I, Segni M, et al. Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone analogues and growth hormone. *J Clin Endocrinol Metab*. 1999;84:449-52.
66. Pucarelli I, Segni M, Ortore M, et al. Effects of combined gonadotropin-releasing hormone agonist and growth hormone therapy on adult height in precocious puberty: a further contribution. *J Pediatr Endocrinol Metab*. 2003;16:1005-10.
67. Oostdijk W, Rikken B, Schreuder S, et al. Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. *Arch Dis Child*. 1996;75:292-297.
68. Tanaka T, Niimi H, Matsuo N, et al. Results of long-term follow-up after treatment of central precocious puberty with leuporelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J Clin Endocrinol Metab*. 2005;90:1371-6.
69. Pasquino AM, Pucarelli I, Accardo F, et al. 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;93:190-5.
70. Antoniazzi F, Arrigo T, Cisternino M, et al. End results in central precocious puberty with GnRH analog treatment: the data of the Italian Study Group for Physiopathology of Puberty. *J Pediatr Endocrinol Metab*. 2000;13 Suppl 1:773-80.
71. Mul D, Oostdijk W, Otten BJ, et al. Final height after gonadotrophin releasing hormone agonist treatment for central precocious puberty: the Dutch experience. *J Pediatr Endocrinol Metab*. 2000;13 Suppl 1:765-72.
72. Partsch CJ, Heger S, Sippell WG. Treatment of central precocious puberty: lessons from a 15 years prospective trial. German Decapeptyl Study Group. *J Pediatr Endocrinol Metab*. 2000;13 Suppl 1:747-58.
73. Cassio A, Cacciari E, Balsamo A, et al. 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;81:329-32.
74. Cassio A, Bal MO, Orsini LF, et al. Reproductive outcome in patients treated and not treated for idiopathic early puberty: long-term results of a randomized trial in adults. *J Pediatr*. 2006;149:532-6.
75. Feuillan PP, Jones JV, Barnes K, et al. Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab*. 1999;84:44-49.
76. Arrigo T, De Luca F, Antoniazzi F, et al. Menstrual cycle pattern during the first gynaecological years in girls with precocious puberty following gonadotropin-releasing hormone analogue treatment. *Eur J Pediatr*. 2007;166:73-4.
77. Heger S, Muller M, Ranke M, et al. Long-term GnRH agonist treatment for female central precocious puberty does not impair reproductive function. *Mol Cell Endocrinol*. 2006;254-255:217-20.
78. Feuillan PP, Jones JV, Barnes KM, et al. Boys with precocious puberty due to hypothalamic hamartoma: reproductive axis after discontinuation of gonadotropin-releasing hormone analog therapy. *J Clin Endocrinol Metab*. 2000;85:4036-8.
79. Bertelloni S, Baroncelli GI, Ferdeghini M, et al. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *Eur J Pediatr*. 2000;159:369-74.
80. Palmert MR, Mansfield MJ, Crowley WFJ, et al. Is obesity an outcome of gonadotropin-releasing hormone agonist administration? Analysis of growth and body composition in 110 patients with central precocious puberty. *J Clin Endocrinol Metab*. 1999;84:4480-8.
81. van der Sluis IM, Boot AM, Krenning EP, et al. Longitudinal follow-up of bone density and body composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. *J Clin Endocrinol Metab*. 2002;87:506-12.
82. Antoniazzi F, Zamboni G, Bertoldo F, et al. Bone mass at final height in precocious puberty after gonadotropin-releasing hormone agonist with and without calcium supplementation. *J Clin Endocrinol Metab*. 2003;88:1096-101.
83. Arrigo T, De Luca F, Antoniazzi F, et al. Reduction of baseline body mass index under gonadotropin-suppressive therapy in girls with idiopathic precocious puberty. *Eur J Endocrinol*. 2004;150:533-7.
84. Messaoui A, Massa G, Tenoutasse S, et al. [Treatment of central precocious puberty with Gonadotropin-Releasing Hormone agonist (triptorelin) in girls: breast development, skeletal maturation, height and weight evolution during and after treatment]. *Rev Med Brux*. 2005;26:27-32.
85. Traggiai C, Perucchin PP, Zerbini K, et al. Outcome after depot gonadotrophin-releasing hormone agonist treatment for central precocious puberty: effects on body mass index and final height. *Eur J Endocrinol*. 2005;153:463-4.
86. Lazar L, Kauli R, Pertzalan A, et al. 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*

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Metab. 2002;87:2090-4.

87. Bertelloni S, Baroncelli GI, Sorrentino MC, et al. Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr.* 1998;157:363-7.

88. Escobar ME, Ropelato MG, Ballerini MG, et al. Acceleration of Luteinizing Hormone Pulse Frequency in Adolescent Girls with a History of Central Precocious Puberty with versus without Hyperandrogenism. *Horm Res.* 2007;68:278-285.

89. Cisternino M, Pasquino A, Bozzola M, et al. Final height attainment and gonadal function in girls with precocious puberty treated with cyproterone acetate. *Horm Res.* 1992;37:86-90.

90. Palmert MR, Hayden DL, Mansfield MJ, et al. The longitudinal study of adrenal maturation during gonadal suppression: evidence that adrenarche is a gradual process. *J Clin Endocrinol Metab.* 2001;86:4536-42.

91. Jensen AM, Brocks V, Holm K, et al. Central precocious puberty in girls: internal genitalia before, during, and after treatment with long-acting gonadotropin-releasing hormone analogues. *J Pediatr.* 1998;132:105-8.

92. Rosenfield RL. Identifying children at risk of polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2007;92:787-796.

93. Lazar L, Kauli R, Bruchis C, et al. High prevalence of abnormal adrenal response in girls with central precocious puberty at early pubertal stages. *Eur J Endocrinol.* 1995;133:407-11.

94. Lazar L, Kauli R, Bruchis C, et al. Early polycystic ovary-like syndrome in girls with central precocious puberty and exaggerated adrenal response. *Eur J Endocrinol.* 1995;133:403-6.

95. Steinberg L, Morris AS. Adolescent development. *Annual Review of Psychology.* 2001;52:83-110.

96. Weichold K, Silbereisen RK, Schmitt-Rodermund E. Short-and long-term consequences of early versus late physical maturation in adolescents. In: Hayward C, editor. *Puberty and psychopathology.* Cambridge, MA: Cambridge University Press; 2003. p. 241-276.

97. Susman EJ, Rogol AD. Puberty and psychological development. In: Lerner RM, Steinberg L, editors. *Handbook of adolescent psychology.* 2nd ed. Hoboken, NJ: Wiley; 2004. p. 15-44.

98. Sisk CL, Zehr JL. Pubertal hormones organize the adolescent brain and behavior. *Frontiers in Neuroendocrinology.* 2005;26:163-174.

99. Dorn LD. Psychological and social problems in children with premature adrenarche and precocious puberty. In: Pescovitz OH, Walvoord EC, editors. *When puberty is precocious: Scientific and clinical aspects.* Totowa, NJ: Humana Press; 2007. p. 309-327.

100. Xhrouet-Heinrichs D, Lagrou K, Heinrichs C, et al. Longitudinal study of behavioral and affective patterns in girls with central precocious puberty during long-acting triptorelin therapy. *Acta Paediatr.* 1997;86:808-15.

101. Grigorova M, Sherwin BB, Tulandi T. Effects of treatment with leuprolide acetate depot on working memory and executive functions in young premenopausal women. *Psychoneuroendocrinology*. 2006;31:935-947.
102. Pereyra Pacheco B, Mendez Ribas JM, Milone G, et al. Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report. *Gynecol Oncol*. 2001;81:391-7.
103. Waxman JH, Ahmed R, Smith D, et al. Failure to preserve fertility in patients with Hodgkin's disease. *Cancer Chemother Pharmacol*. 1987;19:159-62.
104. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol*. 2006;24:2917-31.
105. Antoniazzi F, Cisternino M, Nizzoli G, et al. Final height in girls with central precocious puberty: comparison of two different luteinizing hormone-releasing hormone agonist treatments. *Acta Paediatr*. 1994;83:1052-1056.
106. Carel JC, Hay F, Coutant R, et al. Gonadotropin releasing hormone agonist treatment of girls with constitutional short stature and normal pubertal development. *J Clin Endocrinol Metab*. 1996;81:3318-3322.
107. Bouvattier C, Coste J, Rodrigue D, 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;84:3575-3578.
108. 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;348:908-17.
109. Lanes R, Soros A, Jakubowicz S. Accelerated versus slowly progressive forms of puberty in girls with precocious and early puberty. Gonadotropin suppressive effect and final height obtained with two different analogs. *J Pediatr Endocrinol Metab*. 2004;17:759-66.
110. Tuvemo T. Treatment of central precocious puberty. *Expert Opin Investig Drugs*. 2006;15:495-505.
111. Carel JC. Management of short stature with GnRH agonist and co-treatment with growth hormone: a controversial issue. *Mol Cell Endocrinol*. 2006;254-255:226-33.
112. Pasquino AM, Pucarelli I, Roggini M, et al. Adult height in short normal girls treated with gonadotropin-releasing hormone analogs and growth hormone. *J Clin Endocrinol Metab*. 2000;85:619-622.
113. van Gool SA, Kamp GA, Visser-van Balen H, 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;92:1402-8.
114. Mul D, Oostdijk W, Waelkens JJ, et al. 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;63:185-90.

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115. Clayton PE, Cianfarani S, Czernichow P, et al. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocrinol Metab.* 2007;92:804-10.
116. Teng L, Bui H, Bachrach L, et al. Catch-up growth in severe juvenile hypothyroidism: treatment with a GnRH analog. *J Pediatr Endocrinol Metab.* 2004;17:345-54.
117. Carel JC, Ecosse E, Nicolino M, et al. Adult height after long-term recombinant growth hormone treatment for idiopathic isolated growth hormone deficiency: observational follow-up study of the French population-based registry. *BMJ.* 2002;325:70-73.
118. Reiter EO, Lindberg A, Ranke MB, 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;60:68-73.
119. Mul D, Wit JM, Oostdijk W, et al. The effect of pubertal delay by GnRH agonist in GH-deficient children on final height. *J Clin Endocrinol Metab.* 2001;86:4655-6.
120. Mericq MV, Eggers M, Avila A, et al. 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;85:569-73.
121. Saggese G, Federico G, Barsanti S, et al. 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;86:1900-4.
122. Tanaka T, Satoh M, Yasunaga T, et al. When and how to combine growth hormone with a luteinizing hormone-releasing hormone analogue. *Acta Paediatr Suppl.* 1999;88:85-8.
123. Mericq V, Gajardo H, Eggers M, et al. 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;87:84-9.
124. Lin-Su K, Vogiatzi MG, Marshall I, 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;90:3318-25.
125. Geier DA, Geier MR. A clinical trial of combined anti-androgen and anti-heavy metal therapy in autistic disorders. *Neuro Endocrinol Lett.* 2006;27:833-8.