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Treatment of Central Precocious Puberty

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Long-acting analogs of GnRH (GnRHas) have been the gold-standard treatment of central precocious puberty (CPP) worldwide and have an enviable track record of safety and efficacy. Recent years have witnessed much growth in the availability of longer-acting and sustained-release forms of GnRHas. Although all available agents appear promising, limited long-term follow-up and/or comparative data are available. In this review, important issues pertaining to the treatment of children with CPP are discussed. In addition to an assessment of the newer extended-release GnRHa formulations, a delineation of factors essential in determining which children should be treated is offered. Outstanding uncertainties in clinical management are highlighted and areas in need of future research identified. Literature searches for this review were performed in PubMed and OVID, with a focus on English-language publications using the terms "central precocious puberty" and "treatment."

Freeform/Key Words: precocious puberty, treatment, GnRH analogs

Central precocious puberty (CPP) refers to early activation of the hypothalamic-pituitary-gonadal (HPG) axis and occurs in 1 in 5000 to 10,000 children [1]. CPP is far more common in girls, in whom it is usually idiopathic. Safe and effective treatment of CPP in the form of long-acting GnRH analogs (GnRHas) has been available for many years [2].

The development of GnRHas was based on the recognition that sustained high concentrations of GnRH resulted in a paradoxical downregulation and subsequent suppression of the HPG axis [3]. In the early 1980s, several different formulations of GnRHas were developed with different durations of action and routes of administration. Historically, the most commonly used preparation in the United States for the treatment of CPP was monthly IM depot leuprolide [4]. However, during the past decade or so, there has been a substantial increase in the number of extended-release formulations of GnRHas, resulting in a broad array of therapeutic options for patients and providers. These include 3-monthly (*i.e.*, once every 3 months) depot IM preparations, 6-monthly (*i.e.*, once every 6 months) depot IM preparations, and a subcutaneous implant that is marketed for annual use [5].

Although these longer-acting formulations are expected to improve compliance, the cost of GnRHas developed for use in children has remained extremely high. While minimal comparative information about the extended-release options is available in the short term, how they will stack up in contrast to monthly depot leuprolide regarding long-term safety and efficacy. Despite the excellent track record achieved in the arena of pharmacologic treatment of CPP, several notable queries remain about clinical management of affected children. These include criteria for treatment, the role of psychological considerations, whether brain MRI scanning should be mandatory, how therapy should be monitored, and when it should be discontinued. This review discusses each of the extended-release GnRHa formulations

Abbreviations: CNS, central nervous system; CPP, central precocious puberty; GnRHa, GnRH analog; HPG, hypothalamic-pituitary-gonadal.

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currently in the therapeutic armamentarium, describes areas of uncertainly in clinical management, and highlights unanswered questions and future directions.

1. Extended-Release GnRHa Preparations

A. Three-Monthly Depot GnRHas

Although 3-monthly depot GnRHas have been used in Europe for the treatment of CPP for many years [6], the first US Food and Drug Administration approval of a 3-monthly form of depot leuprolide for pediatric use occurred in 2011. While clinical indices of pubertal suppression have been reassuring, the 11.25-mg 3-monthly dose resulted in <100% HPG-axis suppression in several studies. These have included trials investigating 1- vs 3-monthly depot leuprolide [7, 8], a 3-year study of two different doses of depot leuprolide [9], and a meta-analysis of 3-monthly triptorelin for 1 year [10]. In contrast, one small retrospective study found no differences in adult height between girls treated with monthly vs 3-monthly triptorelin at the 11.25-mg dose [11]. Longer and larger-scale follow-up studies are needed to determine if there are meaningful discrepancies in clinical outcomes resulting from different doses of 3-monthly GnRHas as compared with monthly treatment.

B. Six-Monthly Depot GnRHas

A 6-monthly form of depot triptorelin was approved in 2017 by the US Food and Drug Administration for use in CPP. This approval was based on findings from an international, multicenter study conducted in 44 patients [12]. Appropriate HPG-axis suppression was noted in 93% of the subjects at 6 months and in 97.7% at 12 months. As with 3-monthly preparations, parameters indicating efficacy in terms of pubertal progression were favorable. However, given the limited amount of information available, no firm conclusions can be made yet about 6-monthly depot GnRHas. Trials investigating additional 6-monthly preparations besides triptorelin are underway.

C. Subcutaneous Histrelin Implant

A subcutaneous implant containing 50 mg of the potent GnRHa histrelin has been available for the treatment of CPP since 2007. Constructed of a soft hydrogel, the device releases histrelin at a rate of ~65 μg/d and results in profound HPG-axis suppression within 1 month [13]. The implant is typically inserted in the upper inner arm using local anesthesia in most cases [14]. After 5 years of treatment, predicted adult heights in children naïve to treatment increased by 9 to 10 cm [15]. Although marketed for annual use, the recognition that a single implant lasts at least 2 years has the potential to decrease costs and numbers of surgical procedures in children treated with this modality [16]. Routes of administration, available doses, and duration of action of each of the extended-release GnRHa preparations available for use in the United States are summarized in Table 1.

Table 1. Extended-Release Preparations of GnRH Analogs Available in the United States

Generic Name	Brand Name (Manufacturer)	Route of Administration	Available Doses (mg)	Duration of Action
3-Monthly leuprolide	Lupron Depot-PED 3 mo (AbbVie, Chicago, IL)	IM	11.25, 30	3 mo
6-Monthly triptorelin	Triptodur (Arbor Pharmaceuticals, Atlanta, GA)	IM	22.5	6 mo
Histrelin implant	Supprelin LA (Endo Pharmaceuticals, Malvern, PA)	Subcutaneous implant	50	≥2 y

2. Safety of GnRHas

GnRHas have an admirable safety profile. The most commonly reported adverse events are injection-site reactions which are typically mild and self-limited. However, sterile abscess formation has been reported in the setting of IM injections [17] and the histrelin implant [18]. The most problematic issue encountered with the histrelin implant is a propensity for the device to fracture during explanation, which in rare cases has necessitated ultrasound guidance to remove remaining fragments [19]. During treatment, growth velocity can significantly decline, particularly in patients with a markedly advanced bone age. This may necessitate addition of adjunctive treatment in the form of GH or oxandrolone [20]. Although some children may experience weight gain while on therapy, the preponderance of evidence suggests that GnRHas do not have a negative effect on body mass index in patients being treated for CPP [21, 22]. Bone mineral density is typically increased for age at diagnosis and progressively decreases during GnRHa treatment. However, follow-up of patients several years after cessation of therapy reveals bone mineral accrual to be within the normal range compared with population norms [23].

3. Criteria for Treatment

The main goal of treatment in children with CPP is the preservation of height potential. Although this sounds straightforward, any consideration of height outcomes must acknowledge several limitations. One is that no randomized controlled studies examining the effect of treatment vs no treatment on height in CPP have ever been conducted, to this author's knowledge. Another is that outcome in terms of height is generally based on the difference between predicted adult height at diagnosis and ultimate adult height at the end of treatment [24–28]. By definition, height predictions are based on bone-age radiographs, which are highly imprecise and subject to substantial variability in interpretation. In addition, bone ages typically over-predict height in CPP [29]. Thus, it is very difficult to accurately predict height outcome for any individual child. In addition to the caveats already mentioned, the degree of height gained also depends on multiple factors, including chronological age, pubertal stage, skeletal maturation, and tempo of pubertal development. It has long been recognized that a subset of children with CPP have a slowly progressive form of early puberty that does not benefit from intervention in terms of adult height [30]. The challenge lies in identifying which patients will ultimately belong in this category as compared with those who will lose a substantial degree of height potential without treatment. Therefore, a period of observation of ~6 months has been recommended unless puberty is quite advanced (Tanner stage ≥3 breast development in girls) at initial presentation [31]. Paradoxically, the suggestion to wait for some time before initiating therapy is in direct contradiction to the observation that the benefit gained in terms of height is inversely proportional to the age at which treatment is started. Girls in whom GnRHa therapy is initiated at age ≤6 years derive the greatest benefit from intervention, whereas those who are treated at between 6 and 8 years have a variable outcome [32, 33]. In contrast, no increase in adult height is seen in girls who are treated after age 8 years [34, 35]. Despite broad acknowledgment of a lack of increase in adult stature in girls treated when they are older than 8 years, GnRHa treatment continues to be initiated in many children who are well above this age threshold [36]. This likely reflects parental anxiety regarding impending menses as well as effective marketing by the producers of GnRHas. Insufficient data regarding boys with CPP have hampered the establishment of analogous age cutoffs for treatment efficacy in boys. The other concern often used as a rationale for treatment is negative psychosocial consequences of precocious puberty, particularly in girls. Because of conflicting conclusions in the medical literature in this area, no clear consensus regarding the risk of psychopathology in children with CPP exists [37]. Although some studies have indicated increased stress and anxiety in girls with CPP [38, 39], others have found no differences in psychological functioning as compared with control subjects [40, 41]. This is an area in which more research is

definitely needed. Table 2 summarizes the results of several studies reporting adult height outcomes in girls treated for CPP.

4. Controversies in Management of CPP

A. Need for Brain MRI

Once a diagnosis of CPP has been made, clinicians are faced with the decision of whether to order a brain MRI. This decision only pertains to girls, because the much higher rate of intracranial pathology mandates central nervous system (CNS) imaging in all boys with CPP. It has been suggested that brain MRI scanning may not be necessary in girls older than age 6 years who have no neurologic symptoms [42]. However, others have advocated for routine brain MRIs regardless of age, because of the finding of CNS abnormalities in girls with CPP who are older than age 6 years [43]. Potential consequences of unnecessary MRIs include cost, parental anxiety, and need for repeated imaging when incidental findings are uncovered. A meta-analysis of MRI findings in children with CPP revealed a total prevalence of CNS lesions of 9%, which decreased to 7% when only those possibility related to early puberty were included [44]. Notably, however, only 1.6% of these required intervention, because the vast majority were hypothalamic hamartomas which respond to medical therapy. Given that a small risk of important CNS abnormalities does exist, it is unlikely that the controversy surrounding this aspect of management will be resolved any time soon. For now, the recommendation is to discuss the pros and cons of MRI scanning with parents and allow them to participate in the decision of whether or not to pursue this test [45].

In children with a family history of CPP, genetic testing for an *MKRN3* mutation, the most common monogenetic cause of precocious puberty, will likely supersede CNS imaging, rendering this issue moot in many cases [46]. A second genetic etiology underlying familial CPP is deletions in *DLK1*, which encodes for Delta-Like 1 Homolog [47]. Both *MKRN3* and *DLK1* are maternally imprinted genes that are expressed only from the paternal allele. Thus, a family history of CPP on the father's side should increase the index of suspicion for a

Table 2. Examples of Studies Reporting Adult Height in Girls Treated With a GnRHa for CPP

First Author	Year of Publication	No. of Girls Participating	Modality Used and Duration of GnRH Treatment[a]	Adult Height Achieved, Mean ± SD (cm)	Height Increase Above Predicted at Baseline (cm)
Heger [24]	1999	50	Depot triptorelin 4.4 ± 2.1 y	160.6 ± 8.0	5.7
Antoniazzi [25]	2000	71	Depot triptorelin, buserelin nasal spray 16–56 mo	154.4 ± 5.6	2-7
Lazar [32]	2007	115	Depot decapeptyl 2.8–4.8 y	160.35 ± 5.05	5
Pasquino [26]	2008	87	Depot triptorelin 4.2 ± 1.6 y	159.8 ± 5.3	5.1
Nabhan [27]	2009	26	Depot leuprolide 3.6 ± 2.1 y	163 ± 7.6	4.5
Magiakou [22]	2010	33	Depot triptorelin 2.75 y	158.5	6.95
Poomthavorn [21]	2011	47	Depot leuprolide or triptorelin 3.4 ± 1.5 y	158.6 ± 5.2	4.7
Bertelloni [11]	2015	25	Depot triptorelin, 3.05 ± 0.9 y	158.25 ± 5.8	3
Lee [28]	2018	84	Depot leuprolide 2.98 ± 0.73 y	160.1 ± 5	4

[a]Duration data reported as mean ± SD or as a range.

mutation in one of these genes. Other genetic causes of CPP include activating mutations in kisspeptin and its receptor, *KISS1R* [48, 49]. However, each of these has been described as causing CPP in only a single patient thus far [50].

B. Monitoring of Treatment

There is no systematic strategy for monitoring whether adequate suppression of the HPG axis has been achieved in children being treated for CPP [51]. Although there is unanimity regarding the value of auxologic indices such as growth velocity, Tanner staging, and skeletal maturation, no agreement exists on the need for biochemical measures of treatment efficacy [52]. In fact, unexpected pitfalls are sometimes encountered when assumptions are made about hormonal studies in CPP. A case in point is the use of random ultrasensitive LH concentrations, which are helpful in the diagnosis of CPP and were postulated to adequately reflect HPG-axis suppression during treatment. Unexpectedly, random ultrasensitive LH values frequently remain in the pubertal range in children receiving GnRHa therapy that otherwise provides adequate HPG-axis suppression, and therefore these values can be misleading [53, 54]. Given the lack of evidence for any association between biochemical monitoring and adult height, it is reasonable to forgo any routine blood testing in children being treated for CPP. If treatment failure is suspected on clinical grounds, a GnRHa stimulation test is recommended.

C. Discontinuation of Therapy

A final area of uncertainty in the management of CPP relates to the optimal age of discontinuation of treatment. There are essentially no studies in which age at treatment cessation has been standardized. However, cumulative evidence suggests that optimal height gains are realized when treatment is stopped at a bone age of ~12 years in girls and ~13 years in boys [37, 55, 56]. Regardless, the decision of when to halt therapy is individualized and incorporates numerous patient-specific characteristics including absolute and predicted height, chronological age, psychosocial factors, pubertal stage, and family preferences.

D. Gonadal Function After GnRHa Therapy

Information regarding long-term outcomes of patients treated with GnRHas with respect to gonadal function are reassuring. Unsurprisingly, the vast majority of existing data pertain only to women. Menstrual cycles are reported to be normal with respect to duration and timing, and mean ovarian volumes similar to those in the general population. There have been no perceived health consequences to offspring of mothers who were treated with GnRHas and no increased need for assisted reproductive technology [57, 58]. Limited follow-up in adolescent boys previously treated with a GnRHa for CPP reveals similarly normal testicular function and sperm counts within the normal range [59], although more data in men are needed.

5. Conclusion

The therapeutic armamentarium for the treatment of children with CPP has rapidly expanded, resulting in the availability of several newer extended-release GnRHa formulations. Although the efficacy and safety of these longer-acting agents are not expected to diverge from historically used preparations, only a modicum of information regarding some of them is available. Likewise, a lack of head-to-head comparison data renders it impossible to determine whether any relative superiority among these different treatment options exists. Despite the highly favorable treatment profile of CPP in general, there are several unresolved questions pertaining to clinical management of affected children. Areas particularly in need of additional research include psychological sequelae of CPP and height outcomes in boys.

Efforts aimed at determining the optimal strategy for monitoring treatment and time for discontinuation of GnRHa therapy are also needed.

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