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Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children

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ABSTRACT

OBJECTIVE. Gonadotropin-releasing hormone analogs revolutionized the treatment of central precocious puberty. However, questions remain regarding their optimal use in central precocious puberty and other conditions. The Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology convened a consensus conference to review the clinical use of gonadotropin-releasing hormone analogs 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, an equal male/female ratio, and a balanced spectrum of professional seniority and expertise.

EVIDENCE. Preference was given to articles written in English with long-term outcome data. The US Public Health grading system was used to grade evidence and rate the strength of conclusions. When evidence was insufficient, conclusions were based on expert opinion.

CONSENSUS PROCESS. Participants were put into working groups with assigned topics and specific questions. Written materials were prepared and distributed before the conference, revised on the basis of 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 gonadotropin-releasing hormone analogs in increasing adult height is undisputed only in early-onset (girls <6 years old) central precocious puberty. Other key areas, such as the psychosocial effects of central precocious puberty and their alteration by gonadotropin-releasing hormone analogs, need additional study. Few controlled prospective studies have been performed with gonadotropin-releasing hormone analogs in children, and many conclusions rely in part on collective expert opinion. The conference did not endorse commonly voiced concerns regarding the use of gonadotropin-releasing hormone analogs, such as promotion of weight gain or long-term diminution of bone mineral density. Use of gonadotropin-releasing hormone analogs for conditions other than central precocious puberty requires additional investigation and cannot be suggested routinely. *Pediatrics* 2009;123:e752–e762

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Key Words

precocious puberty, GnRH analogs, development

Abbreviations

GnRHa—gonadotropin-releasing hormone analog
 CPP—central precocious puberty
 ESPE—European Society for Pediatric Endocrinology
 LWPES—Lawson Wilkins Pediatric Endocrine Society
 AH—adult height
 BA—bone age
 CA—chronological age
 LH—luteinizing hormone
 FSH—follicle-stimulating hormone
 SDS—SD score
 GH—growth hormone
 BMD—bone mineral density
 PCOS—polycystic ovarian syndrome
 ISS—idiopathic short stature
 SGA—small for gestational age
 CAH—congenital adrenal hyperplasia

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GONADOTROPIN-RELEASING HORMONE ANALOGS (GnRHAs) 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 Pediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES) convened a consensus conference to examine GnRHa therapy in pediatric patients. We 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 before 8 years of age in girls and 9 years of age in boys.

METHODS

Participant Selection

Consideration was given to equal representation from North America (United States and Canada) and Europe, an equal male/female ratio, and a balanced spectrum of professional seniority and expertise.

Process

Thirty participants were put into 1 of 6 groups with assigned topics and designated chairpersons. Each participant prepared a summary of the literature regarding a question that was distributed before 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 on the basis of a vote of all participants. This report is organized around the questions that were addressed; it has been approved by the participants and endorsed by the 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 US Public Health grading system¹ was used to grade the evidence and strength of the recommendations.* Grading was reviewed by the full conference under the guidance of a methodologist/biostatistician. This report is not a practice guideline; nonetheless, we aimed to adhere to modified appraisal of guidelines research and evaluation (AGREE) criteria.²

INITIATION OF GnRHa THERAPY FOR CPP

Clinical Criteria

The most important clinical criterion for GnRHa treatment is documented progression of pubertal development, which is based on the recognition that many patients with CPP have a slowly progressive or nonprogressive form and achieve adult height (AH) within their target range without GnRHAs.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- to 6-month period before GnRHa therapy. This observational period may not be necessary if the child is at or past Tanner stage III (breast), particularly with advanced skeletal maturation (CIII).

*The qualities of evidence are I (data from ≥ 1 properly randomized, controlled trial), II (data from other clinical studies), and III (data from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees), and the strengths of recommendation are A (good evidence to support use), B (moderate evidence to support use), C (poor evidence to support recommendation), D (moderate evidence against use), and E (strong evidence against use).

Chronological Age 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 methods⁹; however, in some instances, it may overpredict height by several centimeters.^{10,11}

The greatest height gain has been observed in girls with onset of puberty at < 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 CA to height outcomes among boys.¹⁷

Data regarding the psychosocial impact of untreated or treated CPP are inconclusive, and whether delaying puberty with GnRHAs 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, GnRHAs are only one of several therapeutic options, including progestogens, that could be considered.¹⁹

Conclusions: Girls with onset of progressive CPP before 6 years of age benefit most in terms of height from GnRHAs. The decision to initiate therapy in girls with onset after the age of 6 should be individualized (BII). Treatment should be considered for all boys with onset of progressive CPP before 9 years of age who have compromised height potential (CIII). The use of GnRHAs solely to influence the psychosocial consequences of CPP or to delay menarche should be considered carefully given the absence of convincing data (CIII). Additional studies to evaluate 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 for boys.^{20,21} Response to GnRHAs in adopted girls with precocious or early normal puberty seems comparable with that seen in nonadopted 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 well-being.²⁴

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

Hormonal Criteria

Luteinizing hormone (LH) measurements are the most valuable biochemical parameter for the diagnosis of CPP.

TABLE 1 Characteristics of GnRHs

	Rapid Acting	Monthly Depot	3-mo Depot	12-mo Implant
Dosing	3–4 times daily (intranasal) or every day (subcutaneous)	Every 28 d	Every 90 d	Every year
Peak serum concentrations	10–45 min	4 h	4–8 h	1 mo
Onset of therapeutic suppression	2–4 wk	1 mo	1 mo	1 mo
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

Because prepubertal LH levels are <0.1 IU/L, LH assays used should have a detection limit near 0.1 IU/L.^{25–27} In 1 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 the 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 minutes^{27–29}) or with a GnRHa such as aqueous leuprolide (single sample at 60 minutes^{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 have hampered the development of diagnostic cutoffs for CPP, although an (assay-specific) prepubertal limit of peak LH at 3.3 to 5.0 IU/L has been suggested.^{25,27,28}

LH levels provide more information than those of follicle-stimulating hormone (FSH). However, the stimulated LH/FSH ratio may help differentiate progressive CPP (which tends to have higher LH/FSH ratios) from nonprogressive variants that do not require GnRHa therapy.^{32–34}

For estradiol, the most sensitive measurements (tandem mass spectrometry) have shown that prepubertal levels may be <1 pg/mL (3.7 pmol/L) and undetectable with commonly available assays.³⁵ Thus, in non-mass spectrometry assays, measurable estradiol only confirms relatively advanced puberty. Similarly, testosterone assays with detection limits of >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 the 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

Female patients with CPP have increased ovarian and uterine dimensions compared with 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 ($\sim 100\%$) but less sensitive (42%–87%).³⁴ The cutoffs for a pubertal ovarian volume range between 1 and 3 mL (volume = length \times width \times height $\times 0.5233$).³⁸

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

Central Nervous System Imaging

CPP may be a sign of central nervous system pathology. Unsuspected intracranial pathology has been reported in 8% of girls^{39,40} and 40% of boys⁴¹ without neurologic findings or neurofibromatosis. The percentage of children with unsuspected intracranial pathology decreases with age.^{39–41} Only 2% to 7% of girls who have onset of CPP between the ages of 6 and 8 years have unsuspected pathology, and only $\sim 1\%$ 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 <6 years of age should have a head MRI. It is controversial whether all girls who develop CPP between 6 and 8 years of age require head MRI. Girls with neurologic findings and rapid pubertal progression are more likely to have intracranial pathology and require an MRI examination (BII).

AVAILABLE GnRHs AND THERAPEUTIC REGIMENS FOR CPP

Currently Available Therapeutic Regimens

All available GnRHs are effective despite their different routes of administration, dosing, and duration of action (Tables 1–3).^{42,43} The depot preparations are preferred be-

TABLE 2 Rapid-Acting Formulations of GnRHs

GnRHa	Administration	Starting Dose, per day
Nafarelin	Nasal spray	800 μ g twice
Buserelin	Nasal spray	20–40 μ g/kg
Buserelin	Subcutaneous	1200–1800 μ g
Leuprolide	Subcutaneous	50 μ g/kg
Deslorelin	Subcutaneous	4–8 μ g/kg
Histrelin	Subcutaneous	8–10 μ g/kg
Triptorelin	Subcutaneous	20–40 μ g/kg

TABLE 3 Depot GnRHa Formulations^{42,47,48}

Depot Preparation	Brand Name	Starting Dose
Goserelin	Zoladex LA	3.6 mg every month 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 month or 11.25 mg every 3 mo
	Prostap SR	3.75 mg every month
	Lupron depot PED	7.5, 11.25, or 15 mg every month (0.2–0.3 mg/kg per mo) or 11.25 mg every 3 mo ^a
Triptorelin	Decapeptyl, Gonapeptyl	3 or 3.75 mg every month or 11.25 mg every 3 mo
Histrelin	Supprelin LA	50 mg implant every year

^a No data are available on the use of the 22.5-mg 3-month depot in children.

cause of improved compliance.^{44–46} In most children, monthly injections adequately suppress the gonadotropic axis, but some children require more frequent injections or higher-than-standard doses. The 3-month formulations are comparable with monthly dosing, but no randomized comparative trial is available.^{42,47–49} In 1 prospective trial, 7.5 mg of leuprolide monthly suppressed LH more effectively than 11.25 mg every 3 months, although sex-steroid concentrations were equally inhibited.⁵⁰ The 50-mg histrelin-acetate implant provides sustained suppression for 12 months.^{51,52}

Conclusions: A variety of GnRHa formulations are available and efficacious. The choice of a particular agent depends on patient and physician preference and on local marketing approval (CIII).

Treatment Monitoring

Progression of breast or testicular development is suggestive of treatment failure,^{52–56} but progression of pubic hair may indicate normal adrenarche. Growth velocity, height SD score (SDS), and BA advancement should decline during treatment. Vaginal bleeding may occur after the first administration of GnRHAs, but subsequent bleeding suggests lack of efficacy or incorrect diagnosis. Markedly decreased growth velocity (less than or equal to a –2 SDS) or rapid BA advancement should also prompt reassessment. BA can be used to update AH prediction understanding that the Bayley-Pinneau method may overestimate AH.⁵⁷ If elevated, random LH levels obtained by using an ultrasensitive assay indicate lack of suppression. Stimulated LH values (using GnRH, aqueous GnRHAs, or the free GnRHAs contained in depot preparations) can also be used to assess effectiveness. FSH levels are not normally used to monitor suppression. If measured, testosterone and estradiol levels should be in a prepubertal range for the assay used.^{44,51,53–56,58} No long-term data have provided compelling support for any specific short-term monitoring scheme.

Conclusions: GnRHa-injection dates should be recorded and adherence with the dosing interval monitored (BII). Tanner stage and growth should be assessed every 3 to 6 months, and BA should be monitored periodically (BII). There was no consensus about the

routine use of random or stimulated measurements of gonadotropins or sex steroids for monitoring therapy. For patients with suboptimal clinical response, there was consensus about need for comprehensive reassessment (CIII). Additional information on the relationship between on-treatment measures of gonadotropic axis suppression and outcomes are needed.

Adverse Events

GnRHAs are generally well tolerated in children and adolescents. Systemic complaints such as headaches or hot flashes occur occasionally but are usually short-term and do not interfere with therapy. Local adverse events occur in ~10% to 15% of patients and necessitate a change in agent when persistent, because they can result in sterile abscesses in a fraction of the patients.^{54,55,59} Although exceedingly rare, anaphylaxis has been described.

Potential New Therapeutic Agents for the Treatment of CPP

GnRH antagonists cause immediate and direct inhibition at the level of pituitary GnRH receptors.⁶⁰ Theoretical advantages over GnRHAs include eliminating the initial “flare” in gonadotropic axis activation and rapid recovery of suppression once therapy is withdrawn. Depot and nonpeptide orally active GnRH antagonists are under development⁶¹ and could be evaluated in children with CPP in the future.

Therapeutic Agents That Can Be Combined With GnRHAs for the Treatment of CPP

Adjunctive therapies that may improve outcomes (AH, for example) of GnRHa therapy include pure or selective estradiol estrogen receptor blockers, aromatase inhibitors,⁶² pure antiandrogens, sex steroids,⁶³ or nonaromatizable anabolic steroids.⁶⁴ The addition of oxandrolone increased AH compared with GnRHAs alone in a small ($n = 10$) nonrandomized study.⁶⁴ The addition of growth hormone (GH) increased AH compared with GnRHAs alone in girls with CPP and slow growth velocity in small ($n = 10$ and 17) nonrandomized series.^{65,66} The addition of GH increased height outcome in a randomized, controlled study ($n = 46$) of adopted girls with precocious or early puberty.²² However, to date, no large-scale randomized, controlled trials evaluating the addition of GH to GnRHAs for CPP have been performed.

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

DISCONTINUATION OF GnRHa THERAPY IN CPP

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 affect 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, because these variables are interrelated. Undue delay in initiation of therapy (>1-2 years) may compromise AH.

Parent/Patient Preference, Anticipated Time of Menarche, CA, and BA

In the studies we examined, 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 years, with mean BA ranging from 12.1 to 13.9 years and mean age at menarche of ~12.3 years. Discontinuation at a CA of ~11.0 years¹³ and a BA of ~12.0 years^{14,67} has been associated with maximum AH. However, BA is not an appropriate single variable, because a BA of ~12.0 years can be observed at different CAs and because BA is unreliable for predicting height gain after treatment.^{12-15,72} One study has suggested that height gain after treatment may be higher for those with early (<6 years) versus 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. For 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). Therefore, it is reasonable to consider these parameters and informed parent and patient preferences, with the goal of menarche occurring near the population norms (CIII).

OUTCOMES OF GnRHa THERAPY FOR CPP

Reproductive Function

Follow-up studies have been performed with girls in their late teens^{68,69,74-76} and women up to 31 years in 1 study⁷⁷ and have reported that ovarian function was not impaired.^{68,69,74,75,78,79} Menses began 2 to 61 months (mean: ~16 months) after the 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} Three small studies showed no differences from controls in gonadal function for boys at the ages 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 with GnRHAs (BII). Nevertheless, available data are limited. Long-term data on fecundity and ovarian reserve of treated patients with CPP are needed.

BMI and Correlates of Metabolic Syndrome

Childhood obesity is associated with earlier pubertal development in girls, and early sexual maturation is associated with increased prevalence of overweight and obesity. There has been concern that GnRHa therapy may affect BMI. Eleven studies addressed BMI outcome in girls with CPP,^{6,12,49,69,75,80-85} 2 included boys,^{78,80} and 1 included girls with early puberty (onset at the ages of 8 and 9 years).⁸⁶ Before GnRHa treatment, mean BMI SDS was above average in girls with CPP in all studies, whereas results were split in boys.^{78,80} The combined analysis indicates that BMI SDS did not increase after treatment irrespective of age at presentation. At AH, mean BMI SDS ranged from 0.1 to 1.7, with an overall slight decrease from pretreatment BMI. No reports regarding metabolic syndrome and GnRHa treatment were identified.

Conclusions: Above-average BMI is frequent at diagnosis of CPP. Long-term GnRHa treatment does not seem to cause or aggravate obesity, as judged from BMI (BII). Studies of body composition and fat distribution are needed.

Bone Mineral Density

Bone mineral density (BMD) may decrease during GnRHa therapy. However, subsequent bone mass accrual is preserved, and peak bone mass does not seem to be negatively affected by treatment.^{12,82,87} There is some suggestion that discontinuation of treatment in girls with a BA of ≤11.5 years may lead to greater BMD⁸⁷ and that, as in all adolescents, optimum calcium and vitamin D intake and skeletal-loading exercise may positively influence bone mass.⁸²

Conclusions: Young adults treated with GnRHAs for CPP in childhood ultimately accrue BMD within the normal range for age (BII).

Risk of Polycystic Ovarian Syndrome

The possibility that CPP is a first manifestation of polycystic ovarian syndrome (PCOS) has been raised.⁸⁸ PCOS occurred in 0% to 12% of girls with CPP followed prospectively^{12,89-91} compared with 5% to 10% in the general population.⁹² Single studies have reported (1) an increased average ovarian size after CPP resulting from hypothalamic hamartoma,⁷⁵ (2) a higher prevalence of exaggerated adrenarche in patients with CPP than in controls,⁹³ and (3) the occurrence of signs of PCOS 0.5 to 4.0 years after menarche.⁹⁴

Conclusions: Follow-up of treated or untreated girls with CPP into the midteenage years 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.

PSYCHOSOCIAL DEVELOPMENT

Potential psychological consequences of CPP, including risk for emotional distress and problem behavior, are often used to justify treatment with GnRHAs.^{95,96} Hormonally induced behavioral changes (eg, aggression, sexuality) that occur during normal puberty⁹⁷ 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. GnRHAs 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 GnRHAs are associated with improved psychological outcome (CIII). Thus, no recommendations related to psychosocial outcomes are possible. Controlled studies with standardized instruments are needed.

USE OF GnRHAs FOR CONDITIONS OTHER THAN CPP

Gonadal Protection for Children Undergoing Chemotherapy

Infertility represents one of the main long-term consequences of chemotherapy. Studies that evaluated the effects of ovarian suppression by GnRHAs during chemotherapy in adult and adolescent patients have yielded inconsistent results.¹⁰²⁻¹⁰⁴ Prospective, randomized trials in adult women are ongoing (see NCT00196846, NCT0090844, NCT00380406, NCT00068601 at <http://clinicaltrials.gov/>).

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

Increasing AH of Children With Idiopathic Short Stature

The effect of GnRHa therapy on AH has been evaluated in girls with idiopathic short stature (ISS) and normal puberty (8–10 years of age), with a mean gain compared with predicted height of 0 to 4.2 cm.† In boys with rapidly progressing puberty, GnRHa therapy increased AH compared with 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 versus –0.5 to 6.1 cm in untreated controls.^{112,113} In these studies, one cannot definitively separate the effects of GH from GnRHAs. In 2 randomized studies of adopted girls with normal puberty, GnRHAs plus GH was compared with GnRHAs alone, with a 3-cm height gain demonstrated with combination ther-

apy.^{22,114} Disadvantages of the use of GnRHAs in children with ISS include absence of pubertal growth acceleration, delayed puberty with potential psychosocial disadvantage, and decreased BMD. Long-term follow-up studies are lacking.

Conclusions: GnRHa therapy alone in children with ISS and normally timed puberty is minimally effective in increasing AH, may compromise BMD, 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 GnRHAs in children with ISS being treated with GH cannot be suggested (CIII).

Increasing AH of Children Born Small for Gestational Age

Short children born small for gestational age (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 GnRHAs are limited.¹¹³

Conclusions: Routine use of the combination of GnRHAs 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 GnRHAs and levothyroxine and levothyroxine alone produced similar gains in height SDS.¹¹⁶

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

Increasing AH of Children With GH Deficiency

Some children with GH deficiency are short at the start of puberty and at risk for short adult stature. Retrospective studies that evaluated the addition of GnRHAs to GH involved a limited number of subjects and provided controversial results.¹¹⁷⁻¹¹⁹ Three prospective studies that reported near-AH or AH have shown an ~1-SD height gain,¹²⁰⁻¹²² possibly without detrimental effect on BMD.¹²³

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

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

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

Children With Autism

Conclusions: Despite 1 controversial article reporting that GnRHAs may benefit behavioral symptoms in chil-

†Refs 6, 14, 15, 57, 69, 71, 73, and 105–110.

dren with autism,¹²⁵ the consensus is that there is no current evidence for GnRHa therapy for this indication (CIII).

CONCLUSIONS

Several important observations emerged from this conference. Despite a considerable body of literature on the use of GnRHAs, 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 additional research in key areas such as the psychosocial effects of GnRHa treatment for CPP. The efficacy in increasing AH is undisputed only in early-onset progressive CPP, which 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. Our systematic review also highlighted the lack of objective support for commonly voiced concerns such as the propensity for GnRHAs to promote weight gain or to lead to long-term diminution of BMD. Use of GnRHAs for conditions other than CPP requires additional investigation and cannot be routinely suggested.

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