Management and Outcomes of Idiopathic Central Precocious Puberty in Girls

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Abstract: The sequelae of early development are not merely transient but are predictive of difficulties and challenges that persist into adulthood. In fact, the diagnosis and appropriate treatment of early puberty is essential in order to avoid permanent auxological and emotional consequences. GnRH analogues are the treatment of choice for central precocious puberty (CPP), whose main objective is to recover the height potential that is compromised by the premature fusion of growth cartilages**.** Several active principles and formulations are available. Depot formulations are generally preferred because of better patient compliance; GnRH-a is generally safe and well tolerated. Drug choice depends on the physician's experience, patient needs, and government regulations of drug prescription.

The aim of this review is to examine the treatment of Idiopathic Central CPP taking in account clinical practice and international literature.

Keywords: Puberty, Precocious puberty, Pubertal progression, Early puberty, Gonadotropin-releasing hormone (GnRH), GnRH agonists, GnRHa histrelin.

INTRODUCTION

The sequelae of early development are not merely transient but are predictive of difficulties and challenges that persist into adulthood. In fact, the diagnosis and appropriate treatment of early puberty is essential in order to avoid permanent auxological and emotional sequelae.

Early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion (which remains unexplained in most cases) is considered to be the most common mechanism under lying progressive precocious puberty (PP) [1]. Therefore, the primary aim of treatment of central precocious puberty (CPP) is to inhibit pituitary gonadotropin secretion, and consequently to suppress sex steroids. The aim of this review was to examine the treatment of Idiopathic Central CPP taking in account clinical practice and international literature.

AIMS OF THERAPY

Two main aims make the treatment of PP important**.** First of all, the treatment of progressive PP must interrupt sexual maturation until the age of normal pubertal development is reached. Secondly, it is necessary to revert or stabilize sexual characteristics, delay skeletal maturation, preserve normal height potential, and promote psychosocial adjustment of the patients and their families. The therapy also reduces the risk of estrogen-dependent cancer, mainly of the breast, which is associated with early menarche [2].

Untreated girls affected by CPP show early epiphyseal fusion, which significantly compromises adult stature [3]. The primary goal of treatment is to

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preserve final adult height within the range of the patient's target height. However, the amount of height gained is quite variable and closely related to the age at which treatment commences. Numerous studies have indicated that an arrest of puberty in girls at 8 years of age or older does not result in any substantial improvement in adult stature [4]. In contrast, girls age 6 or younger might gain as much as 10 cm in predicted adult height as a result of treatment with analogs whereas those between 6 and 8 years of age have inconsistent outcomes.

In historical series of untreated patients, mean heights ranged from 150 to 154 cm in girls, corresponding to a loss of about 12 cm compared with normal adult height**.** Height loss due to precocious puberty is inversely correlated with age at the onset of puberty [5]. Evaluation of the effect of sex steroids on epiphyseal maturation can be obtained using the reference atlas of Greulich and Pyle. The bone age of patients with precocious puberty is generally greater than their chronologic age. Bone age can also be used to predict adult height, albeit imprecisely, and predictions tend to overestimate adult height in girls with CPP [6].

INDICATIONS FOR TREATMENT

Pubertal arrest is recommended in patients with progressive PP of any etiology with accelerated pubertal development (*i.e*. average progression from one pubertal stage to another in a shorter period than the usual six months). Both clinical and anthropometric data, and bone age (BA) advance are crucial in deciding whether or not to treat CPP girls. Sometimes, a period of 3-6 months follow-up can be useful to evaluate the "progressive" pattern of CPP.

Despite great advances in knowledge regarding the assessment and management of CPP, several challenges remain for the clinician who must distinguish normal pubertal development (*i.e*. benign variants or non-progressive forms of sexual precocity) from pathological disorders. In at least 50% of cases of precocious pubertal development, pubertal manifestations may regress or stop progressing, and thus no treatment is necessary [7]. Although the underlying mechanisms of nonprogressive precocious puberty are unknown, it is noteworthy that the gonadotropic axis is not activated. It may happen that small ovarian cysts in the infant ovary may transiently secrete estradiol and then regress spontaneously**.** In fact, some patients have a nonprogressive form of CPP, and can achieve normal adult height without any medical intervention [8]. In cases where PP progresses, the clinician must consider the risk of early menarche and short adult stature due to early epiphyseal fusion, as well as adverse psychosocial outcomes [9]. Parents are often in favor of treatment in girls because they fear early menarche [10] but it is difficult to predict the age at which menarche will occur after the onset of puberty. In the general population, the time span from breast development to menarche is longer in children with an earlier onset of puberty, ranging from a mean of 2.8 years when breast development begins at the age of 9 years to 1.4 years when breast development begins at the age of 12 [11]. A follow-up every 3 to 6 months in girls aged 6-7 is advisable in order to assess the child clinically for pubertal progression. If progressive CPP is confirmed, treatment is recommended and generally continued until the girl is 11 years old, although the optimal duration of therapy is a matter of some debate. In patients showing a progression of CPP, there is significant variability in the degree of height gained after discontinuation of treatment, even among patients with the same BA [12, 13].

PROPOSAL OF TREATMENT

Since the mid-1980s the gold-standard treatment for CPP is gonadotropin-releasing hormone (GnRH) analog (GnRH-a), which is a synthetic decapeptide that binds stably to the GnRH receptor in the pituitary and is resistant to protease degradation thus prolonging its half-life. In particular, GnRH-a acts on the anterior pituitary competing for the GnRH receptor with endogenous GnRH, promoting endocytosis and reducing the number of GnRH receptors (*i.e*. "down-regulation")[14]. Initially, GnRH-a stimulates both synthesis and secretion of LH and FSH but when administered chronically, it suppresses the production of these hormones. In fact, GnRH-a continuously stimulate the pituitary gonadotrophs leading to desensitization and reduction of the release of LH (100%) and, to a lesser extent, of FSH (60%)[15]. GnRH-a are well-established as standard treatment of CPP worldwide. While numerous delivery systems and routes of administration exist, depot intramuscular injections or sustained-release preparations have been most widely used. These drugs are believed to work by providing a steady concentration of GnRH activity instead of the pulsatile variation in levels that is characteristic of native GnRH release, which results in paradoxical down-regulation and suppression of the HPG axis and to a lesser extent, of FSH. Several GnRH agonists are available in depot forms. In open-

label, noncomparative, longitudinal studies, the use of GnRH agonists consistently resulted in the regression or stabilization of pubertal symptoms. A suppressed LH response to GnRH or GnRH agonist or a suppressed response after an injection of the depot preparation (which contains a fraction of free GnRH agonists) indicates that the therapy is having the desired effect.

FORMS OF DRUGS

For the treatment of CPP, Triptorelin may be used as a GnRH-a at the recommended dose of 3.75 mg i.m. in girls >30 Kg of body weight and 1.87 mg in girls <20 Kg of body weight, every 28 days. Several GnRH agonists are available in various depot forms with a range of delivery systems and durations of action, and their use and doses vary in different countries.

Three-Monthly Depot GnRH-a

Clinical indices of pubertal suppression have been reassuring: the 11.25 mg 3-monthly dose resulted in 100% HPG-axis suppression and treatment of CPP patients with GnRHa every 3 months lead to substantial increases in height and did not affect BMI or BMD [16].

Six-Monthly Depot GnRH-a

Appropriate HPG-axis suppression was noted in 93% of the subjects at 6 months and in 97.7% at 12 months. However, given the limited amount of information available, no firm conclusions can be made yet about 6-monthly depot GnRH-a. [17].

Subcutaneous Histrelin Implant

A subcutaneous implant containing 50 mg of the potent GnRH-a histrelin has been available for the treatment of CPP since 2007. The most problematic issue encountered with the histrelin implant is a propensity for the device to fracture during removal, which in rare cases has necessitated ultrasound guidance to remove the remaining fragments [18].

Figure **1** shows the Extended-Release Preparations of GnRH analogs available.

EFFECTS OF THERAPY

Numerous studies have demonstrated that the greatest gain in final height is achieved in girls with onset of puberty before 6 years of age, although girls with onset between 6 and 8 years of age may still obtain some benefit from treatment. In contrast, girls

Chemical name	Dose formulations (mg)	Frequency of administration	Advantages	Disavantages
Triptorelin; leuprolide	3.75	Every 28 days	Long-terme experience	Frequent injection
Triptorelin; leuprolide	11.25	Every 84 days	Fewer injections with similar efficacy than monthly	Less long-term experience; no less expensive than monthly
Triptorelin	22.5	Every 168 days	Fewer injections	Less long-term experience; no less expensive than monthly
Histrelin	50	Implant is designed to last at least 12 mo	No injections	Needs to be placed by a simple surgical procedure

Figure 1: The Extended-Release Preparations of GnRH analogs available.

over 8 years of age do not seem to benefit from therapy in terms of stature [5]. The consensus statement from the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society highlighted that reasons for treatment include the preservation of adult height potential and avoidance of psychological disorders associated with early puberty [8]. However, no consensus has been reached regarding the use of pubertal arrest exclusively for psychosocial reasons, which include behavioral disorders, emotional immaturity, mental retardation, and seizures. The assessment and management of these conditions remain challenging for pediatric endocrinologists.

LACK OF EFFECT

Progression of breast development in treated girls usually indicates poor compliance, treatment failure, or incorrect diagnosis, and demands further assessment. In non-responder girls, GnRH-a administration is recommended every 21 days instead of 28 days. However, in resistant patients, another treatment used in the past can be tested, for example Medroxyprogesterone acetate (MPA) or Cyproterone acetate (CPA). Both MPA and CPA are useful in blocking puberty progression but have no beneficial impact on final height. MPA inhibits central gonadotropin release by acting on the hypothalamic pulse generator, and it also directly inhibits gonadal steroidogenesis. Moreover, MPA has a glucocorticoid mimetic action resulting in adrenocorticotrophic hormone (ACTH) suppression, hypertension, and bone mineral loss. MPA dosage varies from 50 mg to150 mg per month**.** The usual CPA daily oral doses are 50 to 100 mg/m2. CPA side effects include gastrointestinal symptoms. Patients with inadequate clinical and laboratory control that persists after an increase in GnRH-a dose must be carefully re-evaluated for precocious puberty diagnosis. When the height velocity decreases markedly (below 4 cm/year), growth hormone (GH) may be added to the treatment to promote height gain. The recommended GH dose in these girls is 0.3 mg/kg/week sc, 6 days weekly administered subcutaneously as in GH-deficient patients. The efficacy of this associated therapy on final height in CPP patients has been reported in a few studies that show the beneficial effect of adding GH therapy in children with decreased growth observed during GnRH-a therapy [19]. However, the combination of GH and GnRH cannot be routinely recommended as advantages of GH addition have not yet been fully determined [8].

MONITORING GNRH-A THERAPY

The treatment of CPP with GnRH-a must be monitored through clinical and laboratory evaluations. However, there is no general agreement on how to best monitor children undergoing treatment for CPP. The effect of GnRH-a results in a regression or stabilization of pubertal signs, a decrease in growth velocity to normal prepubertal values, and an improvement in final height prediction.

Laboratory Parameter

The laboratory parameter of choice is the measurement of LH values during GnRH-a administration. The clinician usually uses the serum-stimulated LH value in response to GnRH intravenous injection to assess effectiveness of GnRH-a therapy and monitor gonadotropin suppression [20]. In clinical practice, FSH-stimulated peak level is not normally used to monitor the inhibitory effect of GnRH-a therapy [8]. In fact, GnRH-a continuously stimulate the pituitary gonadotrophs, leading to desensitization and decreases in the release of LH and, to a lesser extent, FSH [21]. On the other hand, frequent GnRH tests during follow-up to confirm the suppression of basal or stimulated LH levels are recommended for monitoring therapy but could be inconvenient for both children and their families. With the development of new and more sensitive immunoassays for measuring serum gonadotropins, a single basal serum LH value has been proposed to monitor GnRH-a therapy [22]. Basal ultrasensitive LH is often within the prepubertal range in early CPP and thus may be falsely reassuring [23]. The possibility of replacing GnRH-stimulated gonadotropin peaks with basal values during the monitoring of GnRH-a treatment would be preferable for both patients and parents. Moreover, E2 levels are not useful for monitoring gonadotropin suppression because they are variable [24]. We recommend the GnRH test during follow up useful up to 30 months from the start of therapy, since it cannot be overlooked without risking excluding the non-responder subjects.

Radiological Parameter

Pelvic Ultrasound Echography

Pelvic ultrasound echography proved to be a useful tool during follow-up but not in the short-term due to the physiological growth of the organ [25]. In girls with CPP during the GnRH-a therapy in long-term ultrasound provides a valid assessment of the suppression of the hypothalamo-pituitary-gonadal axis. The pelvic ultrasound must be performed by a single experienced

operator in order to avoid data heterogeneity. Uterine length and transverse diameter, ovarian volume (calculated using the ellipsoid formula V= D1 x D2 x D3 x 0.5233 where D1 is the largest longitudinal diameter, D2 the largest antero-posterior diameter and D3 the largest transverse diameter) and the presence of an endometrial echo were evaluated by means of thorough pelvic ultrasound echography. Generally, we consider the following as indicators of estrogenic stimulation of the uterus: a uterine length of ≥3.5 cm, a fundus/cervix ratio of >1 and the presence of endometrial echo. An ovarian volume of ≥ 2ml has also been considered indicative of a pubertal state [25-27].

Bone Age (BA)

BA must be monitored annually in cases with adequate clinical and hormonal control. Children who are being treated for CPP should receive regular follow-up during which pubertal progression or suppression can be checked and recorded.

Biochemical markers, bone age, and growth velocity should be monitored during treatment to ensure efficacy.

OUTCOMES

In treated girls the most significant goals in long-term follow-up include final height, body composition, bone mineral density, reproductive function, and psychological characteristics. No randomized controlled trials have assessed long-term outcomes of GnRH therapy in girls with central precocious puberty. GnRH-a treatment is beneficial in preserving the potential genetic height, mainly in those girls starting GnRH-a therapy before 6 years of age [13, 14, 28]. Conversely, CPP diagnosed after the age of 6 results in reduced post-treatment height gain and compromised final height, probably due to intrinsic pre-treatment changes in the growth plate, according Lazar and cols [29]. In 45 Brazilian girls, no significant association between chronological age at the start of therapy and post-treatment linear growth was reported [28]. Most of the girls who achieved normal adult height started GnRH-a therapy after the age of 6, indicating that GnRH-a therapy is effective in preserving the potential genetic height in girls older than 6 [28]. No benefit on final height was demonstrated in those girls with early puberty, although benefits on psychosocial profile and in delaying menarche should be considered [8].

Many studies have reported regular menstrual cycles, pregnancy rates with live birth and long-term reproductive outcomes of girls treated with GnRH-a. Polycystic ovary syndrome (PCOS) occurs more frequently in CPP patients than in those with normal puberty. Incidence of PCOS in GnRH-a treated patients is variable: some authors reported markedly increased rates of PCOS while other authors found little difference. These conflicting results become even more difficult to interpret when we consider that multiple criteria for the diagnosis of PCOS exist. Therefore, no consensus has been reached on whether CPP or treatment with GnRH-a results in an increased risk of PCOS [30]. Limited information exists regarding the long-term effects of CPP treatment on endocrine and reproductive functions [31]. With regard to reproductive function, studies indicate that menstruation occurs on average 16 months after the CPP treatment is suspended. Regular ovarian cycles occur in 60% to 96% of the patients, and infertility has not been reported [32].

PP has been associated with increased risks of obesity, hypertension, type 2 diabetes, stroke, estrogen-dependent cancer, and cardiovascular mortality [33]. Transitional changes in body composition and bone mass may occur without consequences in adulthood [8, 32]. During GnRH-a treatment, Body Mass Density (BMD) is generally stable or declines [32]. However, bone mineral continues to accrue in the teenage years, and BMD is within normal ranges [34].

There are no controlled studies evaluating the short- and long-term effects of therapeutic intervention with GnRH-a on psychosocial characteristics nor of the impact of CPP on health-related quality of life and social, emotive and behavioral competences among children treated with GnRH-a.

CONCLUSION

Puberty is a multifactorial process. The clinical diagnosis of precocious puberty is not always easy, particularly in females, due to variants of normal development with progressive and non-progressive pathological conditions. The decision to treat CPP, mainly in girls, is based on clinical and anthropometric data, and bone age advancement. Sometimes these data obtained at short-term follow-up do not point to a recommendation for CPP treatment. Although the development of more sensitive and specific immunoassays has led to a significant improvement in biochemical diagnosis, standardization is still required due to the abundance of methods and protocols for measuring basal and GnRH-stimulated LH. The latter

results in different cut-off values to confirm the activation of the gonadal axis. Treatment with GnRH-a has shown significant advances in recent years, with more convenient, effective, and safe dosages in both the short- and long-term.

The objective of GnRH-a treatment is to prevent early closure of the growth plate and preserve the genetic growth potential within the range of target height. GnRH-a treatment improves height gain and FAH in girls with CPP. Most studies have reported that earlier age at initial GnRH-a treatment is associated with greater adult height or with height gain.

ABBREVIATIONS

FSH: Follicle stimulating hormone; LH: Luteinizing hormone; GnRH: Gonadotropin- releasing hormone; E2: Estradiol; GnRH-a: Gonadotropin-releasing hormone analog; CPP: Central precocious puberty; EP: Early Puberty; BA: bone age.

AUTHORS' CONTRIBUTIONS

RG and VC wrote the manuscript and revised the literature; GF and MG analyzed data; CMM gave technical assistance; EB, AV and MB designed the study, revised the manuscript and gave conceptual advice. All authors read and approved the final version of the manuscript.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing interests.

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