Prolactin secretion before, during, and after chronic gonadotropin-releasing hormone agonist treatments in children

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Objective: To examine the effect of long-term administration of GnRH agonists (GnRHa) on PRL secretion in children affected by central precocious puberty (CPP) and growth hormone deficiency (GHD).
Design: Prospective analysis of blood sampling before, during, and after GnRHa treatments.
Setting: Pediatric endocrine center.
Patient(s): One hundred nineteen and 93 children with a diagnosis of CPP and GHD, respectively.
Intervention(s): Monthly depot injections of GnRHa drugs (leuprorelin acetate 3.75 mg [LA] and triptorelin 3.75 mg [TR]) administered to CPP and GHD patients for 40 and 24 months, respectively.
Main Outcome Measure(s): Serum PRL levels at baseline and after 6, 12, 18, 24, 30, 36, and 40 months of treatment with GnRHa were compared between CPP and GHD groups. PRL levels at 6 and 12 months after GnRHa withdrawal were also examined.
Result(s): Although serum PRL levels tended to be higher in TR- than in LA-treated patients, no significant difference in circulating PRL in basal condition and during GnRHa treatment was detected between the CPP and GHD groups. However, five children (3.8%) developed hyperprolactinemia during TR treatment.
Conclusion(s): Although there are no general concerns about GnRHa treatment safety, careful PRL monitoring is required in GnRHa-treated children. (Fertil Steril® 2005;84:719–24. ©2005 by American Society for Reproductive Medicine.)

Key Words: Gonadotropin-releasing hormone agonist, growth hormone deficiency, leuprorelin acetate, precocious puberty, prolactin, triptorelin

Gonadotropin-releasing hormone agonists (GnRHa), such as leuprorelin acetate (LA) and triptorelin (TR), have been extensively used to treat a variety of endocrine-related disorders because of their suppressive effects on serum FSH, LH, and, subsequently, gonadal sex steroids, that is, androgens and estrogens. The use of these agents to treat uterine leiomyomata, endometriosis, breast cancer, and prostate disorders in adults is well documented (1–3). GnRHa are also used to delay the effects of premature awakening of the hypothalamic-pituitary-gonadal axis in children with precocious puberty (4–6). On the other hand, there is evidence that slowing pubertal development by administering long-acting GnRHa for a limited time may improve final height in children with growth hormone deficiency (GHD) who do not properly respond to exogenous growth hormone (GH) treatment (7, 8).

Although there are no general concerns about GnRHa treatment safety, reports on the relationship between GnRHa and serum prolactin (PRL) are rather controversial. Some investigators claim that GnRHa inhibits PRL secretion both in vitro and in vivo (9, 10); some report similar plasma PRL levels before and after gonadal suppression by GnRHa (11); and others observe a transient increase in serum PRL levels after GnRHa treatment (12–14). In this regard, Golan et al. (10) suggested that GnRHa may reduce serum PRL in women with hyperprolactinemia, although GnRHa treatment did not lower PRL levels in subjects who were euprolactinemic. Sklar et al. (11) found no difference in unstimulated PRL secretion before and after leuprolide acetate treatment of 11 children with central precocious puberty (CPP). On the other hand, Kauschansky et al. (12) reported a significant increase in PRL levels in all 13 females who underwent TR treatment for CPP and who had normal circulating PRL before the treatment. In addition, these investigators found an overt hyperprolactinemia in some of the treated patients (12).

In this study, we measured circulating levels of PRL before, during, and after monthly LA and TR administration to detect the potential adverse effects of prolonged GnRHa stimulation on the pituitary PRL function in children with CPP and GHD.

MATERIALS AND METHODS

To further assess the behavior of circulating PRL in GnRHa-treated patients, we assayed serum PRL in 119 (105 females and 14 males) and 93 (83 females and 10 males) children affected by CPP and GHD, respectively. All subjects were

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attended as outpatients at the Pediatric Endocrine Center of the Department of Pediatrics, University Hospital of Pisa, Italy, between 1999 and 2003. After receiving local Institutional Review Board approval, informed consent was obtained from all parents of patients before the beginning of the study.

At the time of GnRHa treatment, patients with CPP ranged in age from 5.5 to 9.0 years and had pubertal development in the second to third Tanner's stage for breast, pubic hair, and genital development. Patients with CPP underwent GnRHa treatment by monthly IM injection of a depot preparation of the drug. They were randomly divided into two groups according to the different GnRHa administered; group 1 included 74 of 119 patients who took TR at a dosage of 3.75 mg (Ipsen Pharma Biotech, Toulon Cedex, France), while the remaining 45 of 119, group 2, were treated with LA at a dosage of 3.75 mg (Takeda Chemical Industries, Osaka, Japan). The treatment period lasted 40 months on average. Clinical CPP diagnosis was confirmed by the following laboratory criteria for females and males aged ≤8 years and ≤9 years, respectively: E_2 = 25.0 pg/mL for females, T = 3.0 ng/dL for males, and GnRH-induced rise in LH and FSH blood levels >6.9 IU/L and >5.0 IU/L, respectively. All of these patients had idiopathic CPP.

The 93 patients included in the present study fulfilled diagnostic criteria for GHD (15): they had GH peaks less than 5 μg/L after two provocative pharmacological stimuli (levodopa and insulin tolerance test) and had reduced spontaneous 24-hour GH secretion (mean GH concentration <3 μg/L). They did not show any associated deficiency of other pituitary hormones at diagnosis or during treatment. They received recombinant human GH (rhGH) treatment at a dosage of 30 μg/kg/day, which was given SC at bedtime six times weekly. GnRHa was added to GH treatment in those patients who did not make sufficient improvements in their predicted adult height during GH administration. As mentioned above for CPP subjects, 56 of 93 underwent TR therapy in 3.75 mg doses (Ipsen Pharma Biotech) in addition to rhGH (group 3), while the remaining 37 of 93 patients with GHD were given LA 3.75 mg (Takeda Chemical Industries) (group 4). The GnRHa treatment of GHD lasted 24 months on average. All the GHD patients were in early puberty (second Tanner's stage for breast and pubic hair) when GnRHa treatment was started. Furthermore, GnRH-induced gonadotropin circulating levels were >6.9 IU/L for LH and >5.0 IU/L for FSH.

GnRHa suppression of gonadotropin secretion was checked every 6 months by RIA for blood levels of LH, FSH, E_2, and T in both CPP and GHD children.

Serum circulating levels of PRL were assayed before and during GnRHa treatment at 6-month intervals (i.e., at baseline and at 6, 12, 18, 24, 30, 36, and 40 months for the CPP group and at baseline and at 6, 12, 18, and 24 months for the GHD group). In addition, in all subjects' blood PRL was checked at 6 and 12 months after GnRHa therapy withdrawal.

TABLE 1

Clinical data of central precocious puberty (CPP) and growth hormone deficiency (GHD) patients at the start of GnRHa administration.

At start of GnRHa therapy	CPP (n = 119)	GHD (n = 93)
Sex (F/M)	105/14	83/10
Chronological age (years)	7.8 ± 1.4	8.6 ± 2.1
Pubertal stage, median (range)		
Breasts	2 (2–3)	2 (2–3)
Pubic hair	2 (2–3)	2 (2–3)
LH (IU/L)	1.8 ± 1.6	1.3 ± 0.9
FSH (IU/L)	2.7 ± 0.9	2.0 ± 1.2
E_2 (pg/mL) (females)	27.8 ± 2.1	21.4 ± 3.5
T (ng/dL) (males)	2.7 ± 1.3	1.4 ± 0.4
Leuprorelin acetate-treated subjects	74	56
Triptorelin-treated subjects	45	37
Therapy months	40	24

Note: $P<.05$.

Massart. Child PRL secretion during GnRHa treatments. Fertil Steril 2005.

Circulating PRL values were assayed by an RIA kit (Schering S.p.A., Milan, Italy). The detection limit of the method was 0.1 ng/mL; the intra-assay and interassay coefficients of variation were 5.5% and 7.5%, respectively. All blood samples from each subject were analyzed in a single assay.

Data are expressed as mean ± standard deviation unless otherwise stated. Statistical analysis was performed using Student's *t*-test, analysis of variance (ANOVA), and Fisher's exact test. $P<.05$ was considered statistically significant. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS, Chicago, IL) for Windows version 9.0.

RESULTS

At the start of the GnRHa therapy the auxological characteristics of CPP and GHD subjects treated with TR or LA were similar (Table 1). During GnRHa treatment, down-regulation of the pituitary gland was confirmed by suppressed levels of LH, FSH, E_2, and T. Before GnRHa administration, levels of LH, FSH, E_2 (for females), and T (for males) were 1.6 ± 0.5 IU/L, 2.4 ± 0.7 IU/L, 25.0 ± 3.4 pg/mL, and 2.2 ± 0.8 ng/dL in both the CPP and GHD groups. They fell significantly during GnRHa treatment, with serum values of 0.75 ± 0.4 IU/L, 1.24 ± 0.5 IU/L, 14.5 ± 1.3 pg/mL, and 0.8 ± 0.5 ng/dL, respectively ($P<.001$ for all four hormones as compared with their levels before treatment). No significant difference was found between the