

Serum levels of antimüllerian hormone and inhibin B in central precocious puberty before and during treatment with GnRH agonist.

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Abstract

Background/Aim: Anti - Müllerian hormone (AMH) and inhibin B are considered as possible biomarker of central precocious puberty (CPP). The aim of this study was to evaluate baseline serum levels of AMH and inhibin B and the regulation of these hormones during one year of GnRH agonist treatment in CPP girls.

Methods: In total, 48 girls with CPP and 35 age – matched prepubertal girls were enrolled in the study. The subjects were divided into two groups as CPP patient and control. AMH and inhibin B levels were determined in the two groups. Furthermore AMH and inhibin B level were evaluated at pretreatment, six - months and twelve – months after GnRH agonist (GnRHa) treatment in patient group.

Results: The mean inhibin B levels of the CPP group were significantly higher than control (54.82 ± 48.65 and 16.17 ± 7.01 pg/L, respectively, $p < 0.001$). AMH levels were not different between two groups. Inhibin B was positively correlated with AMH and height SD in control ($r = 0.582$, $p < 0.001$ and $r=0.369$, $p < 0.05$, respectively). Inhibin B was positively correlated with bone age in patient group ($r = 0.337$, $p < 0.05$), but not correlated with AMH. Baseline AMH and inhibin B levels were the highest. After GnRHa treatment, AMH and inhibin B levels were decreased significantly.

Conclusions: Baseline serum AMH were not significantly different between prepubertal girls and CPP girls, but serum inhibin B is much higher in CPP girls. GnRH agonist reduced both ovarian hormone secretion and serum inhibin B value can be helpful to identify CPP and monitor the adequacy of GnRH agonist treatment.

Introduction

Central precocious puberty is defines as appearance of secondary sexual characteristics before age 8 years in girls and 9 in boys, result from early activation of the hypothalamic pituitary gonadal (HPG) axis. Increased secretions of gonadotropin and sex steroid are downregulated by GnRH agonist, return to prepubertal levels and secondary sexual characteristics regress or slow down. The GnRH agonist is safe and effective remedy, but the debate over the safety of reproductive function has not yet completely disappeared. Several studies reported normal reproductive function in young women after depot GnRHa treatment of CPP. Recently, many studies have been conducted to guess ovarian reserve or ovarian function in CPP girls by analyzing AMH levels and inhibin B, but its usefulness is still controversial.

The aim of this study was to evaluate baseline serum levels of AMH and inhibin B and the regulation of these hormones during one year of GnRH agonist treatment in CPP girls.

Subjects and Methods

Subjects

Clinical data were collected retrospectively via chart review of patients treated in the Pediatric endocrine unit at Hallym Unniversity Kangdong Sacred heart hospital from March 1, 2013 and August 31, 2015. A total of 48 girls with idiopathic CPP were included in this study. CPP was diagnosed according to the following criteria; (1) objective breast enlargement appearing before the age of 8 years, (2) bone ages that exceeds chronological age by at least 1 year, and (3) increased pubertal luteinizing hormone (LH) response(cutoff value ≥ 5.0 IU/L) on a chemiluminescent microparticle immunoassay (CLIA) during GnRH stimulation test.

To evaluate whether baseline levels of AMH and inhibin B were affected in CPP girls, we included 35 age – matched healthy girls referred with health screening. Inclusion criteria for the normal control group were follows: no evidence of breast budding and $BA - CA < 1$ year. No prior medical history of conditions associated with altered pubertal timing, gonadal diseases, or intake of medications was reported.

Methods

The GnRH stimulation test was performed to assess pubertal status in all patients. Blood samples were centrifuged, and plasma immediately stored at -80°C until analyses.

Data on height, weight, BMI, pubertal status, and bone age were collected every 6months from clinical charts and electronic medical records. This study protocol was approved by the Institutional Review Board of the Hallym Medical Center (KANGDONG 2013-01-022).

Serum LH, FSH, and estradiol (E_2) were measured only in the patient group. Serum AMH was assayed using an Gen II ELISA (Immunotech, Beckman Coulter Inc, Brea, CA), with a detection limit of 0.08 ng/mL. The intra- and interassay coefficients of variation were 5.4% and 8.5%, respectively. Serum INHB was measured using a Gen II ELISA (Immunotech, Beckman Coulter Inc), with an assay sensitivity of 2.6 pg/mL. Intra- and inter-assay coefficients of variation were 5.4% and 6.7%, respectively.

Results

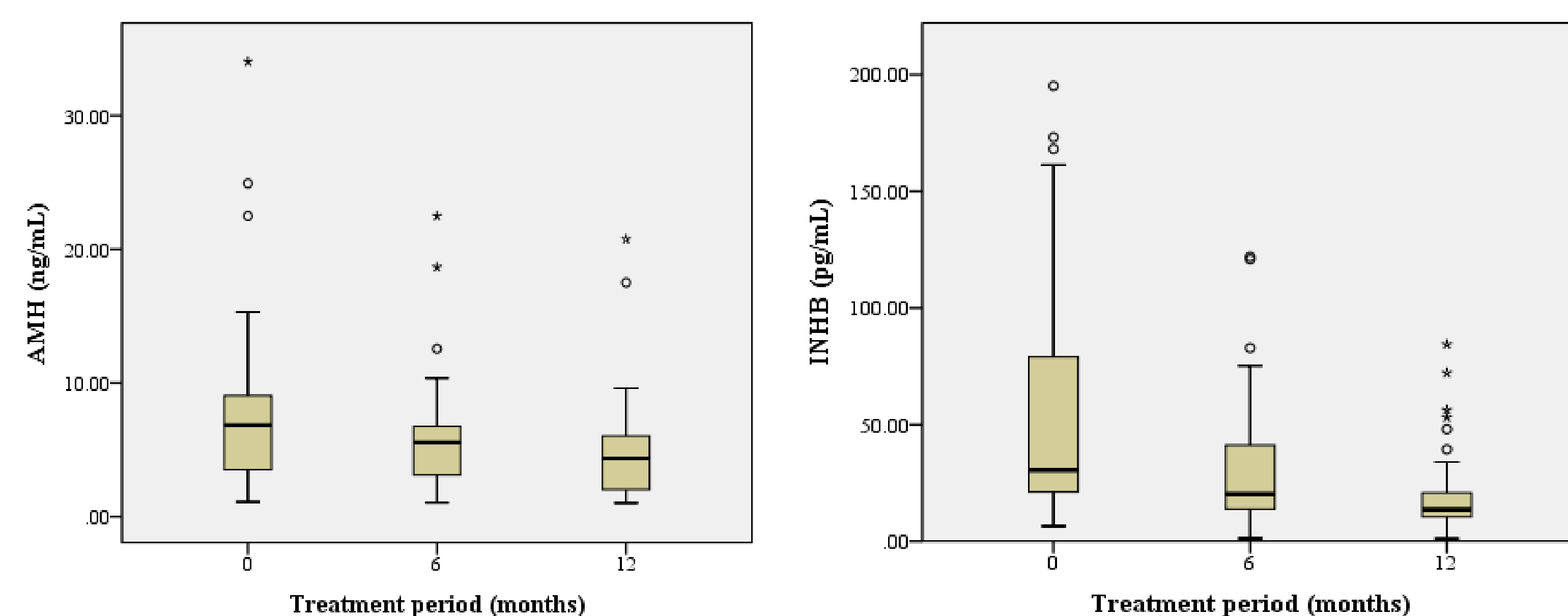
Table 1. Pretreatment clinical characteristics of 48 girls with CPP and 35 normal control girls

	Patient (n=48)	Control (n=35)	p
Age at diagnosis (years)	8.40 ± 0.46	8.20 ± 0.54	0.08
BA – CA (years)	2.05 ± 0.74	-0.22 ± 0.76	<0.001
Height SDS	1.25 ± 0.91	-0.24 ± 0.71	<0.001
Weight SDS	1.16 ± 0.82	-0.23 ± 0.76	<0.001
BMI SDS	0.86 ± 0.85	-0.15 ± 0.86	<0.001
Tanner stage	Stage II 31 (64.6%) Stage III 17 (35.4%)	Stage I 35(100%)	<0.001
Basal LH (IU/L)	1.32 ± 0.96	ns	ns
Peak LH (IU/L)	12.69 ± 8.94	ns	ns
Basal FSH (IU/L)	3.25 ± 1.75	ns	ns
Peak FSH (IU/L)	17.37 ± 6.68	ns	ns
E_2 (pg/mL)	6.52 ± 5.43	ns	ns
AMH (ng/mL)	7.73 ± 6.34	6.90 ± 2.62	0.469
Inhibin B (pg/mL)	54.82 ± 48.65	16.17 ± 7.01	<0.001

Table 2. Pearson's correlation coefficients between baseline serum levels of AMH and inhibin B.

	Patients (n=48)		Control (n=35)	
	AMH	BA	AMH	Ht SDS
Inhibin B	0.166	0.337	0.582	0.369
	$p = 0.258$	$p = 0.019^*$	$p < 0.001^*$	$p = 0.029^*$

Figure 1. The change of the mean serum AMH and inhibin B level at pretreatment, after 6 months and after 12 months of GnRHa.



The mean serum AMH level was the highest at the pretreatment (7.73 ± 6.34 ng/mL) and decreased significantly, after 6month (5.75 ± 4.12 ng/mL) and after 12months (4.89 ± 3.75 ng/mL) of GnRHa treatment. Likewise, the mean serum inhibin B was the highest at the pretreatment (54.82 ± 48.65 pg/mL) and decreased significantly, after 6month (31.59 ± 27.08 pg/mL) and after 12months (19.73 ± 17.17 pg/mL) of GnRHa treatment. After 12months of GnRHa treatment, serum AMH and inhibin B level were the lowest during this study.

Conclusions

Baseline serum AMH were not significantly different between prepubertal girls and CPP girls, but serum inhibin B is much higher in CPP girls. GnRH agonist reduced both ovarian hormone secretion and serum inhibin B value can be helpful to identify CPP and monitor the adequacy of GnRH agonist treatment.