

Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium

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Abstract

This update, written by authors designated by multiple pediatric endocrinology societies (see List of Participating Societies) from around the globe, concisely addresses topics related to changes in GnRHa usage in children and adolescents over the last decade. Topics related to the use of GnRHa in precocious puberty include diagnostic criteria, globally available formulations, considerations of benefit of treatment, monitoring of therapy, adverse events, and long-term outcome data. Additional sections review use in transgender individuals and other pediatric endocrine related conditions. Although there have been many significant changes in GnRHa usage, there is a definite paucity of evidence-based publications to support them. Therefore, this paper is explicitly not intended to evaluate what is recommended in terms of the best use of GnRHa, based on evidence and expert opinion, but rather to describe how these drugs are used, irrespective of any qualitative evaluation. Thus, this paper should be considered a narrative re-

view on GnRHa utilization in precocious puberty and other clinical situations. These changes are reviewed not only to point out deficiencies in the literature but also to stimulate future studies and publications in this area.

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Introduction

Gonadotropin-releasing hormone analogs (GnRHa) have been used primarily in the treatment of central precocious puberty (CPP), in other conditions in which adult stature is compromised (those with a growth hormone [GH] deficiency, those with idiopathic short stature, or those who are small for gestational age [SGA]), or when pubertal hormone suppression is a part of the treatment regimen (transgender individuals). Noteworthy is the fact that the diagnosis of CPP appears to have become more common since the availability of GnRHa, similar to GH deficiency when biosynthetic GH first became available.

The goal of this update, which has been written by members designated by multiple, global pediatric endocrine societies (see List of Participating Societies), is to

concisely address topics related to changes in GnRHa usage during childhood and adolescence since the previous consensus statement was published in 2009 [1]. It is not a consensus statement and hence has not been endorsed by any of the societies that designated participating authors. Clinical care using GnRHa has changed dramatically in recent years based on unpublished knowledge and discussions in numerous settings regarding daily clinical practice. This has been driven by many factors, most of which involve current demands for health care delivery, without verification by publications or controlled studies. Hence the need for a publication such as this.

Examples of changes include:

1. The lack of evidence for weight-based dosing previously recommended for depot forms of GnRHAs
2. Change in the assessment of pituitary gonadotropins, with updated laboratory criteria
3. Fewer GnRH/GnRHa stimulation tests and a greater use of unstimulated luteinizing hormone (LH) concentrations that are above the prepubertal range, with less frequent insistence on stimulation testing by insurance companies in the USA
4. Less hormonal monitoring during therapy, particularly among patients on chronic therapy when other parameters including linear growth rates, lack of pubertal progression, and slowed progression of skeletal age are consistent with suppression, confirming efficacy
5. A shift to longer-acting forms
6. A lack of agreement regarding use of the 11.25-mg and 30-mg 12-week preparation, again raising unanswered questions of how much suppression is needed for efficacy
7. Giving long-acting injections subcutaneously rather than intramuscularly with similar efficacy and much less pain
8. The additional cost of the minor surgical procedures to place and remove the implant at many locations
9. Continued lack of long-term outcome studies even though available information continues to support safety and efficacy
10. Greater usage of GnRHa among older patients with CPP despite advanced skeletal age X-rays as well as in those with borderline early puberty or normally timed puberty, those with a short stature for their age, short pubertal GH-deficient individuals, and short pubertal individuals born SGA after pubertal onset
11. Use among transgender individuals including concerns mentioned above and highlighting concerns regarding impacts on bone mineral density and infertility.

Thus, this publication is considered timely and pertinent since clinical practitioners need to be aware of how GnRHa are being used. Hopefully, these topics will stimulate future prospective studies.

Sections include diagnostic criteria, formulations of GnRHa available globally for therapy, considerations of which patients will benefit from treatment, monitoring of GnRHa therapy, adverse events, long-term outcome data, and use in transgender individuals as well as usage for other situations. The primary focus is to highlight management changes since the 2009 update.

This project was initiated by the European Society for Pediatric Endocrinology (ESPE) Clinical Practice Committee (CPC) and the International Clinical Guidelines Committee (iCGC) at the 2016 ESPE meeting. E. Charmandari and P.A. Lee were asked to coordinate a GnRHa clinical update rather than a consensus statement. It was envisioned that this would be an effort from numerous interested pediatric endocrinology societies and that it would be accomplished via e-mails rather than face-to-face meetings. K. Bangalore Krishna agreed to work as coordinator, provide e-mail communications as needed, and develop a repository of pertinent publications that were made available to all. The project leaders developed an outline and identified potential authors who then chose leaders for each outlined section. These in turn invited additional authors, aiming for representative participation from each society. Each subgroup was responsible for reviewing pertinent literature and writing their own section using knowledge of current practices and primarily recent publications. The section leads were given the responsibility of negotiating content among section authors. In addition, a writing committee was designated to integrate the sections and achieve agreement among the section leaders, and when necessary among section authors.

Grading of evidence was performed by a subgroup of the writing committee. The majority of literature citations have levels of evidence (LoE) graded at level 4 (uncontrolled cohort and case studies) or level 5 (expert opinions, case reports, and personal observations). References with higher levels of evidence are indicated by notations for LoE 1 (homogenous randomized control trials), 2 (meta-analyses or heterogeneous prospective trials), and 3 (case-control studies and retrospective cohorts) [2]. For each topic, an average LoE for the cited references was calculated as follows: section 1: 4.5; section 2: 3.9; section 3: 4.2; section 4: 4.5; section 5: 4.5; section 6: 4.3; section 7: 4.5; and section 8: 4.0.

Table 1. LH is the most valuable biochemical parameter used to diagnose CPP

	Sensitivity, %	Specificity, %	Formulation	Subjects, <i>n</i> (sex)	Method	Study
Unstimulated LH (IU/L)						
>0.3	77	100	–	49 (F)	ICMA	Neely et al. [7]
<0.3 (prepubertal)	93	100		25 (F)	ICMA	Houk et al. [8]
>0.83 (clearly pubertal)						
>0.3 but <0.83 (overlap of prepubertal and pubertal)						
<0.2 (prepubertal)	91	100		59 (F)	ICMA	Harrington et al. [10]
>0.2 (pubertal)						
Peak LH (IU/L)						
5 (+2 SD in Tanner stage 1)	NA	NA	GnRH	8 (F)	ICMA	Neely et al. [21]
4.1 (+2 SD in Tanner stage 1)	NA	NA		10 (M)	ICMA	Resende et al. [22]
3.3 (+2 SD in Tanner stage 1)	NA	NA		10 (F)	ICMA	
>4.9	78	79		80 (F)	ICMA	Pasternak et al. [23]
>6.7	94	100		46 (F)	ECLIA	Freire et al. [14]
Stimulated LH (IU/L)						
(sample time)			GnRHa			
>9.2 (pubertal) (30 min)	NA	NA	Leuprolide	14 (F)	ICMA	Houk et al. [24]
<4.9 (prepubertal) (30 min)	NA	NA	(20 µg/kg)	21 (F)	ICMA	
>5 (2 h)	78	100		39 (F)	ICMA	Sathasivam et al. [13]
Adding stimulated estradiol	100	100				
>50 pg/mL (24 h)						
>5.5 (3 h)	93	100	Leuprolide	61 (F)	ECLIA	Carretto et al. [25]
			(500 µg)			
>6 (60 min)	89	91	Triptorelin	101 (F)	ICMA	Poomthavorn et al. [26]
			(0.1 mg)			
>8 (3 h)	76	100	Triptorelin	46 (F)	ECLIA	Freire et al. [14]
Adding estradiol >80 pg/mL	94	100	(0.1 mg/m ²)			Freire et al. [27]
(24 h)						

Section 1: CPP – Diagnosis, Assessment, Natural History, and Racial Differences

Challenges in diagnosing CPP involve: (1) differences in the normal age range of onset of puberty for different racial groups and (2) the decreasing age at onset of breast development in the general population [3]. Regarding (1), since patients from African-American and Hispanic racial and ethnic groups have an earlier normal range of onset of puberty, different age criteria should be considered when diagnosing CPP. Concerning (2), the earlier onset of breast development may not be progressive as typically occurs in CPP, and it is not necessarily caused by hypothalamic pituitary gonadal (HPG) activation. Thus, the documented decline in the age of thelarche over the past 5 decades does not mean that puberty is occurring earlier. To verify this, clinical progression and docu-

mentation of pubertal HPG activation are necessary. Since the age of menarche has decreased only minimally during this interval [4, 5], it appears that earlier breast development in most instances is due to premature thelarche, which may be related to increased rates of obesity. Nevertheless, an increase in body mass index (BMI) may be one of many factors that accelerate biologic maturation and thus pubertal progression and menarche [4]. Internationally adopted children may have a greater likelihood (10- to 20-fold) of developing CPP [6].

LH is the best biochemical parameter used to diagnose CPP. When measured in ultrasensitive assays (ICMA with a sensitivity of 0.01 U/L or ECLIA with a sensitivity of 0.1 IU/L), randomly obtained serum LH concentrations within the pubertal range confirm the diagnosis of CPP [7–9]. The most recent analyses suggest that a value >0.2 IU/L can be considered a pubertal value [10] (Table

1). However, in the setting of clinically progressive puberty, LH concentrations below the pubertal range do not exclude CPP, suggesting the need for GnRH or GnRHa stimulation testing. Likewise, there is still an overlap between prepubertal and pubertal levels reported by others, i.e., between 0.3 and 0.83 IU/L [11], suggesting the need for stimulation testing if the clinical presentation is not definitive. With stimulation testing, specific cut-offs for LH concentrations that indicate a pubertal HPG axis depend on the use of GnRH or GnRHa as the stimulus, the sampling time, and the assay employed (Table 1). Caution should be exercised when interpreting gonadotropin concentrations in children younger than 2 years, since baseline and peak LH concentrations are higher during infancy and can lead to a misdiagnosis of CPP [11, 12]. Random estradiol concentrations may not verify pubertal activation but may improve the sensitivity of stimulation testing when obtained 18–24 h after GnRH/a administration [13, 14].

Findings from transabdominal pelvic ultrasonography are not a diagnostic criterion for CPP. Nonetheless, uterine and ovarian enlargements are consistent with precocious puberty because uterine growth reflects estrogen stimulation, while gonadotropin stimulation is required for growth of the ovaries. Uterine lengths >3.5–4 cm and ovarian volumes >2 mL are consistent with puberty [15, 16].

In children diagnosed with CPP, central nervous system magnetic resonance imaging (MRI) should be performed in all boys and at least in all girls who are 6 years or younger to exclude intracranial pathology, which has been reported to occur in up to 6.3% of girls [17] and 38% of boys [18] with CPP. However, a meta-analysis of MRI findings in CPP demonstrated that only 1.6% of girls had CNS abnormalities that required an intervention [19]. The goal of imaging is to identify pathologic causes of CPP, which are less likely when there is a family history, genetic findings, or an international adoption, particularly from the developing world. A consequence of obtaining MRI is that there may be incidental findings of unknown significance. Current recommendations are to discuss the pros and cons of MRI scanning with the parents to assist them in making an informed decision [20].

LH is the most valuable biochemical parameter used to diagnose CPP. Studies have shown the specificity and sensitivity of stimulated and unstimulated LH concentrations in diagnosing CPP (Table 1) [7, 8, 10, 13, 14, 21–27].

Section 2: Available GnRHa and Current Therapeutic Regimens

Long-acting GnRHa are the standard of care for the treatment of CPP. They generally have been understood to exert their effect by occupying the GnRH receptor resulting in a desensitization of pituitary gonadotrophs [28] with subsequent suppression of gonadal steroid secretion. Interestingly, animal studies have shown that the total number of membrane receptors during GnRHa treatment does not decrease to below 30% of baseline values, which should result in a normal sensitivity of the gonadotrophs to native GnRH. It has been shown that there are sustained increased levels of free α -subunit during LH and follicle-stimulating hormone suppression by the histrelin implant as well as monthly depot GnRHa preparations [29]. Thus the GnRH receptors are not totally suppressed, but rather they alter their function to produce increased amounts of free α -subunit instead of both components of the glycoprotein hormones [30].

Previously, monthly (4-week) depot GnRHa were most frequently used. However, additional 3-monthly (12-week) and 6-monthly (24-week) formulations, as well as subcutaneous implants, have become available over the past ~10 years. The depot options (leuprolide and triptorelin) are sustained-release formulations administered in various doses and intervals, whereas the subcutaneous histrelin implant requires a minor surgical procedure for insertion and removal and is marketed for annual use. This implanted preparation has been shown to be effective longer, which has the potential to decrease the cost and number of procedures [31]. The starting dose of monthly depot leuprolide acetate approved for pediatric use in the USA ranges from 7.5 to 15 mg and for the 12-week preparation is either 11.25 or 30 mg. Doses are increased if needed to achieve adequate suppression. In Europe and Asia, leuprolide dosing is standardized at 3.75 mg i.m. every 28 days [32, 33]. Weight-based dosing is no longer recommended for the depot forms of leuprolide acetate. The starting dose of triptorelin pamoate is typically 3.75 mg every 28 days and may be titrated up as necessary (to 11.25 mg) [34, 35]. Triptorelin pamoate (22.5 mg) administered at 6-month intervals is effective, but long-term outcome data are not yet available [36]. Prospective extension studies during therapy have demonstrated HPG axis suppression within days of histrelin implant insertion [37], within weeks for higher doses of depot forms, and within 3 months for lower doses and longer-acting depot forms [34, 36, 38]. Biochemical efficacy may be demonstrated by measuring unstimulated

Table 2. Available GnRHa preparations (may vary in different countries)

GnRHa preparation		Dosing
Leuprolide acetate	1-month depot	3.75 mg
		7.5 mg
		11.25 mg
	3-month depot	15 mg
		30 mg
Triptorelin pamoate (embonate)	1-month depot	3.75 mg
		11.25 mg
Histrelin acetate	6-month depot	22.5 mg
	12-month implant	50 mg (65 µg/day)

ultrasensitive LH or stimulated LH concentrations or sampling after a therapeutic depot injection. However, it is important to note that unstimulated LH concentrations above the prepubertal range commonly do not indicate a lack of suppression [39]. Clinical evidence of efficacy includes a slowing growth velocity, regression or lack of progression of clinical signs of puberty, a progressive decrease in the ratio of BA to CA (BA/CA), and an increase in the predicted adult height (PAH). However, the extent of suppression required for clinical efficacy remains unclear. No differences in clinical indices of pubertal progression were seen in studies comparing monthly preparations and 2 doses of the 3-monthly preparations of leuprolide depot [34, 40]. Prospective comparison studies are needed to establish whether there are differences in efficacy among the GnRHa in use today. Clinicians should discuss all of the available options with patients and families, including the expected duration of the therapy, the frequency of administration, and potential short-term and long-term side effects. Considerations may include an implant for patients with an extreme needle phobia and those with special needs, whereas others may opt for extended-release injectable formulations. The sustained-release GnRHa preparations are similar in annual cost and may improve compliance. Table 2 contains a summary of the most commonly used GnRHa preparations.

Section 3: Considerations for GnRH Analog Therapy in Children with CPP: to Treat or Not to Treat

The onset of thelarche in 7- to 8-year-old females is increasingly common [41, 42] and it is frequently associated with obesity [3]; however, pubertal gonadotropin se-

cretion in these girls has not been clearly documented. The physical changes of puberty at this age may be temporary, commonly followed by a slow progression or development within the range of normal puberty, and they culminate in achievement of a normal adult height (AH) without therapeutic intervention [43].

Early GnRHa studies treating CPP primarily included patients who were young (e.g., mean age of onset: 6 years) [44] and also demonstrated a rapid progression of pubertal changes. Subsequently, GnRHa use has considerably expanded to include those with a minimally early onset of puberty (e.g., girls ages 7–9 years) who may not necessarily derive similar significant clinical benefits from treatment.

To determine the benefit of GnRHa treatment for individual patients, the following factors should be considered:

1. Girls younger than 7 years and boys younger than 9 years showing progressive central puberty, or who are more advanced in pubertal development (e.g., sexual maturation rating [SMR; i.e., Tanner stage] 3 breast or genital development) with rapid linear growth apparent at their first visit merit GnRHa treatment. A brisk tempo of pubertal progression increases the risk of adult short stature.
2. For girls older than 7 years with SMR 2 breast development, an observation period of 4–6 months is suggested to assess the tempo of pubertal progression before offering treatment. Height outcomes are much less clear for girls with pubertal onset at age 7 years or older. The increase in AH over the predicted height at the onset of therapy varied in one comprehensive review summarizing 29 studies, i.e., from 2 to 10 cm [43], suggesting that some but not all patients benefit from therapy starting at this age. Another report, i.e., a meta-analysis of 6 studies involving 332 girls treated between the ages of 7 and 10 years reported no increase in AH [45]. In fact, most untreated girls with CPP who were not treated with GnRHa reached a normal AH [46–48], although some were shorter than their mid-parental height range.
3. There have been concerns about psychological morbidity of CPP with early menses, but adverse behavioral profiles occurring with early maturation may not be as common as earlier described [49, 50]. Families should be informed that, when puberty starts close to age 8 years or later, menarche usually does not occur for another 2.5–3 years, so an onset before age 10 years is unlikely [4, 51, 52]. Preparation of early-maturing girls for the onset of menses by a calm and reassuring

parent is a key aid to lessening psychological distress. Suppression of menses can still be an option if menarche occurs early and is stressful for the child.

The following are suggestions for an informed discussion of possible GnRHa treatment for an early-maturing girl (onset: 7–9 years of age):

1. If the height is above average, with a skeletal age that is not markedly advanced, the AH will probably be normal and may not significantly improve with treatment.
2. Adverse psychosocial stress may not occur from early puberty but, if it does, GnRHa treatment may not alleviate such stress.
3. Puberty may progress slowly so that menses may not occur as early as feared. Observation for 4–6 months will help to decide whether a child's puberty is progressing rapidly.
4. Treatment is expensive, and in addition there is the stress associated with having a condition requiring a pharmacologic intervention, clinic visits, and periodic injections or implant insertion/removal, among other factors.
5. Several studies have failed to find any benefit in terms of height in girls treated after age 8 years, and some girls may even lose height as a result of treatment [53–59].

Discussion with the parents and child about the goals of treatment (or not) encourages thoughtful consideration of therapeutic restraint, reassurance, and observation, since the benefit of treatment may be uncertain in this age group [60].

Among males, a similar rationale could be applied in consideration of treatment among those who have a borderline early pubertal onset. Regarding height, unless the skeletal age is markedly advanced, it is unclear whether the adult stature will be increased by GnRHa therapy, especially if the treatment interrupts a robust pubertal growth spurt.

Section 4: Monitoring GnRHa Treatment

The goals of GnRHa therapy for patients with CPP are to halt pubertal progression and progressive physical development, including height for age and differences from age- and sex-matched peers, and to preserve or reclaim the AH potential. Short-term clinical assessment should occur every 3–6 months to evaluate for stabilization of physical changes [36, 61, 62]. The height change velocity generally slows to prepubertal rates within

months of the onset of therapy [63, 64]. The development of pubic hair may stabilize or regress but it is not an accurate indicator of HPG axis suppression since adrenarche may have occurred. The rate of skeletal age advancement should decrease after 6 months of therapy, with a concomitant gradual increase in the PAH, assuming a reasonable growth rate. The HPG axis can be evaluated by measuring unstimulated or stimulated (following GnRH or GnRHa administration) serum LH, sex steroids, or urinary gonadotropin concentrations [24, 65–68]. It is recognized that unstimulated LH concentrations above the prepubertal range do not necessarily indicate a lack of suppression, while concentrations within the prepubertal range likely indicate suppression. However, the lack of correlation between biochemical measurements during treatment and AH outcomes does not support routine biochemical testing in all patients [39, 61, 69].

Indicators of treatment failure, including clinical pubertal progression, a lack of growth deceleration, and continued excessive bone age advancement, should prompt reassessment. Treatment failure may be confirmed on clinical grounds alone or verified by GnRHa-stimulated LH concentrations minimally >4 IU/L [39, 69]. The adherence to and timing of GnRHa administration should be assessed when treatment fails, with confirmation that the precocity is CPP rather than a GnRH-independent cause. If increasing the dose of GnRHa is indicated, decreasing the dosing interval is an option.

Discontinuation of GnRHa Therapy in CPP

No single clinical variable can determine the best age to discontinue GnRHa. The decision to discontinue treatment should be individualized, and it is appropriate to inquire about the parents' and the patient's perceptions of readiness to stop, since it can be anticipated that pubertal maturation will resume within months. Menses may occur from several months to more than 2 years after stopping GnRHa treatment. It is reasonable to discontinue therapy at a time such that puberty progresses concurrently with that of the child's peers. Increased AH has been associated with longer treatment [56, 70–72]. However, at some point further GnRHa therapy does not produce further gains in AH, and treatment beyond a bone age of 12.5 years in girls and 14.0 years in boys may at best result in a minimal increase in height [43, 56, 71, 73]. Hence, the timing of GnRHa treatment discontinuation is based on patient readiness for resumption of puberty, recent growth rates and shifts in height prediction rather than on bone age alone. The patient's AH typically ends

up being greater than the AH predicted when the GnRHa treatment is initiated but less than the predicted height when the therapy is discontinued [71–74].

Section 5: GnRHa Adverse Effects

Adverse effects of GnRHa therapy are rare, and the associations of most reported adverse events with the GnRHa molecule itself are unclear. Decades of experience have shown that GnRHa treatment is both safe and efficacious. The following comments relate to specific adverse events:

1. Allergic or local reactions to GnRHa preparations occur rarely and have been inadequately documented. Local reactions associated with suspensions and histrelin implants occur infrequently. Sterile abscess formation after depot injections is likely a reaction to the inert polymer [53, 75]. Fracture of implants on removal, including the risk of leaving active drug, occurs in 22–28% of cases, more frequently after implants have been left in place for longer than 2 years [31, 62, 76, 77].
2. Withdrawal bleeding due to falling estrogen concentrations may occur after the initiation of GnRHa treatment in girls having a significant endometrial lining. Occurrence beyond 2 months of treatment suggests that gonadotropin suppression has not been achieved or another etiology.
3. Hot flashes are occasionally seen in the initial phases of GnRHa treatment in girls with CPP. This is due to declining estrogen concentrations, but it resolves quickly.
4. Convulsions have been reported in patients receiving GnRHa in postmarketing reports and have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies, or tumors and patients on concomitant medications that have been associated with convulsions, such as bupropion and selective serotonin reuptake inhibitors. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. The data in the literature are limited, consisting of sporadic case reports [78].
5. A prolonged QT interval associated with GnRHa has not been reported in women or children. This has been reported in adult males treated with GnRHa for prostate cancer, attributed to changes in circulating testosterone concentrations and postulated to be related to congenital long QT syndrome, increased

body weight, a reduction in insulin sensitivity, dyslipidemia, concomitant medications, cardiac disease, electrolyte abnormalities, and diuretic therapy [79, 80]. For pediatric cases, a screening ECG is recommended only if the individual is receiving other medications known to cause a prolonged QT interval, has a history of congenital heart disease, arrhythmia, or long QT syndrome, has a family history of long QT syndrome or sudden cardiac death, or has symptoms suggestive of long QT syndrome, including syncope [81]¹.

6. Slipped capital femoral epiphysis has been reported in a small number of patients, occurring during GnRHa treatment or after cessation of GnRHa therapy [82]. As during normally timed puberty, slipped capital femoral epiphysis may be related to a lack of adequate sex hormone exposure at a critical period of bone formation. Prompt evaluation and management are indicated.
7. Pituitary apoplexy is a rare complication reported in men with prostate cancer treated with GnRHa for androgen deprivation and it develops within hours after the GnRHa administration [83]. In 14 males and 1 female, all were found to have pathologic gonadotropin secreting adenomas, suggesting the potential to precipitate pituitary apoplexy. There have been no reported cases of pituitary apoplexy in children or adolescents.

Section 6: Long-Term Outcomes

General Health and Wellness

While studies indicate that early normal puberty is associated with more frequent risk-taking behaviors and functional symptoms in older adolescents [84], there is insufficient data to determine whether those with CPP with or without GnRHa therapy show such behaviors. GnRHa therapy for early puberty may have adverse metabolic profiles as reported among girls with early normal puberty [84, 85]. These girls with early normal puberty, assumed to be related to a longer chronic estrogen exposure, have an increased risk of breast cancer [86] and unverified increased risks of obesity, type 2 diabetes mellitus, cardiovascular disease, and other malignancies [87]. These reports do not control for secular trends in obesity

¹ B.S. Miller and M. Kamboj of the Drug and Therapeutics Committee of the Pediatric Endocrine Society.

and exposure to endocrine disrupting chemicals. The impact of the addition of GnRHa therapy on these risks is unknown.

Reproductive Function and Fertility

There is no substantiated evidence that GnRHa treatment for CPP impairs reproductive function or reduces fertility. In most girls, gonadal function is restored promptly after cessation of therapy, with subsequent menarche and regular ovulatory menstrual cycles [32, 58, 88]. Using structured interviews among 135 adult women with CPP treated with GnRHa, 61 women with untreated CPP, and 466 controls matched for age, education, marital status, and parity [89], pregnancy was uneventful in 90% of all 3 groups. Unassisted pregnancy rates were similar in GnRHa-treated women with CPP and controls (>90%), while, in this series, untreated women with a history of CPP were more likely to require assisted fertility therapy. In another group of 46 women with CPP (aged 19.0–31.3 years), 71% experienced regular, spontaneous menstrual cycles, with normal fertility and offspring. The menstrual history is reported to be normal in all women previously treated with GnRHa for CPP, except for those with organic causes such as anterior pituitary lesions [56]. The outcomes of 113 pregnancies included 97 uneventful pregnancies with healthy children, 5 elective abortions, and 11 early miscarriages.

Limited data exist on reproductive function in males treated for CPP but they include normal serum testosterone [32, 90], gonadotropin concentrations, and semen analysis [90]. Data on paternity rates and fertility are not available.

Polycystic Ovary Syndrome

There is no clear evidence that girls with treated or untreated CPP are more likely to develop polycystic ovary syndrome (PCOS) than their age-matched peers [55, 84, 89, 91–96]. Reports include a significant incidence of PCOS in former CPP patients [97], with a lower prevalence of PCOS in GnRHa-treated girls than in nontreated girls (17.2%, $n = 33$, vs. 30.8%, $n = 14$), with elevated DHEAS and androstenedione concentrations in 56% of those receiving GnRHa versus 23.6% among those who did not [55]. Another report using single logistic regression analysis found that GnRHa treatment correlated with PCOS ($p = 0.03$) when comparing 36% of 25 girls diagnosed with PCOS who had been previously treated with GnRHa for CPP with 14.5% of 55 girls who had had CPP untreated with GnRHa [95]. However, these percentages are high and it is unclear whether there was rep-

resentative sampling and whether diagnostic criteria fit published incidence studies that indicate a lower frequency [98]. Further, since data do not determine whether hyperandrogenemia preceded the diagnosis or treatment of CPP, it is possible that this is a preselected biased group. Future studies should use the Recent International Consortium Update [99] to classify both treated and untreated CPP subjects.

Psychological Outcome

Some early studies suggested that psychological and social problems occur among girls with CPP [100–102], citing anxiety about breast development and other physical differences from peers. Subsequent reports have not substantiated such findings. A study of 19 girls with CPP, 22 girls with premature adrenarche, and 21 girls with early normal puberty found no significant differences in peer acceptance or child psychological adjustment [103]. No significant differences in anxiety, depression, somatization, attention deficit, offensive behavior, or academic performance were found before or after 24 weeks of GnRHa treatment in those with CPP. Using adaptation profiles, social competency was not significantly higher than that of peers before treatment onset [101]. Another report did not show significantly more behavior problems in girls with CPP than in age-matched healthy controls [50]. In contrast, another report found that GnRHa-treated girls with CPP had higher total scores of physical and psychological stress with a depressive component before GnRHa treatment, and stress scores were reduced in all patients after a year of GnRHa treatment [104]. The lack of uniformity regarding the psychological impact of GnRHa treatment in children with CPP is not surprising since individuals are unique, with both innate and environmental factors influencing responses to pubertal changes. Thus, there is no basis for expecting a different incidence of psychological problems among those who had CPP with or without therapy than in the general population, although more research is needed.

Impact on Weight

Although it has been suggested that weight gain occurs with GnRHa treatment of CPP [105–108], a reduction in BMI has also been reported [109]. Long-term studies have not supported the concept of treatment-related weight gain when comparing BMI SD scores before and after therapy, even though there is an increased prevalence of being overweight and obese at diagnosis [58, 109–112]. The weight status of women who had CPP resembles that of the general population [113]. A higher

BMI percentile at presentation and during therapy was associated with being overweight or obese during young adulthood. Thus, GnRHa treatment appears not to influence the long-term progression of these children toward obesity during adolescence or adulthood.

Bone Mineral Density

Children with CPP often have an elevated bone mineral density (BMD) for their age at diagnosis. GnRHa treatment slows mineral accrual, but after discontinuation BMD appears not to be significantly different from that of their peers by late adolescence. Reports of BMD among children and adolescents verified a decrement in BMD at the achievement of near AH, while accrual resumed after therapy, regardless of whether or not calcium supplementation was given. By late adolescence, all subjects had BMD within the normal range [114, 115]. A recent report of assessment during therapy suggested structural alterations, but those adolescents were not evaluated after stopping therapy [116]. Data suggest that, while children treated with GnRHa have a diminished bone accrual during treatment, it is likely that BMD is within the normal range after cessation of therapy by late adolescent ages.

Section 7: Use of GnRHa in the Management of Transgender Adolescents

Current guidelines include criteria for initiating treatment with GnRHa [117, 119]. Therapy should only be initiated after the individual has begun clinical puberty (breast or genital SMR 2 and testicular volume ≥ 4 mL) [117]. In transgender boys, GnRHa may be continued until subsequent testosterone therapy has resulted in serum concentrations within the adult reference range. In contrast, adult dose estrogens frequently do not suppress testosterone production in transgender girls, so GnRHa therapy may be continued if the testes remain in situ [117]. Initial treatment of young transgender adolescents with GnRHa is commonly recommended to prevent the development of undesired secondary sex characteristics [117, 118]. Such reversible treatment enables an extended diagnostic phase for gender clarification before electing to proceed with further gender-affirming hormone treatment [119, 120].

GnRHa suppress the HPG axis, resulting in a decreased testicular volume and the cessation of menses [121, 122]. Additional changes include a decrease in height SDS and BMD along with alterations in body composition consist-

ing of increased body fat and a decreased lean body mass [121]. The impact on BMD is concerning since lumbar spine Z-scores at age 22 years were found to be lower than those observed prior to treatment [122, 123], suggesting a possible permanent decrement in BMD. Thus, it is unclear how long GnRHa can safely be administered. The effects of GnRHa on adolescent brain maturation are unclear. GnRHa therapy prevents maturation of primary oocytes and spermatogonia and may preclude gamete maturation, and currently there are no proven methods to preserve fertility in early pubertal transgender adolescents. Care for each adolescent must be individualized, with awareness of gender fluidity and ethical guidelines [124].

Section 8: Use of GnRHa in Other Conditions

GH Deficiency

In GH-deficient children, the addition of GnRHa may be considered in 2 situations:

1. Children treated for malignancy with a resultant GH deficiency and CPP. In this group of patients, GnRHa and GH therapy increases the PAH and the AH [125–128].
2. Children with a GH deficiency who have not experienced catch-up growth at the onset of puberty since an insufficient height at pubertal onset will result in a short AH. Therapeutic combinations in this situation have involved increased GH doses [129], the addition of aromatase inhibitors [130], and the addition of GnRHa to halt pubertal progression and allow more GH-augmented prepubertal growth. The addition of a GnRHa to GH at the onset of puberty and treatment for at least 2 years resulted in gains of AH ranging from 6 to 9 cm (~ 1 – 1.5 SD) [131, 132]. These situations are not the usual practice for patients diagnosed with an isolated GH deficiency and treated in a timely manner with GH. Such use of GnRHa or aromatase inhibitors remains controversial and is not standard of care.

Non-GH-Deficient Short Stature

Adolescent growth has been the focus of several interventions aimed at increasing the amplitude of the adolescent growth spurt. Favorable results with GnRHa in precocious puberty have encouraged attempts to increase the duration of the adolescent growth spurt by delaying normal puberty in short subjects using GnRHa with or without GH treatment. Controlled prospective [133,

134], uncontrolled prospective [135], and retrospective analyses [136] indicate that the use of GnRHa alone in these cases lacks efficacy. In a randomized, placebo-controlled trial in short adolescents with normally timed puberty (most having idiopathic short stature), 18 boys and 32 girls with baseline predicted AH of -3.3 ± 1.2 SD were randomized to receiving either placebo or GnRHa. Those who received GnRHa had a 0.6 SD increase in AH (~ 4.2 cm, range 1.7–6.7 cm) compared to the predicted AH at baseline ($p = 0.01$) after a mean duration of 3.5 ± 0.9 years; however, they also demonstrated a significant reduction in BMD [115]. A recent study of GnRHa treatment of idiopathic short stature during puberty reported that AH in treated girls was significantly greater than among untreated girls but not boys [137]. It should be noted, however, that the treated (21 girls and 7 boys) and untreated (14 girls and 17 boys) groups were not matched, with the latter group being those offered but declining GnRHa therapy. There was considerable variation in response to therapy, and the group size for girls may have been sufficiently large to yield a statistically significant response, while the group of boys may have been too small. Some studies have shown that combined GH and GnRHa treatment for 3 or more years may result in a greater increase in AH [138–142], particularly in adoptive girls [140, 141].

However, a recent publication regarding combined therapy found that, not unexpectedly, patients treated with the combination grew more slowly than those receiving GH alone during the first 2–3 years of treatment. Statistical comparison of near AH SDS between the 2 groups was not possible [143]. In addition to height, the cost-benefit of such invasive treatments should also be considered, and further larger, long-term, and adequately powered clinical trials, focusing on efficacy, safety, and clinical significance, are needed to fully evaluate the combination of GH and GnRHa in short adolescents. Meanwhile, these approaches should be considered as experimental.

Small for Gestational Age

Pubertal height gain is less than expected in children born SGA, as a result of an earlier onset of puberty, an earlier peak height velocity, and accelerated bone maturation [144, 145]. Evidence suggests that combined GH and GnRHa treatment may increase AH in SGA children who are short at the start of puberty (<140 cm) and who have a subnormal PAH [146]. The mean height gain from the onset of puberty until AH, including the height gain during 2 years of GnRHa treatment, was 25.4 cm in girls and

33.0 cm in boys, i.e., 6.6 cm more than girls and boys treated with GH alone [147]. Hence, although the data are limited, it is appropriate to consider the potential advantages and disadvantages of treatment with GH and GnRHa in this population.

Fertility Preservation

GnRHa treatment has been administered just before and during chemotherapy to minimize the risk of premature ovarian insufficiency by reducing exposure to cytotoxic agents and protecting the developmental process of primordial follicles [148]. Systematic reviews and meta-analyses show a higher recovery rate of cyclic ovarian function after chemotherapy in patients treated with GnRHa before and during chemotherapy than untreated groups [149–154]. However, the results were mixed depending on the type of tumor [155–159]. Additionally, there are no long-term randomized, controlled studies. Thus, the efficacy of fertility preservation by GnRHa in adults is still controversial. Furthermore, there are few efficacy data in adolescent girls [160, 161]. Because primordial follicles and eggs do not originally have receptors for GnRH and thus GnRHa cannot directly protect primitive follicles from chemotherapy toxicity [160], and because the efficacy of fertility preservation of GnRHa is still controversial, the use of GnRHa before and during chemotherapy for all adolescents with malignancies is currently not recommended outside of clinical trials.

Autism, Problematic Behavior, and Developmental Impairment

GnRHa treatment cannot be recommended for autism as there is no validated evidence of efficacy. A single article reported that GnRHa usage in both prepubertal and pubertal children with autism improved behavioral symptoms (e.g., reduced aggressiveness and inappropriate sexual behavior) in the short term [162]. Attempts to replicate these data have not been successful. There is no evidence of any longstanding improvement in patients' inappropriate behavior or use of such therapy in children with autism [163]. Although GnRHAs have been used to treat patients with developmental problems (i.e., males who masturbate in public and females unable to care for themselves during menstruation), preventing pubertal progression can be seen, at best, as a temporary measure.

Conclusion

While much of the information discussed above is not published in well-controlled studies or even published at all, this concise summary has included items that are pertinent to the diagnosis and care of those treated with GnRHa. It is clear that many changes have occurred in the clinical use of GnRHa without the benefit of peer-reviewed publications. These changes appear to have been driven by an understanding that detailed testing may not be necessary to diagnose CPP or to monitor GnRHa therapy as well as the demands for pragmatic clinical approaches. Hence, when a single LH verifies pubertal secretion or when the clinical findings for patients on treatment are consistent with suppression, additional testing may be considered unnecessary. Nevertheless, carefully conducted outcome studies, preferably prospective controlled studies, are needed to verify dosing, monitoring, and long-term outcomes. Likewise, research is required to determine a basis for weight-based dosing of depot preparations, to compare efficacy and safety profiles of depot injections, and to assess subcutaneous versus intramuscular administration, as well as to examine other unpublished changes that are listed in the Introduction.

Disclosure Statement

The authors declare no conflict of interests relevant to this paper.

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List of Participating Societies

Pediatric Endocrine Society (PES), ESPE, Australasian Pediatric Endocrine Group (APEG), Asia Pacific Paediatric Endocrine Society (APPES), African Society for Paediatric and Adolescent Endocrinology (ASPAE), Japanese Society for Pediatric Endocrinology (JSPE), Sociedad Latinoamericana de Endocrinología Pediátrica (SLEP), Chinese Society for Pediatric Endocrinology and Metabolism (CSPEM), Indian Society for Paediatric and Adolescent Endocrinology (ISPAE), Canadian Pediatric Endocrine Society (CPES), and Sociedad Mexicana de Endocrinología Pediátrica (SMEP).

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