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·Review·

Treatment of central precocious puberty by GnRH analogs: long-term outcome in men

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Abstract

In boys, central precocious puberty (CPP) is the appearance of secondary sex characteristics driven by pituitary gonadotropin secretion before the age of 9 years. In the last years, relevant improvements in the treatment of CPP have been achieved. Because CPP is rare in boys, the majority of papers on this issue focus on girls and do not address specific features of male patients regarding end results and safety. In the present paper, recent advances of CPP management with GnRH analogs in men are summarized. End results in untreated and treated patients are also reviewed by an analysis of the recently published literature on treatment of CPP in men. The available data indicate that therapy with GnRH analogs can improve final height into the range of target height without significant adverse short-term and long-term effects, but longer follow-up of larger series of patients is still required to draw definitive conclusions. *(Asian J Androl 2008 Jul; 10: 525–534)*

Keywords: adolescent; male; central precocious puberty; gonadotropin-releasing hormone analog treatment; gonadotropin-releasing hormone analog safety; long-term outcome; adult height

1 Introduction

Central precocious puberty (CPP) is a distinct pediatric disease that can have important physical and psychosocial consequences [1, 2]. In boys, it occurs when a gonadotropin dependent onset of puberty starts before the age of 9 years [2]. CPP is due to identifiable organic disorders of the central nervous system (such as tumors, infections, trauma or radiation) or can be idiopathic [2]. The former is more frequent in men and the latter in women (Table 1).

Currently, gonadotropin-releasing hormone (GnRH) analogs are the drugs of choice for treatment of CPP [1, 3, 4]. In fact, these drugs are able to modify the natural course of CPP, restoring growth potential in treated patients, at least as has been demonstrated in girls [1, 3, 4]. However, because CPP is less common in boys than in girls (Table 1) [2, 5–10], very little data is available on the long-term efficacy and safety of GnRH analog treatment in men with CPP.

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Table 1. Central precocious puberty: aetiology in boy and girls and male/female ratio. UCSF, University of California; San Francisco; ISGPP, Italian Study Group for Physiopathology of Puberty.

Author	Year	Country	Total number (male + female)	Organic *vs.* idiopathic (%)		Ratio (male: female)
				male	female	
Thamdrup [5]	1961	Denmark	56	64/36	24/76	1: 4.1
UCSF [2]	1981	USA	205	67/33	27/73	1: 4.2
Bridges *et al.* [6]	1994	UK	95	100/–	6/94	1: 23.0
ISGPP [7, 8]	2000	Italy	473	40/60	18/82	1: 9.5
Chemaitilly *et al.* [9]	2001	France	256	73/27	19/81	1: 8.8
Oerter-Klein *et al.* [10]	2001	USA	98	83/17	32/68	1: 4.4

Table 2. Central precocious puberty: final height in untreated boys and girls. SDS, standard deviation score *vs.* reference values. [a]According to the reference values of Tanner *et al.* [14]; [b]According to the NCSH reference values [13].

Author	Year	Male			Female		
		n	Final height (cm)	SDS[a]	*n*	Final height (cm)	SDS[a]
Thamdrup [5]	1961	8	155.4 ± 8.3	–2.86	26	151.3 ± 8.8	–1.82
Sigurjonsdottir *et al.* [11]	1968	11	156.0 ± 7.3	–2.80	40	152.7 ± 8.0	–1.56
Bovier-Lapierre *et al.* [12]	1972	5	155.8 ± 2.8	–2.84	4	150.5 ± 1.6	–1.95
Paul *et al.* [13]	1995	4	159.6 ± 8.7	–3.70[b]	8	153.8 ± 6.8	–2.40
Pisa [unpublished]	–	4	156.0 ± 4.7	–2.79	7	151.4 ± 4.7	–1.81

Therefore, we review the published literature on the long-term outcomes of boys affected by CPP, both treated and not treated by GnRH analogs and provide a brief overview on the efficacy and safety of GnRH analogs treatment in this sex.

2 Clinical consequences of central precocious puberty in untreated boys

Historical data on untreated boys with CPP shows that the main long-term consequence is reduced adult height; in fact untreated male patients show a final height of approximately –3 standard deviations below the mean for their reference values (Table 2) [5, 11–13]. The attained adult height in men results in a height at least –1 standard deviation score below the mean final height in women with untreated CPP (Table 2) [5, 11–13], suggesting a poorer long-term auxological outcome in boys in comparison with girls. However, historical series have not taken into account the secular trend in height increase or might have overrepresented cases that are more severe than the average patient in series investigated today [15, 16]. In the past 10 years, we had the opportunity to collect data on the final height of untreated children with CPP because parents did not consent to therapy or delayed diagnosis. Both boys and girls appeared to have a reduced final height and this was very close to the height reported in historical series of untreated subjects (Table 2). Although our groups of untreated male and female patients were small in size, these data seem to suggest that the secular trend for an increased height does not lead to an improvement of the statural outcome in untreated men with CPP.

Other concerns related to CPP are altered body proportions in adulthood, with an upper: lower ratio > 1 [1], psycho-social distress in childhood (decreased peer interaction, social withdrawal, impairment in school performance, altered behavioral development, increased aggression, and increased risk of sexual abuse), and early engagement in risk-taking behavior (such as smoking, alcohol or drug abuse, and early unprotected sex) [1, 2, 17], but these items have been poorly documented in boys.

3 Treatment strategies for central precocious puberty

Management of CPP should be primarily directed at the treatment of the underlying cause, when this is possible [1, 2]. Therefore, surgery and radiation therapy

Table 3. Gonadotropin-releasing hormone (GnRH) agonists: main drugs used in boys with central precocious puberty. [a]In respect with native GnRH; [b]Average release 65 μg/day. s.c., subcutaneous.

Agonist	Potency[a]	Preparation	Dose
Buserelin	20	s.c. injection	10–40 μg/kg/daily
		Nasal spray	1.2–1.8 μg/kg/daily
Deslorelin	150	s.c. injection	4–8 μg/kg/daily
Goserelin	100	Monthly depot	3.6 mg/28 days
		Quarterly depot	10.8 mg/3 months
Histrelin	210	Subdermal implant	50 mg/12 months[b]
Leuprorelin	20	s.c. injection	20–50 μg/kg/daily
		Monthly depot	7.5–15 mg/28 days (USA)
		Monthly depot	3.75 mg/28 days (Europe)
		Quarterly depot	11.25 mg/3 months
Triptorelin	35	Monthly depot	3.75 mg/25–28 days
		Quarterly depot	11.25 mg/3 months

could be indicated for the various tumors causing organic CPP [2].

A study comparing surgical resection to medical treatment with GnRH analogs in patients with hypothalamic hamartomas, a main cause of organic CPP in men [2, 8, 9, 10], indicates that medical treatment is more efficacious in suppressing puberty and reducing bone age progression than surgical therapy [18]. In addition, long-term follow-up studies demonstrate the non progressive nature of hypothalamic hamartomas in boys as well as in girls [19, 20].

In boys, as in girls, with no treatable organic cause, medical treatment is advisable [1, 2, 4, 15]. The goal of treatment is the attainment of effective and selective suppression of gonadal sex steroid secretion to stop premature sexual maturation [2, 4]. In addition, treatment should permit the attainment of an adult height adequate for each individual in relation to his or her genetic determinants by suppressing the accelerated skeletal maturation to a larger extent than growth velocity [1]. Prompt reversal of the suppression after the discontinuation of treatment, the absence of toxicity and/or side effects during long-term administration and of inferences with reproductive function in adulthood are important considerations in prescribing medical therapy for CPP [2, 3].

GnRH analogs are the drugs of choice for the medical therapy of CPP [1–4, 15]. These drugs are synthetic analogs of the natural decapeptide, in which chemical substitutions at positions 6 and 10 of the GnRH molecule increase the resistance to enzymatic degradation and increase the affinity to the receptor on pituitary gonadotropes, leading to a desentisization of GnRH receptor and, consequently, inhibition of the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the pituitary gland with a subsequent decrease in gonadal steroids [3, 21]. Some available GnRH analogs show a potency varying from 20 up to 200 times that of natural hormones, with prolonged action and low toxicity [3, 21]. The main commercial formulations of GnRH analogs used in the treatment of CPP in boys are summarized in Table 3. Administration forms and doses are also reported in Table 3. The same drugs are used more extensively in girls because of the higher incidence of CPP in this sex [1–4].

Depot formulations are usually used (Table 3) [3, 4, 21], because compliance with the daily formulations (nasal or subcutaneous) is frequently problematic [1].

In Europe, triptorelin depot is widely used at 28 day intervals [15, 22–25], even though some authors have reported shorter frequency intervals of administration (21–26 days) [26–28]. It is usually administered at a dose of 3.75 mg (approximately 60–75 μg/kg) for children weighting more than 20 kg [22–25]; a half dose has been employed in patients weighting less than 20 kg [23]. Some authors have used higher doses (90–100 μg/kg) [28, 29].

Leuprorelin depot is used at different doses in Europe (3.75 mg/28 days) [30] and in the USA (7.5–15 mg/28 days) [31, 32]. In Japan, the described doses range from 10 to 90 μg/kg/28 days [33, 34]. So, the minimal effective dose required to achieve complete pi-

tuitary desensitization remains a issue for debate. Indeed, some data indicate that even the higher 7.5 mg monthly dose may still be inadequate in some children with CPP [35], which may even exacerbate the disease progression [3]. In addition, the majority of the trials have reported data only in girls [31–35].

Results on goselerin depot are mainly from the United Kingdom and limited to girls [36, 37].

Few papers have explored the new 3-month GnRH analog depot preparations in CPP; they have been done mainly in girls, while very few data are available in boys with CPP [36–42]. Recently, data in 3 boys treated with the new 12 month histrelin subdermal implant (average release 65 mg/day) in a phase III prospective study (1 year duration) have been published; they showed suppression of testosterone levels throughout the study period [43].

Prospective studies comparing the efficacy and the safety of the different formulations in boys are lacking and the choice among the various GnRH analogs remains somewhat arbitrary, depending on personal experience, local practices or different regulation of prescription in various countries more than on evidence-based studies designed to address the pharmacokinetics and the pharmacodynamics of GnRH analogs in the children of the two sexes.

4 End results in boys with central precocious puberty treated by GnRH analog

The data on adult height in boys with CPP treated by GnRH analogs are summarized in Table 4. Although the published studies showed variable end results, adult height was improved in all the studies (Table 4) in comparison with the height of untreated boys (Table 2) [5, 11–13]. An increase in final height over pre-treatment predicted height has been shown in the majority of the studies, but there is a large variability between the populations studied (Table 4).

In a study from the USA, an increased near final height in six boys treated with various GnRH agonist regimens in comparison with the height predicted before therapy is reported by Paul *et al*. [13]; boys treated before the chronological age of 5 years had a better height gain (Table 4); however, the group remained approximately 8.5 cm below target height [13]. In an other US study, Oerter-Klein *et al.* [10] report on 18 boys with CPP, the majority affected by a non-idiopathic form, treated with daily deslorelin administration. Final height remained lower than mid-parental height, but was significantly greater than pre-treatment predicted height (Table 4) [10].

In Europe, the 11 boys reported by Galluzzi *et al*. [24], all with idiopathic CPP and treated with triptorelin depot, showed a final height exceeding the initial prediction by 6.7 cm and were close to target height (Table 4). In subsequent studies from Europe, Israel, and India, all using triptorelin depot, the adult height was greater than the target height [23, 44–46]. In some reports, some patients were treated with more than one drug and final height ranged from 1.8 to 8.2 cm below the target height [27, 29, 45]. In effect, a significant height gain in comparison with predicted adult height before the start of treatment was observed in all but one of these studies (Table 4).

In Japan, Tanaka *et al.* [34] described 13 boys treated with leuprorelin depot for a mean period of 4.1 years; they reached a mean final height that was –4.4 cm below the mean target height [34]; in this study height gain in comparison with predicted adult height before therapy showed a poor outcome (Table 4).

The relative discrepancies among the various studies might be due, at least in part, to the small number of boys enrolled in each trial, the heterogeneity of the patients treated in terms of auxological characteristics at the start of treatment, age at start of therapy, the percentage of idiopathic versus organic forms, and the different drugs and doses [16, 45]. In addition, the discrepancies and the negative height gains in some reports (Table 4) might reflect the difficulties in assessing "height gain", based on predicted height at the onset of puberty and the overestimation of the true final height in this disorder by the Bayley and Pinneau method used in such studies [16, 47]. Indeed, very little data on the validity of prediction methods based on bone age in boys with CPP is available [15, 16, 44].

To address some of these issues, a European multicentric study was undertaken of the largest series of boys with CPP treated by a standardized GnRH agonist regimen (triptorelin depot, 3.75 mg every 28 days) [16]. This study clearly demonstrated a final height not significantly different from the target height (Table 5) [16]. In addition, the boys who started treatment before the age of 6 years had a significantly better height gain in comparison with those who started therapy after that age (Table 5), but final height was not significantly different

Table 4. Central precocious puberty in boys: final height after gonadotropin-releasing hormone (GnRH) treatment. [a]Height gain was obtained subtracting predict adult height before therapy (by accelerated Bayley-Pinneau tables) from measured final height; [b]Nafarelin (600–800 mg/kg/12 h or deslorelin 4–8 mg/kg/day, then switched to leuprolrelin 30–50 mg/kg/day, then to leuprorelin depot 300 mg/kg/28 days; [c]Calculated from the text; [d]Near final height; [d2]Patients treated at chronological age < 5 years; [d3]Patients treated at chronological age > 5 years; [e]Obtained from figure; [f]mg/28 days (patients weighting less 20 kg received 1.87 mg/28 days); [g]mg/28 days; [h]Nine patients received buserlin (intranasal [53.4 mg/kg/day] or s.c. [36.7 mg/kg/day]) for a variable period of time before triptorelin; [i]Starting dose every 24–28 days (four boys received buserelin [intranasal 1 600 m/day] for a mean period of 1 year before triptorelin); [j]mg/kg/day; [k]Using the average Bayley-Pinneau tables; [l]Using the projected height SD score method, mean height gain was –4.3 cm using the bone age advance adjusted Bayley-Pinneau tables.

Author	Year	Country	*n*	Idiopathic/ Neurogenic	Drug	Mean dose (μg/kg/28 days)	Target height (cm)	Final height (cm)	Mean height gain (cm)[a]
Paul *et al.* [13]	1995	USA	6	–	Mixed[b]	–	174.9[c]	166.3 ± 12.2[d]	+11.1[d2]/6.0[d3]
Galuzzi *et al.* [24]	1998	Italy	11	11/0	Triptorelin	60–120	175.0 ± 7.0[e]	175.5 ± 6.0[e]	+ 6.7
Carel *et al.* [23]	1999	France	8	6/2	Triptorelin	3.75[f]	171.8 ± 3.7	172.8 ± 6.4	– 1.4
Mul *et al.* [22]	2000	the Netherlands	9	5/3	Triptorelin	3.75[g]	179.0 ± 6.0	170.8 ± 7.2	– 0.6
Rizzo *et al.* [29]	2000	Italy	12	9/3	Triptorelin[g]	90[h]	174.2 ± 2.9	176.1 ± 6.1	+ 6.2
Bertelloni *et al.* [27]	2000	Italy	9	4/5	Triptorelin	60[i]	174.0 ± 5.2	172.2 ± 6.9	+ 10.4
Lazar *et al.* [44]	2001	Israel	11	11/0	Triptorelin	3.75[g]	170.6 ± 4.5	172.2 ± 7.0	– 1.8[e]
Klein *et al.* [10]	2001	USA	18	3/15	Deslorelin	4[j]	178.3 ± 5.2	171.1 ± 8.7	+ 15.0
Bajpai *et al.* [46]	2002	India	5	–	Triptorelin	3.75[g]	167.6 ± 2.6	161.9 ± 3.9	+ 7.6[k]
Mul *et al.* [16]	2002	Europe[l]	26	14/12	Triptorelin	3.75[f]	175.1 ± 6.2	172.9 ± 6.6	+ 6.2[l]
Tanaka *et al.* [34]	2005	Japan	13	–	Leuprorelin	10–90	167.6 ± 4.2	163.2 ± 13.0	+ 1.1[l]

Table 5. Central precocious puberty (CPP) in boys: auxological long-term outcome after gonadotropin-releasing hormone (GnRH) agonist treatment [15]. [a]Mid-parental height –0.23 ± 0.75 standard deviation score *vs.* reference values (SDS). ($P > 0.05$); [b]Difference between the predicted adult height before therapy and adult height; [c]Using the average Bayley-Pinneau tables; [d]Mid-parental height –0.16 ± 0.84 SDS ($P > 0.05$); [e]Mid-parental height –0.42 ± 0.62 SDS ($P < 0.01$); $P < 0.05$, organic CPP group *vs.* idiopathic CPP group.

	n	cm
Adult height, SDS (cm)	26	172.9 ± 2.0 (–0.66 ± 1.22 SDS)[a]
Total height gain[b] (cm)	26	6.2 ± 8.7[c]
Final height in patients with pubertal onset < 6 years (cm)	10	174.1 ± 7.2[c]
Final height in patients with pubertal onset > 6 years (cm)	16	171.8 ± 6.5[c]
Height gain[b] in patients with pubertal onset < 6 years (cm)	10	12.5 ± 6.6[c]
Height gain[b] in patients with pubertal onset > 6 years (cm)	16	2.3 ± 7.1[c]
Final height in patients with idiopathic CPP (cm)	14	175.7 ± 6.5 (–0.08 ± 1.06 SDS)[d]
Final height in patients with organic CPP (cm)	12	169.6 ± 5.1 (–1.34 ± 1.06 SDS)[e]

between the two groups and both reached their genetic target (Table 5). Therefore, although the height gain is better in the patients who are younger at the start of GnRH therapy, older boys can benefit from treatment as well [16]. The European multicentric study, including a similar number of patients affected by organic or idiopathic CPP, also showed that from the boys treated with triptorelin depot those with organic CPP attained a lower final height than boys with idiopathic CPP (Table 5). In addition, whereas the boys with idiopathic CPP attained an adult height equal to their genetic target, the patients with organic CPP had a final height significantly below their target (Table 5) [16]. The poorer end-results have been recorded in 5 boys affected by type I neurofibromatosis, a condition which can impair growth per se [48]. Therefore, the cause of CPP should be taken into account in evaluating the long-term efficacy of GnRH analog therapy in boys with CPP. The large standard deviation of some parameters and total height gain in particular (Table 5) can depend on problems related to the method of height prediction (see above) and the retrospective nature of the study, the regional differences in practices, on the use of more (or less) liberal criteria to initiate GnRH analog treatment, and on the different interval between the onset of puberty and the start of treatment in the participating countries [16].

5 Optimization of GnRH analog therapy

The GnRH analog treatment is likely not required for all children with early onset of puberty. In fact, a "slow progressive variant" has been described in both boys and girls [44, 49], which, without any treatment, does not affect adult height [44, 49–51].

Although there is no general consensus on the indication for treatment [1], tentative criteria to select boys with CPP who are candidates for therapy are summarized in Table 6, but it should be kept in mind that clinical follow up is mandatory in all boys with precocious onset of pubertal development, independently from the decision to initiate therapy or not, to ensure the best outcome.

Regarding the discontinuation of therapy, it appears that bone age at the end of treatment correlates negatively with height gain after GnRH analog therapy in girls [1, 23–25, 51, 52]. Indeed, it is reasonable to believe that stopping therapy at an age close to the median physiological age of puberty could improve final height [15, 25, 52]; some authors have reported that longer treatment duration is associated with greater final height independent of age at discontinuation of treatment [10]. In boys, post-treatment growth is highly correlated with bone age at discontinuation of treatment [16]. In boys with normal onset of puberty height, velocity peaks around the chronological age of 13.5–14 years [14]; the discontinuation of treatment at a bone age close to peak height velocity might improve adult height [24].

6 Long-term safety of GnRH agonist treatment in boys

Very little data is available on the long-term safety on GnRH analog treatment in boys in terms of reproductive function, body composition and bone health (which have been better explored in girls) [1]. The outcomes of untreated boys are largely unknown, too, so, comparison between treated and untreated subjects is impossible.

Manasco *et al.* [53] report on serum testosterone levels in four boys with organic CPP, showing that serum hormone concentrations significantly increased and reached values similar to the pre-treatment period only 3 months after the cessation of GnRH analog therapy. One year after discontinuation, serum testosterone levels were in the normal adult range [53]. In the same study, testis volume increased 3 months after the discontinuation of treatment and reached the pre-treatment value after 1 year [53]. Thereafter, the same group [19]

Table 6. Central precocious puberty (CPP) in boys: indications for gonadotropin-releasing hormone (GnRH) agonist treatment. Based on suggestions from references [1, 4, 16, 26, 44] and personal clinical experience.

- clear diagnostic criteria for progressive CPP;
- pubertal levels of testosterone and pubertal LH peak after GnRH stimulation;
- impaired predicted adult height, that is a final height prediction < 3rd centile or < target height range or height for bone age < –2 SD);
- progressive deterioration of predicted adult height: Δ bone age more than > Δ statural age) and/or rapid pubertal development, represented by a progression from one pubertal stage to the next in a markedly shorter period of time than normal;
- psychological and or behavioural problems related to precocious development of secondary sex characteristics.

reported on the development of testicular volume after the discontinuation of therapy in 11 boys, treated for a mean of 8.8 years with GnRH analogs for CPP due to hypothalamic hamartoma. The authors showed a progressive increase of testicular volume values not significantly different from those of 6 controls with normal onset of puberty [19]. Serum testosterone and gonadotrophins rose to the normal range approximately 1 year after discontinuation of treatment and levels were not significantly different from normal values thereafter.

An Italian study described the reproductive axis in nine late adolescent men with CPP treated with the GnRH analog triptorelin depot for a mean period of 5.6 years (44.4% with idiopathic CPP and 55% with organic CPP) [27]. Full pubertal development and normal testicular volume (–0.4 ± 1.1 SDS) was found [27]. The values of LH, testosterone, FSH and inhibin B were into the normal adult range [27]. Sperm analysis, performed in 6 patients, showed results to be normal for age, as well [27]. In these patients, no alteration of testicular structure was detected by ultrasound scanning of the testes (unpublished data), whereas 2 out of 11 patients (18%) reported by Feuillan *et al.* [19] developed a sonographic pattern suggestive of testicular microcalcifications during GnRH analog therapy. Combining our data with that of Feuillan *et al.* [19], a prevalence of 10% results, which is approximately fourfold the prevalence demonstrated in large young male asymptomatic populations [54]. Albeit the clinical significance of ultrasound imaging for testicular microcalcifications in subjects without any other risk factors for testicular neoplasia is still unclear [54, 55], some data suggest a possible association with testicular cancer [56]. Thus, additional studies on this aspect should be undertaken.

Being overweight is reported as a long-term concern of GnRH analog therapy in girls with CPP [57, 58]. In boys, Palmert *et al.* [59] demonstrate that the body mass index (BMI) is above the 85 percentile in approximately 50% of the GnRH analog-treated boys at discontinuation of therapy, but 71% of these patients were above the 85 percentile already before therapy [59]. Other authors exploring BMI in girls with idiopathic CPP conclude that these patients are frequently obese at the onset of GnRHa therapy and that their obesity is neither long-lasting nor related to GnRH analog administration [57, 59, 60]. Recently, we explored body composition by dual energy X-ray densitometry in a group of girls treated by GnRH analogs after the attainment of adult height and found a reduced lean body mass and increased fat mass, while BMI remained unchanged in comparison with values before therapy, suggesting that patients with CPP treated with GnRH analog had slightly more body fat in late adolescence [61], and similar studies will be done in boys.

Regarding the effects on the GnRH analogs on bone mineralization, some authors suggest that the long-term suppression of pituitary-gonadal axis in children might decrease bone mineral density (BMD), possibly impairing the acquisition of peak bone mass [62–64]. While no data have been published on the development of BMD in boys with CPP from the beginning of GnRH analog treatment, normal lumbar areal and volumetric BMD have been reported in a small group of men after attainment of final height [27], suggesting no long-term adverse effects of the therapy on peak bone mass [1, 28, 62].

7 Conclusions

In summary, CPP and its treatment in men have been so far poorly evaluated. Available studies indicate that long-term treatment with GnRH analogs increases final height into the target height range in the majority of boys with CPP. Younger patients and those with idiopathic CPP are likely to receive greater benefit from treatment, whereas boys with organic forms might have poorer long-term height prognosis. Better end results have been reported with triptorelin depot than with others analogs (Table 4), but additional data on larger and more homogeneous series of patients must be collected before definitive conclusions can be made. Comparative randomized studies among the various formulations and schedules of treatment are lacking but are highly advisable. Further studies on larger series of boys with CPP are also needed to better define the criteria for starting and stopping the GnRH analog treatment to optimize the outcome. In addition, the treatment is likely to be safe in terms of testicular function, BMI and BMD in late adolescence, but patients followed until young adulthood should be assessed to draw definitive conclusions. Sonographic evaluation of testicular texture, for example, at the discontinuation of therapy and at final height, should be considered to assess the presence of microcalcifications [19].

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