Time to Menarche and Final Height after Histrelin Implant Treatment for Central Precocious Puberty

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Objective To compare final height, change in body mass index (BMI), and time from end of treatment until menarche in girls with central precocious puberty treated with the histrelin implant versus depot gonadotropin releasing hormone agonist injections.

Study design Chart review, interview, and final height measurements of 2 groups of girls with central precocious puberty; triptorelin depot (TD) group: 23 girls were treated from age 8.4 ± 0.3 with monthly injections of TD, for 26.7 ± 2.5 months; histrelin implant group: 11 girls were treated from age 8.7 ± 0.3 years for 28.4 ± 3.7 months, of whom 9 initially received monthly TD injections for 1.5-39 months. Final height, BMI (pretreatment vs recent), and time between either implant removal or last injection to menarche were compared.

Results Time between removal of implant or last injection and menarche was 9.3 ± 1.5 (histrelin implant group) versus 16.1 ± 1.7 (TD group) months (P = .02). Predicted height at implant insertion was 156.8 ± 2.6 cm, and final height was 161.1 ± 2.0 cm (not significant [NS]). Predicted height for TD was 155.2 ± 1.9 cm and final height was 157.9 ± 1.7 cm (NS). Change from onset of treatment to final BMI-SDS for histrelin implant was −0.41 ± 0.3, and for TD was −0.03 ± 0.2 (NS).

Conclusions Menarche occurred sooner after implant removal. There was no difference in final height or BMI outcomes between the 2 treatment modalities. *(J Pediatr 2013;163:532-6)*.

Treatment goals for central precocious puberty (CPP) in girls include preventing short final height due to early epiphyseal closure, stopping or slowing progression of early breast development, and avoiding premature onset of menarche. Depot preparations of gonadotropin releasing hormone agonists (GnRHa), administered by intramuscular or subcutaneous injections at 3 to 4 week intervals, are generally effective in retarding progression of secondary sexual characteristics, preventing menses, slowing bone age advancement, and improving final height.[1] A subcutaneous hydrogel implant, which releases histrelin continuously for at least 1 year, has been shown to result in greater suppression of luteinizing hormone (LH) and follicle stimulating hormone (FSH) compared with treatment with depot GnRHa.[2,3] Following removal of the implant, gonadotropin secretion recovers rapidly. Free alpha-subunit levels decrease and serum LH and FSH levels increase within 3 weeks after implant removal and a significant rise in 17ß-estradiol levels is observed by 6 weeks after removing the implant.[4] A recent study of 7 girls and 1 boy reported that the mean stimulated LH was 0.30 mIU/mL prior to implant removal and increased to 3.62 mIU/mL (P = .007) 1 month after removal of the implant.[5]

Although several reports have documented efficacy of histrelin implant treatment of CPP,[2,3] there are no reports of long-term follow-up after completion of the treatment course. Specifically, it is not known how long after implant removal menarche occurs. Furthermore, because low levels of estrogen may have a permissive effect on achieving normal linear growth in prepubertal girls,[6] it is possible that the greater suppression of the hypothalamic-pituitary-ovarian axis achieved by histrelin implant treatment might have an adverse effect on final height. Because the girls treated in our original trial[2] have now all reached final or near final height, we had the unique opportunity to compare final heights in girls with CPP treated with the histrelin implant versus final heights in a similar group treated with depot GnRHa monthly injections.

BMI	Body mass index
CPP	Central precocious puberty
FSH	Follicle stimulating hormone
GnRHa	Gonadotropin releasing hormone agonist(s)
LH	Luteinizing hormone
NS	Not significant
PAH	Predicted adult height
TD	Triptorelin depot

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Methods

We reviewed the clinic charts of 34 girls with CPP referred to pediatric endocrinologists (H.H., D.G., or D.S.). Inclusion criteria were Tanner breast stage 2 or greater before age 8 years, increased growth velocity, advanced bone age, elevated LH, FSH, and 17β-estradiol. Indications for treating included short predicted final height, rapid progression of puberty, and/or psychosocial problems related to early puberty. Exclusion criteria were "peripheral" causes of precocious puberty, such as exogenous steroids, tumors, or adrenal disorders.

This investigator-initiated study was approved by the Human Investigation Review Board of Hadassah Hebrew University Medical center. For data collected from patients or parents, written informed consent was obtained prior to interview and/or measurement. The study was designed and the data were analyzed by the academic investigators without involvement of any commercial company.

The histrelin implant group included 11 girls in whom treatment to suppress puberty was initiated at age 8.7 ± 0.3 years. Nine of the 11 previously described,[2] were initially treated prior to implant insertion with monthly triptorelin depot (TD) injections. The duration of TD injections for 7 of these 9 girls was relatively short (ie, 3.1 ± 0.8 months) (range 1.5-7), but 2 of the 9 girls were treated for 18 and 39 months, respectively. Two girls received no other treatment before insertion of the histrelin implant.

The TD group included 23 girls who received intramuscular injections at a dose of 3.75 mg every 3-4 weeks. Treatment in the TD group was initiated at age 8.4 ± 0.3 years and continued for 26.7 ± 2.5 months. Seventeen of the 23 girls received their injections every 4 weeks over the entire period of their pubertal suppressive therapy and 6 girls received injections every 3 weeks for a variable proportion of the TD treatment course.

Final height was determined when 3 years had elapsed from menarche. "Near final height" was defined when at least 2 years had elapsed from menarche and growth velocity was less than 2 cm/year. The final or near final height data were collected from the charts or were updated by measurement in the participating clinics. Height was measured using standard wall-mounted stadiometers in the clinic of each participating physician. Three of the patients in the histrelin implant group and 2 of the patients in the TD group were measured in their homes by one of the authors (G.K.) using a portable stadiometer (Seca 213; Hamburg, Germany). If the age at menarche was not recorded in the medical record, the patient or her mother was asked to provide this information.

The TD preparations – Decapeptyl depot (triptorelin embonate depot 3.75 mg per vial, Ferring, Israel) and Decapeptyl CR (triptorelin acetate depot 3.75 mg per vial, Ferring) are the only available depot GnRHa in use in Israel for CPP. The pharmacodynamic profile of TD preparations is similar to that of leuprolide depot including initial acute stimulation and subsequent suppression of gonadotropin secretion.[7]

Hormonal assays confirming precocious puberty were performed in clinical laboratories, which participate in the Israel laboratory quality control network. Height and body mass index (BMI) data were analyzed as SDS using the Centers for Disease Control and Prevention-2000 reference standards. Bone ages were determined from radiographs of the left hand and wrist using the method of Greulich and Pyle[8] and interpreted by a pediatric endocrinologist.

Target height for each girl was defined as the average of both parental heights minus 6.5 cm. Predicted adult height (PAH) was calculated using the modified Bailey-Pinneau table.[9] We used the "average" column instead of the "advanced" column for this calculation because this approach has been shown to result in more accurate height predictions for girls with precocious puberty.[10]

Statistical Analyses

The outcomes in this study were final height, BMI-SDS (pretreatment vs latest), time between either implant removal (histrelin implant group) or last injection (TD group) to menarche, and age at menarche. Data are presented as mean ± SE unless otherwise reported. Outcomes were compared between the 2 groups using the *t* test for independent samples. Differences in time to menarche were tested using the nonparametric Wilcoxon paired sign rank test. Differences in proportion of advanced Tanner score (those at stages 3 or above for breast or pubic hair stage) between the 2 groups were compared with Fisher exact test. The Pearson correlation coefficient was used to test the association between length of treatment and the time until menarche or between age at initiation of treatment and height gained from treatment (in height SDS). All tests were 2-tailed and a *P* value of .05 or less was considered statistically significant.

Results

Patient characteristics at initiation of treatment are presented in Table I. Average age at menarche in the histrelin implant group was 12.9 ± 0.3 years versus 12.1 ± 0.1 years in the TD

Table I. Baseline measurements (at initiation of treatment) in both groups

Characteristic	TD group (n = 23)	HI group (n = 11)	*P* value
Age	8.4 ± 0.3	8.7 ± 0.3	.648
Bone age	10.0 ± 0.3	10.4 ± 0.4	.633
Bone age minus age	1.7 ± 0.2	1.7 ± 0.3	.937
Height (cm)	134.8 ± 1.96	136.6 ± 1.97	.579
Ht-SDS	0.99 ± 0.26	0.89 ± 0.26	.818
Ht-SDS by bone age	−0.67 ± 0.22	−0.63 ± 0.37	.93
MPH (cm)	160.8 ± 0.75	160.1 ± 0.97	.57
MPH-SDS	−0.50 ± 0.13	−0.62 ± 0.17	.58
MPH-SDS minus PAH-SDS	−0.89 ± 0.25	−0.56 ± 0.38	.47
BMI	18.7 ± 0.50	19.5 ± 0.93	.44
BMI-SDS	0.88 ± 0.19	1.02 ± 0.27	.68
Basal LH (IU/L)	1.04 ± 0.25	2.51 ± 1.08	.22
Basal FSH (IU/L)	2.94 ± 0.37	5.47 ± 1.82	.21
Basal Estradiol (pg/mL)	31.0 ± 3.2	44.9 ± 7.3	.11
Breast stage ≥3 n (%)	16 (70%)	10 (91%)	.04
Pubic hair stage ≥3 n (%)	4 (17%)	4 (36%)	.64

HI, histrelin; *Ht-SDS*, height-SDS; *MPH*, mean parental height.