CLINICAL STUDY

Three-month sustained-release triptorelin (11.25 mg) in the treatment of central precocious puberty

Jean-Claude Carel, Joëlle Blumberg¹, Christine Seymour¹, Catherine Adamsbaum² and Najiba Lahlou³ for the Triptorelin 3-month CPP Study Group*

Department of Pediatric Endocrinology and INSERM U561, Groupe Hospitalier Cochin-Saint Vincent de Paul and Faculté Cochin-Université Paris V, 75014 Paris, France ¹IPSEN laboratory, Paris, France ²Department of Radiology and ³Laboratory of Hormonal Biochemistry, Groupe Hospitalier Cochin-Saint Vincent de Paul, Paris, France

(Correspondence should be addressed to J-C Carel; Email: carel@paris5.inserm.fr)

*Members are listed in the acknowledgements section

Abstract

Objective: Depot GnRH agonists are commonly used in the treatment of central precocious puberty (CPP). The triptorelin 11.25 mg 3-month depot, currently used in adult indications, had not previously been evaluated in CPP.

Design: This was a multicenter, open-label, 12 month trial conducted in 64 CPP children (54 girls and 10 boys), treated quarterly.

Methods: Children with a clinical onset of pubertal development before the age of 8 years (girls) or 9 years (boys), pubertal response of LH to GnRH ≥ 7 IU/L, advanced bone age > 1 year, enlarged uterus (≥ 36 mm) and testosterone level ≥ 0.5 ng/ml (boys), were included. Suppression of gonadotropic activation, as determined from serum LH, FSH, estradiol or testosterone, and pubertal signs were assessed at Months 3, 6 and 12.

Results: GnRH-stimulated peak LH ≤ 3 IU/L, the main efficacy criterion, was met in 53 out of 62 (85%), 60 out of 62 (97%) and 56 out of 59 (95%) of the children at Months 3, 6 and 12 respectively. Serum FSH and sex steroids were also significantly reduced, while pubertal development regressed in most patients. Mean residual triptorelin levels were stable from Month 3 through to Month 12. The triptorelin 3-month depot was well tolerated. Severe injection pain was experienced in only one instance. Five girls experienced mild-to-moderate or severe (one girl) withdrawal bleeding.

Conclusions: The triptorelin 3-month depot efficiently suppresses the pituitary–gonadal axis and pubertal development in children with CPP. This formulation allows a 3-fold reduction, over the once-a-month depot, in the number of i.m. injections required each year.

European Journal of Endocrinology 154 119–124

Introduction

The primary aim of the treatment of central precocious puberty (CPP) is the suppression of gonadotropin secretion, and thereby of gonadal sex steroid secretion. This is in order to stop or reverse the development of secondary sex characteristics, prevent early menarche and early sexual activity, normalize growth velocity, reduce epiphyseal maturation and increase adult height. Hormonal suppression is best achieved by constant exposure to agonistic gonadotropin-releasing hormone (GnRH) analogs, which act via desensitization and down-regulation of pituitary GnRH receptors and their downstream pathway (1–4). Adequate hormonal suppression in children exhibiting CPP is commonly obtained by once-a-month treatments with depot preparations (5–12). Long-term treatments have been

shown to reverse or stabilize sexual development and normalize statural growth without adversely affecting resumption of puberty upon cessation of treatment (6, 7, 13–18).

A new 3-month depot formulation of triptorelin, administered as quarterly i.m. injections, has been developed and is currently used in several countries for the treatment of prostate cancer and endometriosis (19, 20). The treatment of CPP spreads over several years, and monthly injections can hinder the acceptance of the treatment by young children. A reduction in the frequency of injections can provide definite improvements in acceptability and treatment compliance. The aim of the present study was to evaluate the inhibition of the pituitary gonadal axis in children with CPP treated with quarterly i.m. injections of the 3-month 11.25 mg depot formulation of triptorelin.

Patients and methods

Patients

This multicenter European trial (Belgium, France, Italy and Spain) involved 64 children (54 girls and 10 boys). The children were included on the basis of the following inclusion criteria: clinical onset of pubertal development (breasts in girls and testicular enlargement in boys) before the age of 8 years in girls and 9 years in boys; pubertal response of luteinizing hormone (LH) to GnRH stimulation (LH peak ≥ 7 IU/l in both sexes (21)); bone age – chronological age > 1 year; and testosterone levels ≥ 0.5 ng/ml in boys and uterine length ≥ 36 mm, as assessed by ultrasound, in girls. Children exhibiting the following criteria were not included: gonadotropin-independent gonadal or adrenal sex steroid secretion; evolutive brain tumor requiring neurosurgery or brain irradiation; body weight $\geq 125\%$ of the ideal weight for height; previous treatment with a GnRH analog, medroxyprogesterone or cyproterone acetate; and concomitant disease likely to interfere with the study course.

The study was approved by the Ethics Committee of Paris-Cochin in France and by the Ethics Committees of each of the centers in Belgium, Italy and Spain.

Treatment

The triptorelin (D-Trp⁶-GnRH) 3-month depot formulation consists of biocompatible, biodegradable copolymer (lactide-coglycolide) microparticles containing 11.25 mg triptorelin (19) (Ipsen Pharma Biotech, Paris, France). The formulation was suspended in 2 ml vehicle just before use and injected i.m. in the external upper quadrant of the buttock every 3 months (91 ± 3 days).

Methods

The trial duration was 12 months, with four quarterly injections at Day 0, Month 3, Month 6 and Month 9. The primary endpoint of the trial was the percentage of children showing a suppressed LH response to GnRH, defined as an LH peak ≤ 3 IU/l at Month 3 of the study. This cutoff was chosen since 95% of prepubertal children have values below this threshold (21) and Najiba Lahlou and Jean Claude Carel, unpublished observations). Secondary endpoints included GnRH-stimulated peak serum concentrations of LH at Months 6 and 12, peak serum follicle-stimulating hormone (FSH) concentrations, estradiol (girls) and testosterone (boys) concentrations, and progression of clinical signs of puberty. Serum testosterone levels ≤ 0.3 ng/ml (1 nmol/l) and estradiol levels ≤ 20 pg/ml (74 pmol/l), the upper limit of normal values in prepubertal children (21), were defined per protocol as references for adequate sex steroid hormone suppression. Triptorelin plasma

concentrations were measured at Day 0, Months 3 and 6 before the injection, and at Month 12.

The GnRH tests were performed by i.v. injection of $100 \mu\text{g}/\text{m}^2$ GnRH with measurement of LH and FSH serum concentrations determined at baseline, and 20, 40, 60 and 90 min after the injection. FSH and LH serum concentrations were assessed by fluoroimmunoassay (16) with limits of detection of 0.01 IU/l for both parameters. Estradiol and testosterone serum concentrations were determined by RIAs with limits of detection of 2.4 pg/ml and 0.02 ng/ml respectively (16). Triptorelin plasma concentrations were measured by a validated RIA procedure with a limit of detection of 20 pg/ml. Sempé (22) normative data were used for height. Bone age was determined centrally by the method of Greulich & Pyle (23).

Statistics

Two populations were considered in the efficacy analyses: (i) the intent-to-treat (ITT) population, which included all patients who received at least one dose of triptorelin 11.25 mg, and (ii) the per-protocol population, which was a subset of the ITT population. The per-protocol population included all patients who had received all four doses of triptorelin 11.25 mg and had no major protocol violation. Reasons for exclusion from the per-protocol population were: inclusion/exclusion criteria not met (19% of the ITT children); LH peak not assessable (11%); non-compliance for the date of GnRH test (39%), and non-compliance for the injection date (38%). Thus, 26 children (41%) from the ITT population were excluded from the per-protocol population, which therefore comprised 38 children. In both populations, efficacy analyses at each scheduled time point took into account only those patients with available data. Results presented in this paper refer to the ITT population unless otherwise stated.

Descriptive statistics were used for percentages of children with suppressed LH response, and suppressed estradiol and testosterone levels. Hormonal variations from baseline were analyzed using the non-parametric Wilcoxon test.

Results

Patient characteristics at baseline (Table 1)

Several violations of the per-protocol inclusion criteria were noted: seven children (five girls and two boys) had a bone age/chronological age difference < 1 ; two girls had uterine length < 36 mm; and two boys had testosterone levels < 0.5 ng/ml. Nevertheless, all children showed clinical signs of precocious puberty and activation of the gonadotropic axis with stimulated LH peaks > 7 IU/l (21). Most children (70%) were at pubertal stage 3, and four girls and two boys were at pubertal stage 4. One boy was considered to have an intrasellar pituitary tumor that did not require neurosurgery or irradiation treatment.

Table 1 Initial characteristics of the patients.

	Girls	Boys
Number of patients	54	10
Age (years)	8.3±0.9 (4.9; 9.7)	10.2±0.9 (8.7; 11.6)
Height (SDS)	2.1±1.2 (−0.6; 5.9)	1.7±1.7 (−1.5; 3.8)
Growth rate (cm/year)	9.1±2.4 (5.1; 14.2)	8.9±1.4 (7.6; 11.5)
Weight (kg)	32.9±6.0 (20.4; 49.8)	38.3±5.8 (30.0; 47.0)
BMI (SDS)	1.4±1.2 (−1.0; 3.8)	0.9±1.3 (−0.7; 3.8)
Bone age (years)	10.7±1.1 (7.8; 13.3)	12.0±1.1 (9.8; 13.0)
Bone age − chronological age (years)	2.4±1.1 (−0.8; 4.5)	1.9±1.3 (−0.7; 4.0)
Estradiol (pg/ml)	20.7±19.8 (3.8; 11.0)	—
Testosterone (ng/ml)	—	3.0±2.0 (0.2; 6.6)
GnRH-stimulated LH peak (IU/l)	21.6±14.7 (7.6; 86.7)	17.3±4.6 (8.7; 26.0)
GnRH-stimulated FSH peak (IU/l)	11.9±4.2 (5.7; 23.6)	5.6±3.9 (2.0; 15.1)
Pubertal stage, <i>n</i> (%)	B2: 11 (20%) B3: 39 (72%) B4: 4 (7%)	G2: 1 (10%) G3: 7 (70%) G4: 2 (20%)
Uterine length (cm)	43.6±6.5 (33.0; 68.0)	—
Mean testicular volume (ml)	—	13.0±6.7 (6.0; 28.8)

Results are given as mean ± S.D. (range).

B: breast development stage; G: genital development stage.

Gonadotropin suppression (Table 2)

At Month 3, 45 of the 52 girls and eight of the ten boys with available data, i.e. 85% of the children, had suppressed LH peaks (≤ 3 IU/l). LH peaks in the nine children not responsive to treatment at Month 3 were 3.9, 4.1, 4.3, 12, 13, 17, 19, 20 and 39 IU/l. Of these nine children, eight out of nine and six out of seven achieved adequate LH suppression at Month 6 and 12 respectively (two of these children were lost to follow-up at Month 12). In the per-protocol population, all of 33 girls (100%) and four out of five boys (80%), i.e. 97% of the per-protocol children achieved adequate LH suppression.

At Month 6, 60 out of 62 (97%) of the children achieved adequate LH suppression. One girl with an LH peak of 6.3 IU/l had a suppressed LH response at Month 3 (2.2 IU/l) and at Month 12 (2.4 IU/l). This girl had experienced an injection problem that may explain the lack of response. The other unresponsive child, a

boy with an LH peak of 3.6 IU/l (close to threshold level for response), was found to be below the suppressed level at Month 12. At Month 12, only three boys were non-responders. Thus, 95% of the ITT children had a suppressed LH response. In the per-protocol population, the response rate observed at Month 3 remained unchanged, at 97% at Months 6 and 12.

Highly significant decreases in mean LH and FSH peaks were observed at Month 3 and were sustained through Month 12. Similar results were observed in boys and girls.

Suppression of gonadal steroids (Table 3)

Estradiol levels were decreased to prepubertal levels (≤ 20 pg/ml) in 96% of girls at Month 3 (there were two higher values of 22 and 28 pg/ml), in 98% at Month 6 (one higher value of 47 pg/ml) and 100% at Month 12. Interestingly, these three girls with high estradiol values had corresponding LH peaks of 12.2, 38.7 and 6.3 IU/l respectively. Consistent with the results for the percentage of responders, the mean estradiol plasma concentrations were significantly decreased at all time points ($P < 0.001$). As would be expected, 63% of the girls had estradiol levels below the defined threshold for suppression at baseline, due to the pulsatile ovarian secretion. In the per-protocol population, all girls (100%) exhibited prepubertal estradiol levels at all post-baseline time points.

Testosterone levels were decreased to prepubertal levels in 70% of the boys at Month 3 (with the remaining three boys having values of 0.35, 0.4 and 3.5 ng/ml), and at Month 6 (with the remaining three boys having values of 0.4, 0.5 and 1.2 ng/ml), and in 50% at Month 12 (with the remaining five boys having values of 0.35, 0.4, 0.55, 0.6 and 3.1 ng/ml respectively).

Table 2 GnRH-stimulated concentrations of LH and FSH.

	LH		
	LH peak ≤ 3 IU/l <i>n/N</i> (%)	Peak (IU/l)	FSH peak (IU/l)
ITT population (<i>n</i> = 64)			
Baseline	0/64 (0)	21.0±13.7	10.9±4.7
Month 3	53/62 (85)	3.1±6.3***	2.6±3.4***
Month 6	60/62 (97)	1.3±0.9***	1.7±1.1***
Month 12	56/59 (95)	1.7±2.9***	2.0±1.7***
Per-protocol population (<i>n</i> = 38)			
Baseline	0/38 (0)	21.3±14.5	10.7±4.7
Month 3	37/38 (97)	1.2±0.7***	1.4±0.8***
Month 6	37/38 (97)	1.2±0.7***	1.7±1.1***
Month 12	37/38 (97)	1.7±3.2***	2.2±1.9***

Results are given as mean ± S.D.

*** $P < 0.001$ with respect to baseline.

Table 3 Suppression of estradiol (girls) and testosterone (boys).

	Estradiol ^a		Testosterone ^b	
	pg/l	≤ 20 pg/ml n/N (%)	ng/l	≤ 0.3 ng/l n/N (%)
ITT population (N = 54)				
Baseline	20.7 ± 19.8	34/54 (63)	3.0 ± 2.0	1/10 (10)
Month 3	7.0 ± 4.7***	50/52 (96)	0.5 ± 1.1**	7/10 (70)
Month 6	6.7 ± 5.9***	51/52 (98)	0.3 ± 0.3**	7/10 (70)
Month 12	6.5 ± 1.9***	50/50 (100)	0.6 ± 0.9**	5/10 (50)
Per-protocol population (N = 33)				
Baseline	17.1 ± 13.4	23/33 (70)	3.3 ± 2.0*	0/5 (0)
Month 3	5.7 ± 1.4***	33/33 (100)	0.2 ± 0.1*	4/5 (80)
Month 6	6.1 ± 1.5***	33/33 (100)	0.4 ± 0.5	3/5 (60)
Month 12	6.5 ± 1.9***	33/33 (100)	0.8 ± 1.3	3/5 (60)

Estradiol and testosterone concentrations are given as mean ± s.d.

To convert to SI, multiply by 3.67^a, 3.46^b.

*P = 0.06; **P ≤ 0.002; ***P < 0.001 vs baseline.

As was seen in the girls with the high estradiol levels, boys with elevated testosterone levels generally had clearly elevated LH peak responses at the assessment time points. This was particularly the case when the testosterone level exceeded 0.5 ng/ml, the cutoff generally used to define suppression in adults. Mean testosterone levels were significantly decreased at all post-baseline time points ($P \leq 0.002$).

Triptorelin levels

Mean residual plasma concentrations of triptorelin, 3 months after each injection, are shown in Fig. 1. Three children had clearly detectable triptorelin plasma concentrations at baseline (363, 387 and 73 pg/ml respectively), suggesting that sampling had been performed after the first injection. Mean triptorelin residual plasma concentrations ranged from 53 ± 34 pg/ml (Month 3) to 81 ± 82 pg/ml (Month 6). Several children had undetected triptorelin levels at certain time points: at Month 3, triptorelin was not detected in eight children, of whom six had

inadequate LH responses; at Month 6, undetectable levels were found in two children, of whom one had an inadequate LH response; and at Month 12, undetectable levels were found in six children, of whom two had inadequate LH responses.

Clinical efficacy

Assessments at Month 12 showed that breast development was stable in 16 out of 51 girls (31%) and regressed in 35 out of 51 (69%), while mean uterine length decreased from 43.6 ± 6.5 mm at inclusion to 38.6 ± 7.0 mm. Genital development was stable in three out of ten (30%) of the boys and regressed in seven out of ten (70%). Overall, growth velocity decreased from the baseline 9.0 ± 2.3 to 6.2 ± 1.7 cm/year, and the bone age – chronological age difference was unchanged. Body mass index (BMI) slightly increased from 1.3 ± 1.2 SDS units at baseline to 1.5 ± 1.3 SDS units after 12 months of treatment.

Tolerance

The general tolerance to the triptorelin treatment was good. Headache, the most frequent adverse event, was reported in 9 out of 54 girls (17%) and four out of ten boys (40%). Headaches were generally mild or moderate, with only one child reporting severe headache. Mild-to-moderate rhinitis (13% of the children), abdominal pain (9%), gastroenteritis (5%) and rash (5%) were also reported.

Local pain at the injection site was reported in two children. It was mild at all injections in one child and severe only at the Month 3 injection in the other child. Other transient mild-to-moderate local reactions were observed in four children (8%). Five girls experienced withdrawal bleeding, four after the Day 0 injection and one after the Month 3 injection. Withdrawal bleeding episodes were mild or moderate, except in one girl who experienced three episodes after the Day 0 injection, and for whom the second episode was severe and lasted 7 days. None of these events resulted in early withdrawal from the study.

Figure 1 Triptorelin plasma levels. *Three children had detectable values at baseline, suggesting that sampling had been performed after the injection; means ± s.d.

Discussion

In this study, we evaluated in a large sample of patients, screened using a uniform and centralized procedure, the safety and efficacy of the 3-month 11.25 mg depot formulation of triptorelin in children with CPP. The results from this 1 year trial demonstrate that the triptorelin 3-month sustained-release formulation, at a dose of 11.25 mg/3 months, was effective in suppressing gonadotropin and gonadal steroid secretion in most children with CPP. Pharmacodynamic effects were similar to those previously reported with the monthly formulation of the same drug (7).

One strength of this study was to evaluate a large sample of patients including ten boys for 1 year, using a centralized protocol and hormonal measurements, allowing the most thorough assessment to date of 3-month depot GnRH agonists in children. Although our study did not directly compare the results of 1-month and 3-month depot forms of triptorelin, this has been done in other settings. A study in patients with endometriosis (19) and one in patients with prostate cancer (20) have documented the pharmacodynamic equivalence of the 1-month and 3-month formulations over a 3 month treatment period, and the persistence of triptorelin plasma levels over at least 90 days after injection of the 3-month formulation. Mean triptorelin plasma concentrations of 40–60 pg/ml were observed at 90 days in both studies. Similar plasma levels were observed in the present study, although the average weight of the children was 33 kg, roughly half the weight of the treated adults, suggesting the need for a higher dose:weight ratio in children. Residual triptorelin levels were undetectable in 16 out of 177 measurements, correlating with non-suppressed LH peaks in 9 out of 16 instances. Thus, the pharmacodynamic activity of the 3-month formulation generally covered the expected 90 day period, even if residual plasma levels of triptorelin were sometimes not detected 3 months after the injection.

The LH peak threshold of 7 IU/l used in this study to define CPP was higher than that used as a reference (5 IU/l) in most other clinical trials (16). Therefore, children in the present trial were selected on the basis of rather stringent criteria for CPP, likely to correspond to pubertal stage 3 (21). Three of the children defined as non-responders at Month 3 with LH peaks of 3.9, 4.1 and 4.3 IU/l, nevertheless showed some degree of LH suppression with respect to baseline. This also holds true for the two non-responders at Month 6, and for one of the three non-responders at Month 12, who had an LH peak of 3.6 IU/l. Thus, the responder rates observed from Month 3 to Month 12, and the highly significant decreases in mean peak gonadotropins and in mean gonadal hormone levels, reflect an efficient suppression of the pituitary gonadal axis with this 3-month 11.25 mg triptorelin depot formulation. These hormonal results obtained with quarterly injections are similar to those observed with the triptorelin slow-release 3.5 mg formulation administered every 28 days (5, 12, 24, 25). It is interesting to note that at 3 months, eight of the non-responders in the ITT group had protocol violations resulting in either delayed injection resulting in increased inter-injection interval or incomplete injections resulting in decreased drug delivery. This finding emphasizes the need for (i) careful monitoring of the injection and injection schedule of this as well as other depot GnRH agonist preparation, and (ii) careful clinical and hormonal monitoring of depot GnRH

agonist-treated children. When results are not satisfactory, our data would suggest that strict compliance to treatment schedule and drug delivery will result in efficacy in 97% of cases. If this is not the case, our data do not permit recommendations to be made regarding the best option (i.e. increase the dose, reduce the inter-injection interval or change to a 1-month depot form).

Subcutaneous intolerance to depot GnRH agonists has been reported and is mostly due to reaction to the lactide-coglycolide polymer (9, 11, 16, 26, 27). In the present study, mild-to-moderate local reactions at the injection site were reported in 8% of the children, and injection pain in only 3%. None of these cases resulted in withdrawal from the study, although such a situation may well occur with repeated injections, highlighting the advantage of a quarterly treatment over a monthly treatment. Since lactide-coglycolide polymers are constituents of both the 3 mg and 11.25 mg preparation of triptorelin, it should result in similar safety profiles. However, it will be particularly important to monitor the long-term safety of this new preparation when approval for use in children CPP is obtained.

Conclusions

The results of the present study demonstrate that the 3-month 11.25 mg triptorelin depot formulation efficiently suppresses the pituitary–gonadal axis and the progression of CPP in children. They also confirm the need for precise monitoring of gonadotropin secretion in children treated with GnRH agonists. These results confirm the efficacy, tolerability and acceptability of the 3-month formulations of GnRH agonists in children (16).

Acknowledgements

The following investigators participated in the Triptorelin 3-month CPP Study Group: Belgium, Marc Maes (Brussels); France, Anne-Marie Bertrand (Besançon), Michel Bost (Grenoble), Raja Brauner (Paris), Sylvie Cabrol (Paris), Jean-Claude Carel (Paris), Michel Colle (Bordeaux), François Despert (Tours), Monique Jesuran-Perelroizen (Toulouse), Juliane Leger (Paris), Marc Nicolino (Lyon), Elisabeth Sadoul (Nice), Sylvie Soskin (Strasbourg), Charles Sultan (Montpellier), Maïthé Tauber (Toulouse), Cécile Teinturier (Paris); Italy, Maria-Angela Cisternino (Pavia), Anna-Maria Pasquino (Rome), Luciano Tato (Verona); Spain, Antonio Carrascosa (Barcelona), Jorge Del Valle (Seville), Ricardo Gracia Boutelier (Madrid), Lourdes Ibanez (Esplugues De Llobregat), Manuel Pombo Arias (Santiago De Compostela).

References

- 1 Partsch CJ & Sippell WG. Treatment of central precocious puberty. *Best Practice and Research. Clinical Endocrinology and Metabolism* 2002 **16** 165–189.
- 2 Conn PM & Crowley WF Jr. Gonadotropin-releasing hormone and its analogues. *New England Journal of Medicine* 1991 **324** 93–103.
- 3 Crowley WF Jr, Comite F, Vale W, Rivier J, Loriaux DL & Cutler GB Jr. Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty. *Journal of Clinical Endocrinology and Metabolism* 1981 **52** 370–372.
- 4 Comite F, Cutler GB Jr, Rivier J, Vale WW, Loriaux DL & Crowley WF Jr. Short-term treatment of idiopathic precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone. A preliminary report. *New England Journal of Medicine* 1981 **305** 1546–1550.
- 5 Oostdijk W, Hummelink R, Odink RJ, Partsch CJ, Drop SL, Lorenzen F, Sippell WG, van der Velde EA & Schultheiss H. Treatment of children with central precocious puberty by a slow-release gonadotropin-releasing hormone agonist. *European Journal of Pediatrics* 1990 **149** 308–313.
- 6 Carel JC, Roger M, Ispas S, Tondou F, Lahlou N, Blumberg J & Chaussain JL. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 1973–1978.
- 7 Roger M, Chaussain JL, Berlier P, Bost M, Canlorbe P, Colle M, Francois R, Garandeau P, Lahlou N, Morel Y & Schally AV. Long-term treatment of male and female precocious puberty by periodic administration of a long-acting preparation of D-Trp6-luteinizing hormone-releasing hormone microcapsules. *Journal of Clinical Endocrinology and Metabolism* 1986 **62** 670–677.
- 8 Partsch CJ, Hummelink R, Peter M, Sippell WG, Oostdijk W, Odink RJ & Drop SL. Comparison of complete and incomplete suppression of pituitary-gonadal activity in girls with central precocious puberty: influence on growth and predicted final height. The German–Dutch Precocious Puberty Study Group. *Hormone Research* 1993 **39** 111–117.
- 9 Carel JC, Lahlou N, Guazzarotti L, Joubert-Collin M, Roger M, Colle M & Chaussain JL. Treatment of central precocious puberty with depot leuporelin. French Leuporelin Trial Group. *European Journal of Endocrinology* 1995 **132** 699–704.
- 10 Parker KL, Baens-Bailon RG & Lee PA. Depot leuprolide acetate dosage for sexual precocity. *Journal of Clinical Endocrinology and Metabolism* 1991 **73** 50–52.
- 11 Neely EK, Hintz RL, Parker B, Bachrach LK, Cohen P, Olney R & Wilson DM. Two-year results of treatment with depot leuprolide acetate for central precocious puberty. *Journal of Pediatrics* 1992 **121** 634–640.
- 12 Antoniazzi F, Cisternino M, Nizzoli G, Bozzola M, Corrias A, De Luca F, De Sanctis C, Rigon F, Zamboni G, Bernasconi S, Chiumello G, Severi F & Tato L. Final height in girls with central precocious puberty: comparison of two different luteinizing hormone-releasing hormone agonist treatments. *Acta Paediatrica* 1994 **83** 1052–1056.
- 13 Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL & Cutler GB Jr. Resumption of puberty after long-term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 368–372.
- 14 Kauli R, Kornreich L & Laron Z. Pubertal development, growth and final height in girls with sexual precocity after therapy with the GnRH analogue D-TRP-6-LHRH. A report on 15 girls, followed after cessation of gonadotrophin suppressive therapy. *Hormone Research* 1990 **33** 11–17.
- 15 Oostdijk W, Drop SL, Odink RJ, Hummelink R, Partsch CJ & Sippell WG. Long-term results with a slow-release gonadotrophin-releasing hormone agonist in central precocious puberty. Dutch–German Precocious Puberty Study Group. *Acta Paediatrica Scandinavica. Supplement* 1991 **372** 39–46.
- 16 Carel JC, Lahlou N, Jaramillo O, Montauban V, Teinturier C, Colle M, Lucas C & Chaussain JL. Treatment of central precocious puberty by subcutaneous injections of leuporelin 3-month depot (11.25 mg). *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 4111–4116.
- 17 Trueman JA, Tillmann V, Cusick CF, Foster P, Patel L, Hall CM, Price DA & Clayton PE. Suppression of puberty with long-acting goserelin (Zoladex-LA): effect on gonadotrophin response to GnRH in the first treatment cycle. *Clinical Endocrinology* 2002 **57** 223–230.
- 18 Carel JC, Lahlou N, Roger M & Chaussain JL. Precocious puberty and statural growth. *Human Reproduction Update* 2004 **10** 135–147.
- 19 Donnez J, Dewart PJ, Hedon B, Perino A, Schindler AE, Blumberg J & Querleu D. Equivalence of the 3-month and 28-day formulations of triptorelin with regard to achievement and maintenance of medical castration in women with endometriosis. *Fertility and Sterility* 2004 **81** 297–304.
- 20 Bouchot O, Soret JY, Jacqmin D, Lahlou N, Roger M & Blumberg J. Three-month sustained-release form of triptorelin in patients with advanced prostatic adenocarcinoma: results of an open pharmacodynamic and pharmacokinetic multicenter study. *Hormone Research* 1998 **50** 89–93.
- 21 Roger M, Lahlou N & Chaussain JL. Gonadotropin-releasing hormone testing in pediatrics. In *Diagnostics of endocrine function in children and adolescents*, pp 346–369. Ed MB Ranke. Heidelberg–Leipzig: Johann Ambrosius Barth Verlag, 1996.
- 22 Sempé M, Pédrón G & Roy P. *Auxologie, Méthodes et Conséquences*. Paris: Thérapix, 1979.
- 23 Greulich WW & Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford, CA: Stanford University Press, 1959.
- 24 Saggese G, Bertelloni S, Baroncelli GI, Di Nero G & Battini R. Growth velocity and serum aminoterminal propeptide of type III procollagen in precocious puberty during gonadotropin-releasing hormone analogue treatment. *Acta Paediatrica* 1993 **82** 261–266.
- 25 Heinrichs C, Craen M, Vanderschueren-Lodeweyckx M, Malvaux P, Fawe L & Bourguignon JP. Variations in pituitary–gonadal suppression during intranasal buserelin and intramuscular depot-triptorelin therapy for central precocious puberty. Belgian Study Group for Pediatric Endocrinology. *Acta Paediatrica* 1994 **83** 627–633.
- 26 Kaplan SL, Paul DL & Grumbach MM. Long-term therapy of children with true precocious puberty with three GnRH agonists administered by different modes. In *Sexual Precocity: Etiology, Diagnosis and Treatment*, pp 61–68. Eds GD Grave & GB Cutler. New York: Raven Press Ltd, 1993.
- 27 Manasco PK, Pescovitz OH & Blizzard RM. Local reactions to depot leuprolide therapy for central precocious puberty. *Journal of Pediatrics* 1993 **123** 334–335.

Received 6 June 2005

Accepted 16 September 2005