The Histrelin Implant: A Novel Treatment for Central Precocious Puberty

Harry J. Hirsch, MD*‡; David Gillis, MD§; David Strich, MD‖; Boris Chertin, MD¶; Amicur Farkas, MD¶; Tzina Lindenberg, MA‡; Hadassa Gelber, BSc‡; and Irving M. Spitz, MD, DSc, FRCP‡

ABSTRACT. *Objective.* **Standard treatment of central precocious puberty (CPP) consists of intramuscular or subcutaneous administration of a gonadotropin-releasing hormone (GnRH) agonist (GnRHa) at 3- to 4-week intervals. Although generally effective in suppressing clinical and laboratory parameters of puberty, GnRHa injections are painful, and the need for monthly clinic visits may contribute to poor compliance. Recently, a subcutaneous implant was developed that releases the GnRHa histrelin at an average rate of 65 μg/day. The aims of this study were to determine if a histrelin implant would suppress gonadotropin and estradiol (E_2) in girls with CPP for 1 year and to compare the suppression to standard treatment.**

Methods. **We studied 11 girls with CPP to determine if the histrelin implant can maintain long-term gonadotropin suppression. Mean age at diagnosis was 6½ years (range: 2–9 years). GnRH (100 μg intravenously) stimulation tests (GnRH-STs) showed peak luteinizing hormone and follicle-stimulating hormone responses of 23 ± 28 (mean ± SD) and 20 ± 25 mIU/mL, respectively. All subjects were initially treated with depot intramuscular GnRHa triptorelin embonate. Implants were inserted subcutaneously under local anesthesia, and depot GnRHa treatment was discontinued. Six girls were followed for 15 months after insertion (group A). For the remaining 5 girls, the implant was removed after 9 months, and a new implant was inserted at the same incision site (group B). GnRH-STs were performed before depot GnRHa treatment, immediately before implant insertion, at the 6- and 9-month visits for each patient and the 12- and 15-month visit for those girls followed for 15 months.**

Results. **In all girls, breast development regressed, growth velocity decreased, and bone-age advancement was slowed. Basal gonadotropins and their responses to GnRH-STs and E_2 levels were suppressed. Peak luteinizing hormone and follicle-stimulating hormone responses to GnRH-STs at preinsertion versus 9 months were 1.30 ± 1.34 vs 0.25 ± 0.08 and 1.68 ± 1.08 vs 1.13 ± 0.55 mIU/mL, respectively. Basal and stimulated gonadotropin levels and E_2 level remained suppressed in all 6 patients followed for 15 months after implant insertion. Patients and parents reported less pain and discomfort and less interference with school activity and work with the implant compared with standard monthly injections.**

Conclusions. **The histrelin implant consistently suppresses clinical and laboratory parameters of puberty for 1 year and is a promising new technique for treating CPP without the pain and inconvenience of monthly injections.** *Pediatrics* **2005;116:e798–e802. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0538;** ***precocious puberty, gonadotropins, estradiol, GnRH agonists, histrelin.***

ABBREVIATIONS. CPP, central precocious puberty; LH, luteinizing hormone; FSH, follicle-stimulating hormone; E_2, estradiol; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone agonist(s); GnRH-ST, gonadotropin-releasing hormone stimulation test; CBC, complete blood count; IM, intramuscular(ly); SDS, standard deviation score.

Precocious puberty is defined as the onset of secondary sexual characteristics associated with increased linear growth velocity and accelerated bone maturation occurring before the age of 7 to 8 years in girls and 9 years in boys.[1,2] If untreated, precocious puberty results in early epiphyseal closure and short final height.[3] The most common cause in girls is idiopathic central precocious puberty (CPP) caused by the early onset of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) secretion.[4]

Standard treatment of CPP consists of depot parenteral preparations of gonadotropin-releasing hormone agonists (GnRHa), usually at 4-week intervals.[5] GnRHa are generally effective in retarding progression of secondary sexual characteristics, preventing menses, slowing bone-age advancement, and improving final height. Injections are painful, however, and the need for monthly clinic visits may contribute to poor compliance.

Chertin et al[6] observed that insertion of a subcutaneous hydrogel implant containing the potent GnRHa histrelin suppresses LH and testosterone in metastatic prostate cancer for at least 1 year. The same investigators then proposed to the manufacturer that they assess a revised implant (that releases more drug on a daily basis) for children with CPP. If effective, this implant could be more convenient and less painful than monthly injections. The aims of the present study were to determine if a histrelin im-

From the *Pediatric Day Hospital, ¶Department of Urology, and ‡Institute of Hormone Research, Shaare Zedek Medical Center and the Faculty of Health Sciences, Ben Gurion University of the Negev, Jerusalem, Israel; §Department of Pediatrics and Pediatric Endocrinology Clinic, Hadassah University Hospital, Ein-Kerem, Jerusalem, Israel; and ‖Specialty Pediatric Clinics, Endocrinology and Diabetes, Clalit Health Service, Jerusalem, Israel.

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Conflict of interest: Dr Spitz is a consultant for Valera Pharmaceuticals Inc, manufacturer of the histrelin implant.

Reprint requests to (I.M.S.) Institute of Hormone Research, Shaare Zedek Medical Center, POB 3235, Jerusalem 91031, Israel. E-mail: irving@spitz.com

plant would suppress gonadotropin and E_2 in girls with CPP for 12 months and to compare the suppression to standard treatment.

METHODS

Subjects

Eleven girls with CPP referred to pediatric endocrinologists (H.J.H., D.G., or D.S.) were studied. Inclusion criteria were age of <11 years at initial enrollment, advanced bone age, serum E_2 level of >20 pg/mL (73 pmol/L), and pubertal gonadotropin responses to a standard GnRH stimulation test (GnRH-ST).[7–9] Patients with gonadotropin-independent precocious puberty, children in whom treatment would be needed for <1 year, those with other illnesses that would interfere with follow-up, and those with a history of noncompliance were excluded.

Mean age was 6½ years (range: 2–9 years) at initial diagnosis and 8½ years (range: 3.75–11 years) at implant insertion. BMI exceeded the 50th percentile in 9 girls and exceeded the 95th percentile in 4 girls. Pelvic ultrasound showed no ovarian pathology. Routine laboratory tests (urinalysis, complete blood count [CBC], biochemical screening, thyroid function) were normal.

Prior GnRHa Treatment

Treatment with the GnRHa triptorelin embonate (Decapeptyl; Ferring, Kiel, Germany) 3.75 mg given intramuscularly (IM) at 3- to 4-week intervals was begun in all children before study enrollment. Ten girls were treated from 1 to 26 months and 1 for 39 months.

Histrelin Implant

The subdermal implant (length: 30 mm; diameter: 3.5 mm; wall thickness: 0.5 mm) consists of a microporous hydrogel containing 50 mg of histrelin.[10] Histrelin diffuses through the implant wall at an average rate of 65 μg/day. This version of the implant releases more histrelin than the one used for prostate cancer.[10]

Before insertion of the implant, a topical preparation of lidocaine and prilocaine (EMLA; AstraZeneca, Wilmington, DE) was applied to the medial aspect of the upper arm, after which the skin was infiltrated with ~5 mL of 2% lidocaine. Pediatric surgeons (B.C. and A.F.) performed the implant insertions. In 2 patients, mild sedation was achieved by oral midazolam hydrochloride syrup (Rafa Laboratories, Jerusalem, Israel) at a dose of 0.25 to 0.5 mg/kg. One or 2 implants were inserted through a 1-cm incision that was closed with 2 or 3 sutures. In girls weighing <40 kg, 1 implant was inserted; those weighing >40 kg received 1 or 2 implants. Two of the first patients enrolled developed minor local infections. Subsequently, an oral cephalosporin antibiotic was prescribed for 2 days beginning on the morning of insertion.

Study Design

Six girls were followed for 15 months after insertion (group A). In the remaining 5 girls, the implant was removed after 9 months, and a new implant was inserted using the same incision site (group B). Assignment into groups A or B was random, and there were no differences in chronological age, bone age, or Tanner stage between the groups. Evaluation of the girls in group B enabled us to assess the feasibility of implant removal and replacement. Study participants were seen at 1, 3, 6, 9, 12, and 15 months. At each visit, height and weight were measured, Tanner pubertal stage was assessed, and blood samples for gonadotropin and E_2 levels were drawn. GnRH-STs were performed before depot GnRHa treatment, immediately before implant insertion, at the 6- and 9-month visits for each patient, and the 12- and 15-month visit for those girls followed for 15 months. In this test, gonadorelin (synthetic GnRH; Hoechst AG, Frankfurt, Germany) 100 μg/m^2 (to a maximum of 100 μg) was administered intravenously, and blood samples for gonadotropins were drawn at 0, 20, 40, and 60 minutes.[11]

Urinalysis, CBC, biochemical screening, screening for free thyroxine, thyrotropin, and prolactin levels, radiographs to determine bone age, and transabdominal pelvic ultrasound were performed before insertion and at the 9-month visit. During treatment with triptorelin embonate and at the 9-month follow-up visit, parents answered the following questions (recorded on a scale of 0 to 10): "To what extent is your child's current treatment uncomfortable or painful?"; and "To what extent is your child's current treatment regimen inconvenient or disruptive to school, work, or other activities?"

This investigator-initiated study was approved by the human investigation committee of each participating institution. Written informed consent was obtained from the parents before enrollment. The study was designed and the data were analyzed by the academic investigators.

Auxological Data

Height was measured with a wall-mounted stadiometer. Growth velocity, calculated by comparing height measurements at 6-month intervals, was converted to a standard deviation score (GV − SDS) by using Tanner's reference data.[12] Bone age was determined from radiographs of the left hand and wrist by using the method of Greulich and Pyle.[13] BMI (weight [kg]/height [meters^2]) percentiles were determined by using the Centers for Disease Control and Prevention 2000 growth charts.[14]

Hormonal Assays

LH and FSH were measured by a chemiluminescent microparticle 2-step immunoassay (Abbott Laboratories, Abbott Park, IL). The lower limits of sensitivity of the LH and FSH assays were 0.07 and 0.05 mIU/mL, respectively. In the low range of gonadotropin levels, intraassay and interassay variations were 2.1% and 3.4% for LH and 2.8% and 3.6% for FSH. E_2 was measured by using a radioimmunoassay-coated kit (CIS Bio International-Schering, Gif sur Yvette, France). The reported lower limit of sensitivity was 1.4 pg/mL. Serum E_2 levels in prepubertal girls are typically <20 pg/mL (73 pmol/L).[11,15] At this range of E_2 levels, the intraassay and interassay variations were 13.3% and 17.6%, respectively.

Statistics

The statistical analysis was performed by using the nonparametric Wilcoxon paired sign-rank test.

RESULTS

No menstrual bleeding occurred during the implant treatment. Mean breast development was Tanner stage 3.3 (range: 2–4) at implant insertion and 2.7 (range: 1–3) at 9 months. Bone age was 1.7 ± 0.5 years greater than the chronological age at insertion ($P < .003$). Bone-age advancement decreased to 0.6 ± 0.4 years at 9 months ($P < .003$). Growth velocity (GV − SDS ± SD) was increased before initial treatment (2.5 ± 1.7) and decreased significantly to −3.1 ± 2.2 by 9 months ($P < .005$).

Basal LH and FSH levels decreased significantly ($P < .01$ and $P < .005$, respectively) on depot triptorelin embonate treatment (Table 1 and Figs 1 and 2). Gonadotropin suppression was maintained after implant insertion. When compared with preinsertion, basal LH levels were significantly lower at 6 and 9 months after implant insertion (Table 1).

GnRHa resulted in blunted gonadotropin responses to GnRH stimulation. The duration of standard GnRHa treatment did not seem to affect the degree of gonadotropin suppression (data not shown). Suppression of peak LH and FSH levels to GnRH testing was maintained for 9 months after implant insertion in all 11 girls and in the 6 girls followed for 15 months (Table 1 and Figs 1 and 2). Peak LH responses to GnRH were significantly lower at each follow-up visit compared with GnRHa. Peak FSH responses remained suppressed at each visit and were significantly lower at 6 and 9 months.

Serum E_2 levels decreased significantly on GnRHa and remained in the prepubertal range after implant insertion. At 12 months, E_2 levels in the patients who

TABLE 1. Basal Gonadotropin and E_2 and Peak Gonadotropin Reponses Pretreatment, Preinsertion and at Successive Intervals After Implant Insertion

	No. of Subjects	Basal LH, mIU/mL	Peak LH, mIU/mL	Basal FSH, mIU/mL	Peak FSH, mIU/mL	E_2, pg/mL
All subjects						
Preinsertion	11	0.47 ± 0.36	1.3 ± 1.34	1.22 ± 0.42	1.68 ± 1.08	9.83 ± 6.39
1 mo	11	0.26 ± 0.16		1.07 ± 0.53		9.73 ± 5.27
3 mo	11	0.25 ± 0.2		1.11 ± 0.6		10.26 ± 5.02
6 mo	11	0.2 ± 0.14*	0.2 ± 0.06†	1.08 ± 0.52	1.13 ± 0.53*	8.86 ± 6.03
9 mo	11	0.2 ± 0.12†	0.25 ± 0.08‡	1.07 ± 0.53	1.13 ± 0.55*	7.19 ± 5.36
Group A (continuing with original implant)						
12 mo	6	0.2 ± 0.06	0.28 ± 0.08*	0.93 ± 0.5	0.97 ± 0.54	6.52 ± 4.02*
15 mo	6	0.22 ± 0.08	0.25 ± 0.08*	0.88 ± 0.33	0.93 ± 0.38	8.34 ± 4.51

Significant differences between pretreatment and preinsertion values and between preinsertion and values at 1, 6, 9, 12, and 15 months: * $P < .05$; † $P < .01$; and ‡ $P < .005$.

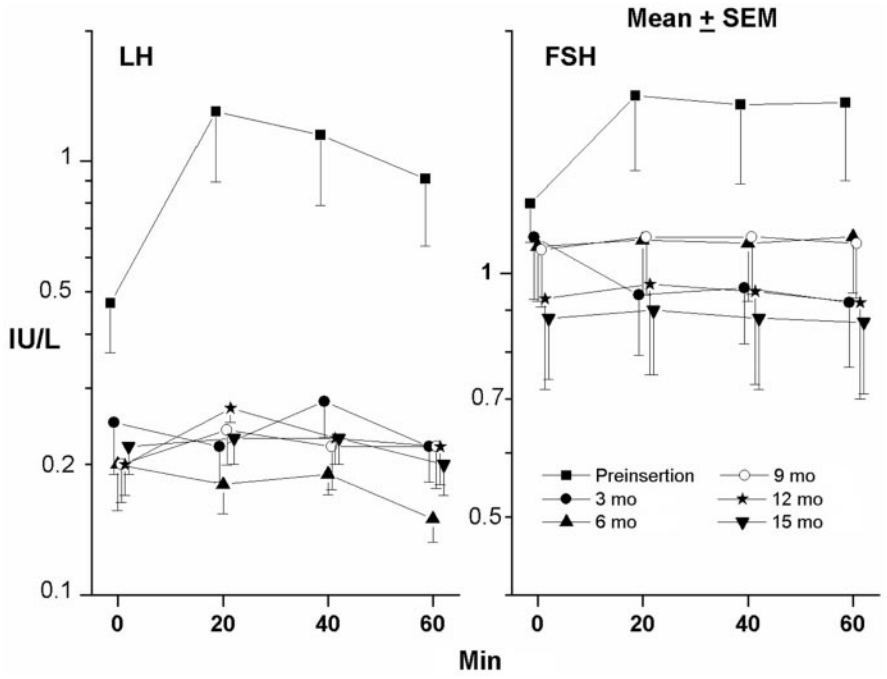

Fig 1. Mean ± SEM levels of LH and FSH (shown on a logarithmic scale) 0, 20, 40, and 60 minutes after a bolus intravenous injection of GnRH (indicated by arrows). The GnRH-ST was performed before initiating depot GnRHa treatment in 10 girls and immediately before implant insertion during standard depot GnRHa treatment in 11 girls. After implant insertion, GnRH tests were repeated in all 11 girls at 6 and 9 months and in 6 girls at 12 and 15 months.

received the implant were significantly lower than on GnRHa (Table 1). One implant was as effective as 2 (data not shown). No abnormalities in routine urinalysis, CBC, renal and liver-function tests, or free thyroxine, thyrotropin, and prolactin levels were noted during the study.

A total of 16 implant insertions were performed: 11 at the time of initial enrollment and 5 after the implant removal. Twelve insertions were completely uneventful. Six months after the insertion, the incision site was barely noticeable, as shown in Fig 3. A minor local infection developed in 1 patient at the beginning of the study. Subsequently, a short course of antibiotics was prescribed, and no additional infections occurred. A suture was inadvertently inserted into the implant in 1 patient. Spontaneous extrusion of the implant occurred in another patient 6 weeks after insertion. No major or serious adverse events have occurred. In 5 patients scheduled for implant removal, this was successful in all, and a new implant was inserted through the same incision.

At 9 months, all patients reported less pain and discomfort ($P < .005$) and less interference with school activity and work ($P < .05$) with the implant compared with standard monthly injections (Fig 4).

DISCUSSION

Our observations show that the histrelin implant maintains suppression of gonadotropins and E_2 in girls with CPP for 15 months. GnRH-STs at 3, 6, 9, 12, and 15 months demonstrated that the degree of LH suppression (both basal and after GnRH stimulation) achieved by the implant was more complete than that achieved by the IM agonist.

GnRHa initially stimulate pituitary gonadotropins, leading to a transient rise and subsequent fall in gonadotropins and E_2.[16] Transient withdrawal bleeding, occurring early after implant insertion, might have discouraged continued participation. To avoid this complication, all girls were treated initially with an IM depot GnRHa, which also enabled comparison of the implant with standard treatment.

No clinical progression of puberty was observed throughout the study and, in some, breast development regressed. Growth velocity, initially increased for chronological age, decreased during treatment.

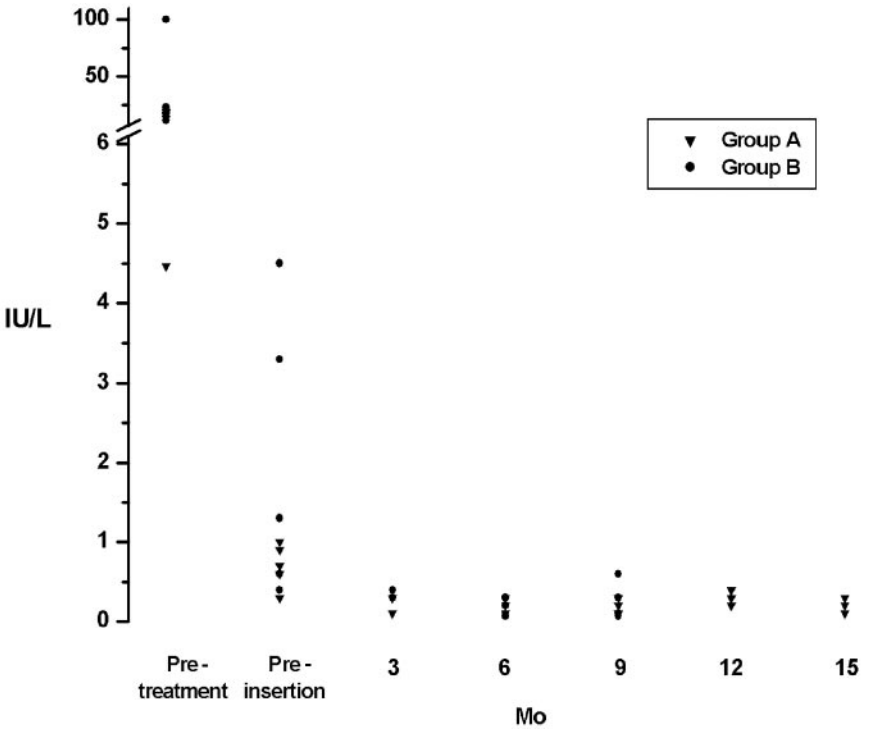

Fig 2. Peak LH levels (in response to GnRH-STs) in the individual patients immediately before initiating depot GnRHa (pretreatment), immediately before implant insertion while patients were on depot GnRHa treatment (preinsertion), and 6, 9, 12, and 15 months after histrelin implant insertion. See the Fig 1 legend for the numbers of girls studied at each time interval.

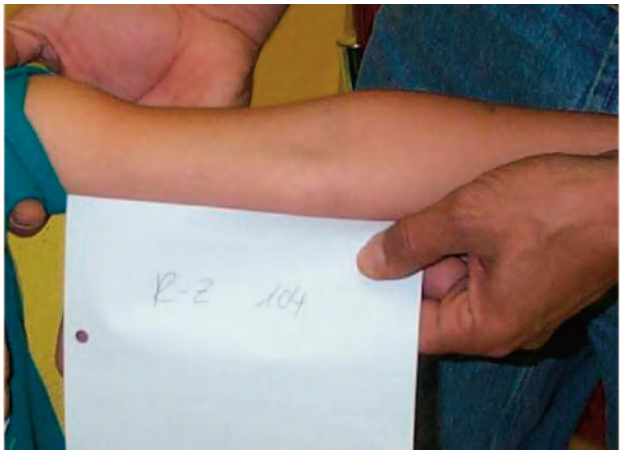

Fig 3. Implant site in 1 patient 6 months after implant insertion.

Skeletal maturation, advanced at the time of implant insertion, progressed more slowly during treatment.

Because most clinical E_2 assays cannot measure levels below the pubertal threshold (<20 pg/mL)[15,17] serum E_2 is not an ideal measure of pubertal suppression.[3,18] Also, serum E_2 levels fluctuate, and a single blood sample may not be representative.[19] Furthermore, most girls in our study were overweight. Aromatization of androgen precursors by adipocytes contributes to serum E_2 even in the presence of ovarian suppression.[20] Despite these limitations, E_2 levels after implant insertion were suppressed to the prepubertal range observed during standard GnRHa treatment.[21,22]

Patients and their families expressed a strong preference for the implant over standard monthly injections. Patients reported no pain or discomfort after the insertion procedure performed under local anesthesia and lasting ~5 minutes. Compared with painful parenteral injections, requiring visits to a clinic nurse every 3 to 4 weeks, the implant allows a full 12-month course of treatment with total compliance assured. In addition to being more comfortable for the children, the economic benefits in terms of time lost from work for the parents may be considerable.

Although based on a small number of participants, we observed consistent and complete suppression of E_2 and basal and peak gonadotropin responses to GnRH, without exception, in >40 GnRH-STs performed over 15 months along with arrest of clinical progression of puberty in each patient. Therefore, instead of 12 or more painful monthly injections, CPP can be treated safely, effectively, and conveniently with a single, simple implant insertion and removal procedure. Because of the importance of ensuring that suppression is maintained for a full year, we extended the study to 15 months. Thus, in the event that there is a delay in returning to the clinic for implant reinsertion, the physician and parents can rest assured that suppression will be maintained over this time frame.

The histrelin implant consistently suppresses clinical and laboratory parameters of puberty for 1 year and is a promising new technique for treating CPP without the pain and inconvenience of monthly injections.

EDITOR'S NOTE

During revision of this manuscript, data collected at 18 months were deleted from the article by the authors at the request of the manufacturer of the histrelin implant, Valera Pharmaceuticals Inc. At the request of *Pediatrics*, David Tierney, MD, president and CEO of Valera Pharmaceuticals Inc, provided this explanation:

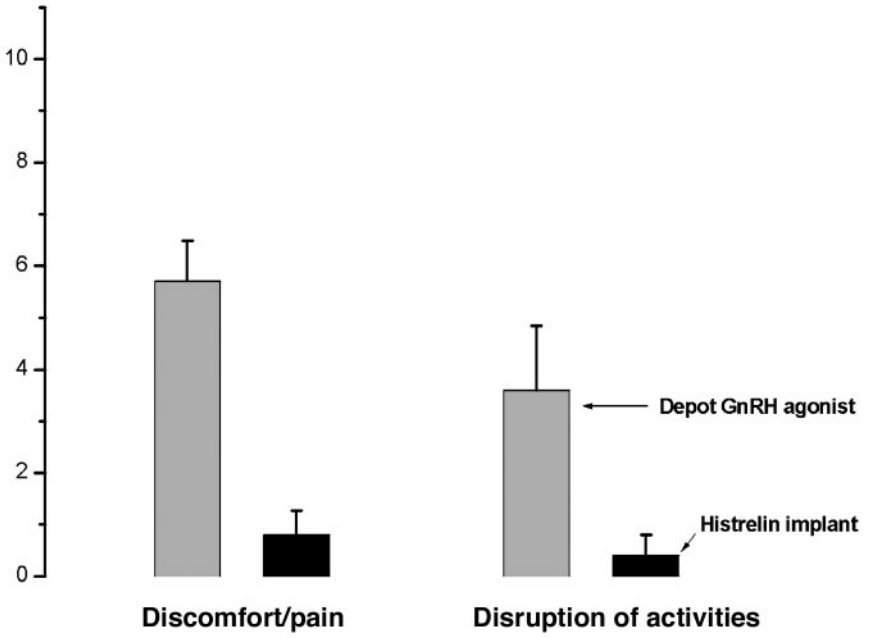

Fig 4. Quality-of-life questionnaire. The bar graphs indicate the patients' replies to a questionnaire that assessed satisfaction with and preferences for the histrelin implant compared with IM depot GnRHa treatment for CPP. Patients reported less pain and/or discomfort associated with the implant compared with depot GnRHa treatment ($P < .005$). Patients reported less disruption of school, work, and other activities during implant treatment as compared with standard therapy ($P < .05$).

"The histrelin implant designed for this study contains 50 mg of histrelin. The packing height of the histrelin in the implant, the ratio of water/histrelin, as well as the thickness of the implant have been formulated specifically to release histrelin for only 1 year. The implant will be marketed as a 1-year device. Valera Pharmaceuticals Inc can only guarantee that histrelin will be released for 1 year. We did prolong the study to 15 months. The reason is that if patients are delayed in returning to the clinic, there will still be adequate release to cover them for an additional 3 months but not beyond that. Furthermore, because only 6 patients were studied beyond 12 months, this number is too small of a sample to claim a reliable suppression for >1 year. We will be sending the wrong message to potential users by publishing data for 18 months, because the implant is not designed to last that long and there could be hormonal escape. At a later stage, we may well formulate a new implant with different characteristics that could last for > 1 year."

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