A Cost-Benefit of GnRH Stimulation Test in Diagnosis of Central Precocious Puberty (CPP)

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Abstract

The GnRH stimulation test is the gold standard to diagnose central precocious puberty (CPP). Conventionally, we need at least 2 hours to finish the test which seems to be costly and time consuming. In this study, we described the pattern of LH and FSH levels during the GnRH test in 27 girls who presented with various degrees of precocious puberty. We found that the blood samples at 90 and 120 min after GnRH were not necessary. To save the cost of diagnosis, the basal LH/FSH ratio > 0.2, the 30 min LH/FSH ratio after GnRH > 0.9 and the peak LH/FSH ratio > 1.0 can be used to diagnose CPP with positive predictive values (PPV) of 87.3, 89.4 and 93.8 per cent respectively.

Key word : Precocious Puberty

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BACKGROUND

Normal pubertal development in humans requires the activation of the luteinizing hormone releasing hormone (LHRH) pulse generator at the appropriate time, 9-13 years in girls and 10-14 years in boys. During the prepubertal period, the LHRH pulse generator is in the juvenile pause secreting very low levels of gonadotropin. Any conditions affecting the early activation of LHRH pulse generator may cause central or true precocious puberty. However, not all girls presenting with early breast development may have precocious puberty. They may have the benign condition which is called premature thelarche and treatment is not required. A previous study hypothesized that premature thelarche and central precocious puberty may represent different positions along a continuum of hypothalamic LHRH neuron activation[1]. The diagnosis of central precocious puberty (CPP) requires many factors including age of onset, degree of advancement in sexual and skeletal maturation, tempo of

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progression and the standard laboratory confirmation of central precocious puberty which is the maximal serum luteinizing hormone (LH) concentration after gonadotropin-releasing hormone (GnRH) stimulation(2). Because bone age advancement is usually found in CPP, eventually, resulting in short adult height if treatment does not intervene(3). The conventional test requires 5 blood samples including the basal sample for LH, FSH and estradiol and subsequently every 30 minutes after 100 microgram of GnRH (Relisorm-L) for LH, FSH at 30, 60, 90 minutes and for LH, FSH and estradiol at 120 minutes. The test seems to be costly and time-consuming.

In this study, we describe the pattern of LHRH pulse generator during GnRH stimulation test in girls presenting with breast development and in those with early breast development and other signs of puberty such as increased height velocity, pubic hair and menstruation. Regarding the cost-benefit of conventional GnRH test, we evaluated the basal LH, FSH levels and LH/FSH ratio to determine whether they could be used instead of the conventional test to confirm CPP.

MATERIAL AND METHOD

All girls who presented with early breast development before 8 years of age were included in this study and divided into 3 groups depending on the severity of precocious puberty. (Table 1)

Group I : Nine girls presented with early breast enlargement and no other signs of puberty. No advancement of bone age and no history of increased height velocity.

Group II : Ten girls presented with early breast enlargement and no other signs of puberty. Bone age advancement at least one year over the chronological age was demonstrated. Some of them also had history of increased height velocity.

Group III : Eight girls presented with early breast development and other signs of puberty such as pubic hair development or menstruation.

GnRH stimulation tests were performed in all girls and FSH, LH were measured at 0, 30, 60, 90, 120 min and estradiol at 0 and 120 min after giving synthetic GnRH (Relisorm 100 ug) intravenously. The bone age was estimated by the Greulich & Pyle method. Pelvic ultrasonography was performed to exclude ovarian tumor or functional ovarian cysts. Tumor markers including hCG and alpha-fetoprotein were also measured.

Serum FSH, LH and estradiol levels were measured by fluoroimmunoassay.

The mean FSH, LH and estradiol levels were compared between the groups and within the group but at different times.

The statistics used in this study were *t* test and ANOVA and $p < 0.5$ was considered significant.

RESULTS

From all 27 GnRH tests, 20/27 (74.1%) had the peak serum LH at 30 min after GnRH, 6/27 (22.2%) at 60 min and 1/27 (3.7%) at 90 min. No one had peak LH at 120 min.

The peak FSH occurred at 30 min in 7 out of 27 (26%), 10/27 (37%) at 60 min, 5/27 (18.5%) at 90 min and 5/27 (18.5%) at 120 min.

In group I, the mean peak LH was 7.1±4.1 IU/L and FSH 13.46 ± 2.7 IU/L. (Table 2)

The basal LH/FSH ratio was 0.07±0.05 and the peak LH/FSH was 0.53 ± 0.34 (Fig. 1, 2).

Table 1. The clinical data of patients in 3 groups.

Group	N	CA (yr)	Breast stage	Pubic hair	Menstruation
I	9	7.4±1.2	2.1±0.3	I	no
II	10	7.8±0.8	2.7±0.5	I	no
III	8	8.8±4.0	3.5±0.8	1.8±0.5	all
Group	**BA (yr)**	**HtSDS**	**HtSDS for BA**	**Wt SDS**	
I	7.4±1.1	0.5±0.9	0.3±0.5	0.5±1.0	
II	10.5±0.7	1.6±0.7	-0.3±0.7	1.5±0.8	
III	11.7±1.5	2.9±1.4	-0.1±1.2	3.7±1.9	

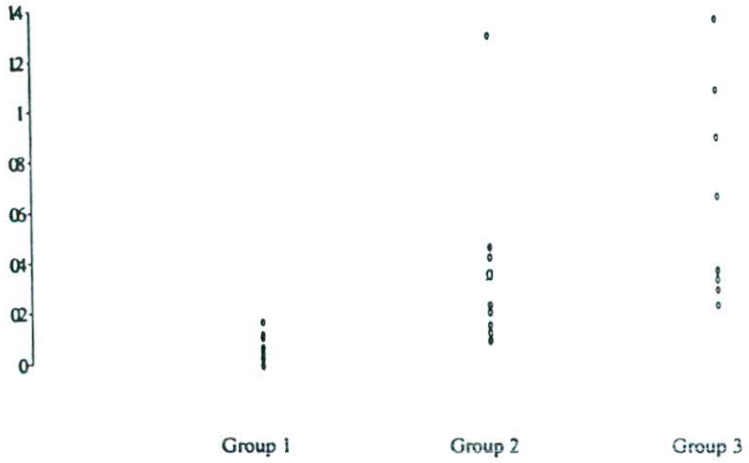

Fig. 1. The basal LH/FSH ratio in 3 groups.

Fig. 2. The peak LH/FSH ratio in 3 groups.

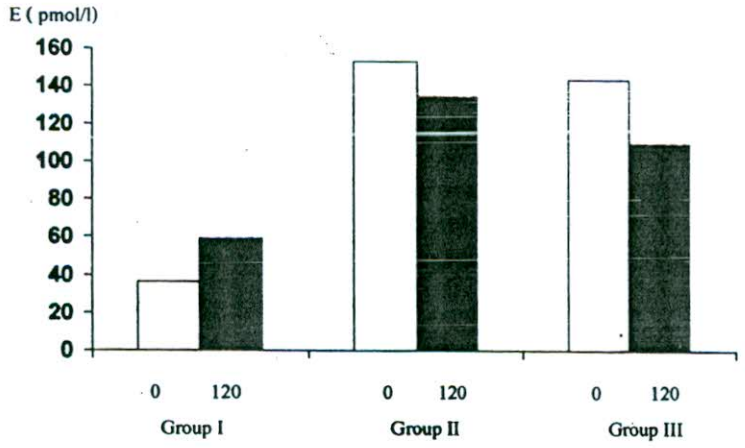

Fig. 3. Estradiol (E) at 0 and 120 min in 3 groups.

Table 2. Serum LH, FSH, LH/FSH, estradiol in 3 groups.

Group	Basal LH (IU/L)	Basal FSH (IU/L)	Peak LH (IU/L)	Peak FSH (IU/L)
I	0.2±0.17	3.98±3.91	7.1±4.1	13.46±2.7
II	1.86±1.45	5.06±1.38	18.75±11.5	12.44±4.76
III	3.65±2.52	5.21±1.85	24.08±13.15	9.31±2.37
Group	Basal LH/FSH	Peak LH/FSH	Basal E2 (pmol/l)	120 min E2 (pmol/l)
I	0.07±0.05	0.53±0.34	36.19±22.05	59.21±73.96
II	0.38±0.35	1.57±0.77	153.5±148.5	134.8±113.6
III	0.66±0.41	2.96±1.92	144.2±116.8	110.0±54.1

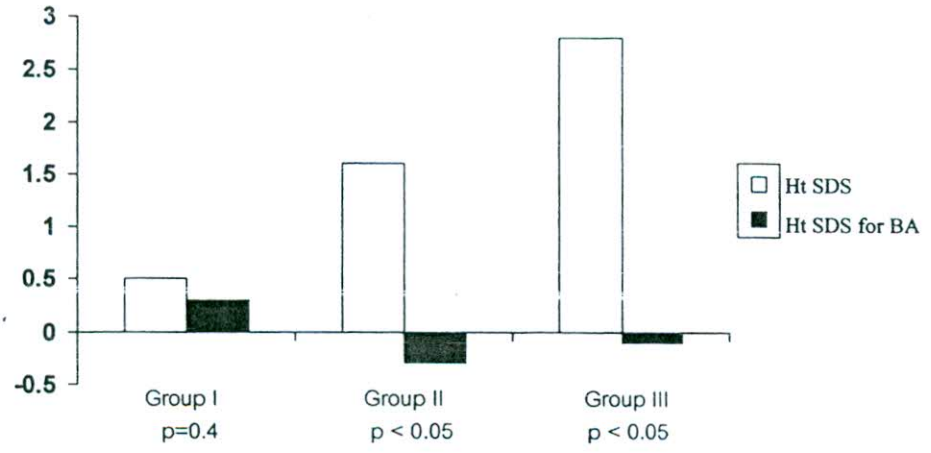

Fig. 4. Ht SDS and Ht SDS for BA in 3 groups.

The means of estradiol at 0 and 120 min were 36.19 ± 22.05 and 59.21 ± 73.96 pmol/l which were not significantly different. (Fig. 3)

In group II, the mean peak LH was 18.75 ± 11.5 IU/L and FSH 12.44 ± 4.76 IU/L (Table 2).

The basal LH/FSH ratio was 0.38 ± 0.35 and the peak LH/FSH 1.57 ± 0.77. (Fig. 1, 2)

The means of estradiol at 0 and 120 min were 153.5 ± 148.5 and 134.8 ± 113.6 pmol/l which were not significantly different. (Fig. 3)

In group III, the mean peak LH was 24.08 ±13.15 IU/L and FSH 9.31 ± 2.37 IU/L. (Table 2)

The basal LH/FSH ratio was 0.66 ± 0.41 and peak LH/FSH 2.96 ± 1.92. (Fig. 1, 2)

The means of estradiol at 0 and 120 min were 144.2 ± 116.8 and 110.0 ± 54.1 pmol/l which were not significantly different. (Fig. 3)

In contrast to the patients in group II and III, the patients in group I had good height prognosis because Ht SDS and Ht SDS for BA were not significantly different. (Fig. 4) If we considered the peak LH > 10 IU/L as the laboratory confirmation of CPP, we found that all patients in group III, 8 of 10 patients in group II and 1 of 9 patients in group I had CPP. Therefore, most of the patients in group I were in the benign group called premature thelarche but most of them in group II and III were in the more serious group (CPP) and treatment should be considered.

The peak LH/FSH ratio of 1.0 may be used to differentiate between premature thelarche and CPP with the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 88.2, 90, 93.8, 81.8 per cent respectively.